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APPLICATION NUMBER:

206192Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review	
NDA/SDN	NDA 206192 \\CDSESUB1\evsprod\NDA206192\
Type/Category	NME (Priority)
	Orphan drug and fast track designation
Brand Name	COTELLIC
Generic Name	Cobimetinib (GDC-0973)
Receipt Date	Part 1: October 30, 2014 Part 2: December 11, 2014
PDUFA Date	August 11, 2015
Proposed Indication	Treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations in combination with vemurafenib
Dosage Form	20 mg tablet
Route of Administration	Oral
Dosing Regimen and Strength	60 mg once daily for 21 days followed by 7-day rest
Applicant	Genentech, Inc.
OND Division	Division of Oncology Products 2 (DOP2)
OCP Divisions	Division of Clinical Pharmacology V (DCPV) Division of Pharmacometrics (DPM)
OCP Reviewers	Ruby Leong, Pharm.D. (DCPV) Anshu Marathe, Ph.D. (DPM) Ping Zhao, Ph.D. (DPM)
OCP Team Leaders/Secondary Reviewers	Hong Zhao, Ph.D. (DCPV) Yaning Wang, Ph.D. (DPM) Vikram Sinha, Ph.D. (DPM)

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1 EXECUTIVE SUMMARY

The Applicant seeks approval of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations. The proposed dosing regimen is 60 mg once daily (QD) for 21 consecutive days followed by a 7-day rest period with or without food in each 28-day cycle until disease progression or unacceptable toxicity.

The efficacy and safety of cobimetinib was established in a randomized (1:1), double-blind, active-controlled trial in previously untreated patients with locally advanced or unresectable metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test (cobas® 4800). Treatment with cobimetinib in combination with vemurafenib resulted in a statistically significant improvement in Investigator-assessed median progression-free survival (PFS) of 3.7 months (9.9 versus 6.2 months; HR 0.51 [95% CI: 0.39, 0.68]) as compared with vemurafenib alone. The most common adverse reactions (≥ 20%) of cobimetinib in combination with vemurafenib were diarrhea, photosensitivity, nausea, pyrexia, and vomiting.

The Clinical Pharmacology Section of the NDA is supported by food effect, ADME (absorption, distribution, metabolism, excretion), absolute bioavailability, relative bioavailability between the clinical trial and to-be-marketed formulations, and two drug-drug interaction (DDI) studies in healthy subjects; single and repeat dose pharmacokinetics (PK) studies of cobimetinib as a single agent and in combination with vemurafenib in cancer patients; and in vitro studies to assess the drug interaction potential of cobimetinib with cytochrome P450 (CYP) and transporters. Population pharmacokinetic (PopPK) analyses using data from patients with advanced solid tumors and BRAF V600E mutation-positive metastatic melanoma did not identify clinically important covariates influencing cobimetinib PK. There were no evident exposure-response (E-R) relationships for efficacy (PFS) or for adverse reactions (Grade ≥ 3 rash, diarrhea; Grade ≥ 2 creatine phosphokinase elevation, photosensitivity, laboratory elevations in ALT, AST, alkaline phosphatase or total bilirubin; any grade retinal detachment or serous retinopathy). The proposed dosing regimen of 60 mg orally once daily (QD) for 21 days followed by a 7-day rest period appears acceptable.

1.1 RECOMMENDATIONS

The NDA 206192 is acceptable from a clinical pharmacology perspective provided that the Applicant and the FDA come to an agreement regarding the labeling language and the identified clinical pharmacology trial to be conducted as a postmarketing requirement (PMR). The adequacy of the clinical pharmacology program in the overall drug development plan of cobimetinib is summarized in the table below.

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Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed dosing regimen of 60 mg QD for 21 days followed by 7-day rest with or without food	☒ Yes ☐ No Refer to **Section 2.2.4.4**	**Labeling Recommendations:** The recommended dose of COTELLIC is 60 mg orally once daily for 21 consecutive days followed by a 7-day break until disease progression or unacceptable toxicity. Administer COTELLIC with or without food.
Dose adjustment in patients with organ impairment	☐ Yes ☒ No Refer to **Section 2.3.1**	**Labeling Recommendations:** Dose adjustment is not recommended in patients with mild hepatic impairment. The recommended dose has not been determined in patients with moderate and severe hepatic impairment. **PMR:** Hepatic impairment study. Refer to **Section 1.2.1**.
Dose adjustment in patients with comedications that affect the PK of cobimetinib	☒ Yes ☐ No Refer to **Section 2.4.2.7** and **2.4.2.8**	**Labeling Recommendations:** CYP3A Inhibitors or Inducers: Avoid concurrent use of strong or moderate CYP3A inhibitors and inducers. If concomitant short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable, reduce cobimetinib dose to 20 mg during treatment with a moderate CYP3A inhibitor.
Proposed commercial tablet formulation	☒ Yes ☐ No Refer to **Section 2.5.2**	**Comments:** The proposed commercial tablet formulation was administered in the registration trial (Study GO28141). The PK profile of the commercial tablet was comparable to the powder-in-capsule formulation utilized in the dose escalation trial to determine the Recommended Phase 2 dose of cobimetinib in combination with vemurafenib (Study NO25395).

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

1.2.1 Postmarketing Requirements (PMR)

The Applicant is required to conduct the following clinical pharmacology trial under the PMR provision. The PMR trial will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

Drug Development Question	Rationale	PMR
Should the dose of cobimetinib be reduced in patients with moderate and severe hepatic impairment?	76.5% (6.6% as unchanged drug) of the administered dose was recovered in the feces, indicating that hepatic elimination is the major elimination pathway.	Complete a pharmacokinetic study to determine the appropriate dose of cobimetinib in patients with hepatic impairment. Final Protocol Submission: Submitted Trial Completion: January 2015 Final Report Submission: July 2015

Signatures:

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Reviewer: Ping Zhao, Ph.D. Division of Pharmacometrics	PBPK Secondary Reviewer: Vikram Sinha, Ph.D. Division of Pharmacometrics
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Cc: DOP2: RPM – M Libeg; MO – R Giusti; MTL – M Theoret
DCPV: DDD – B Booth; Office of Clinical Pharmacology Director – I Zineh

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1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Proposed Dosing Regimen

The proposed dosing regimen for cobimetinib is 60 mg QD for 21 days followed by 7-day rest with or without food in each 28-day cycle until disease progression or unacceptable toxicity. Dosing regimens of 0.05, 0.10, or 0.20 mg/kg, 10, 20, 40, 60, or 80 mg QD on a 21 day on / 7 day off (21/7) dose schedule and dosing regimens of 60, 80, 100, or 125 mg on a 14 day on / 14 day off (14/14) dose schedule were evaluated for cobimetinib as a single agent in Study MEK4592g. The maximum tolerated dose (MTD) of cobimetinib as a single agent was determined to be 60 mg QD on the 21/7 schedule and 100 mg QD on the 14/14 schedule. Dosing regimens of cobimetinib 60 mg QD on a 21/7 dose schedule plus vemurafenib 720 or 960 mg BID; cobimetinib 60, 80, or 100 mg QD on a 14/14 dose schedule plus vemurafenib 720 mg BID and 60 or 80 mg QD on a 14/14 dose schedule plus vemurafenib 960 mg BID; cobimetinib 60 mg QD continuously in each 28-day cycle plus vemurafenib 720 or 960 mg BID were evaluated in Study NO25395. The Applicant states that the 21/7 dose schedule provides a longer duration of cobimetinib exposure and prolonged suppression of MEK, and is associated with a lower incidence of AEs (including Grade ≥ 3 AEs) than the 14/14 dose schedule.

A food effect study conducted in healthy subjects with a single 20 mg cobimetinib dose showed that a high-fat meal had no effect on cobimetinib AUC and C_{max} as compared with the fasted state.

Exposure-Response Relationships

There were no evident exposure-response (E-R) relationships for efficacy (progression-free survival [PFS]) or for adverse reactions (Grade ≥ 3 rash, diarrhea; Grade ≥ 2 creatine phosphokinase elevation, photosensitivity, laboratory elevations in ALT, AST, alkaline phosphatase or total bilirubin; any grade retinal detachment or serous retinopathy).

Population concentration-QTc analyses using time-matched ECG and PK data showed that there was no evident concentration-QTc relationship for cobimetinib as a single agent. No large changes (i.e., > 20 ms) in QTcF intervals were detected with cobimetinib as a single agent at doses up to 125 mg. Clinically relevant QT prolongation has been reported with vemurafenib as a single agent; however, substantial further increase in QTc was not observed with cobimetinib 60 mg in combination with vemurafenib. Following administration of cobimetinib 60 mg in combination with vemurafenib 960 mg, the largest mean change from baseline (ΔQTcF) was 7.8 ms with the upper bound of the 2-sided 90% confidence interval (CI) of 8.6 ms.

ADME

The mean absolute bioavailability of cobimetinib is 46% (90% CI: 40%, 53%). Following oral administration of cobimetinib 60 mg once daily in cancer patients, the median time to achieve peak plasma levels (T_{max}) was 2.4 (1, 24) hours with a mean elimination half-life ($t_{1/2}$) of 44 (23-

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70) hours. The geometric mean steady-state $AUC_{0\text{-}24h}$ was 4340 ng·h/mL (61% CV) and C_{max} was 273 ng/mL (60% CV). Cobimetinib exhibits linear time-independent PK, with exposures that are approximately dose proportional after single and repeat doses in the range of 10 to 100 mg. Following cobimetinib 60 mg QD, steady state is achieved within 9 days with 2.4-fold accumulation. The mean apparent clearance (CL/F) following multiple doses of cobimetinib 60 mg in cancer patients was 13.8 L/hr (61% CV).

Potential DDIs

Cobimetinib is primarily metabolized by CYP3A and UGT2B7 in vitro. Coadministration of itraconazole (a strong CYP3A inhibitor) 200 mg QD for 14 days and a single dose of 10 mg cobimetinib increased cobimetinib AUC by 6.7-fold and C_{max} by 3.2-fold in healthy subjects. Therefore, concomitant use of strong CYP3A inhibitors with cobimetinib should be avoided. Concomitant use of strong CYP3A inducers should also be avoided given that labeling for vemurafenib recommends avoiding concomitant administration with strong CYP3A4 inhibitors or inducers and cobimetinib is administered in combination with vemurafenib. Physiologically-based pharmacokinetic modeling (PBPK) predicts that rifampin can decrease cobimetinib exposure (AUC) by 83%. PBPK simulations also suggested that erythromycin and diltiazem (moderate CYP3A inhibitors) can increase cobimetinib exposure (AUC) by 3 to 4-fold; efavirenz (moderate CYP3A inducer) can decrease cobimetinib AUC by 73%. Therefore, concomitant use of moderate CYP3A inhibitors or inducers should be avoided. If avoiding concomitant moderate CYP3A inhibitors is not possible, it is recommended to reduce the dose of cobimetinib to 20 mg during treatment with a moderate CYP3A inhibitor (e.g., antibiotics including erythromycin or ciprofloxacin) for 14 days or less. After discontinuation of a moderate CYP3A inhibitor, the cobimetinib dose that was taken prior to initiating the moderate CYP3A4 inhibitor should be resumed. PBPK simulations predict that fluvoxamine (weak CYP3A inhibitor) does not change cobimetinib exposure.

Cobimetinib is a reversible inhibitor of CYP3A4 and CYP2D6 and also a time-dependent inhibitor of CYP3A4 in vitro. Coadministration of cobimetinib 60 mg QD for 15 days with a single 2 mg doses of midazolam (sensitive CYP3A4 substrate) and dextromethorphan (sensitive CYP2D6 substrate) did not result in clinically important changes in systemic exposure of midazolam or dextromethorphan.

Coadministration of rabeprazole (a proton pump inhibitor) 20 mg QD for 5 days with a single dose of 20 mg cobimetinib increased cobimetinib AUC by 11% and did not affect C_{max} as compared with cobimetinib alone. Cobimetinib may be administered concomitantly with acid reducing drugs.

Organ Dysfunction

The ADME study showed that hepatic elimination is the major route of elimination (76.5% of the administered radiolabeled dose was recovered in feces with 6.6% as unchanged drug), indicating that hepatic impairment may increase the systemic exposure of cobimetinib. The Applicant is

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requested to submit the results of an ongoing hepatic impairment study under a PMR to determine the appropriate cobimetinib dose in patients with hepatic dysfunction. No dose adjustment is recommended for mild hepatic impairment according to the National Cancer Institute (NCI) liver dysfunction criteria (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1.0 to 1.5 times ULN and any AST) because popPK estimated steady-state AUC was similar between patients with mild hepatic impairment and patients with normal hepatic function.

The ADME study showed that renal excretion is not a major route of elimination (17.8% of the administered radiolabeled dose was recovered in urine with 1.6% of dose excreted unchanged). Dose adjustments are not recommended for patients with mild (CLcr 60 to < 90 mL/min) or moderate (CLcr 30 to < 60 mL/min) renal impairment based on popPK analysis which showed that estimated steady-state AUC was similar between patients with mild and moderate renal impairment and patients with normal renal function.

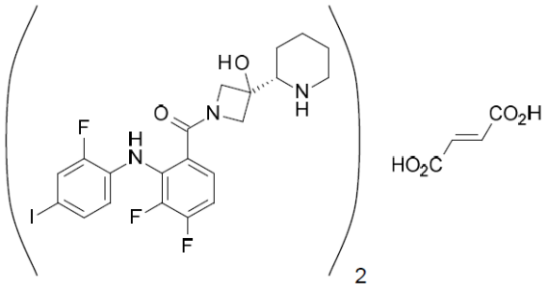
2 QUESTION-BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The molecular weight of cobimetinib is 531 g/mol as free base and 1179 g/mol as hemifumarate salt (**Figure 1**). The proposed drug product is available as 20 mg tablets.

Figure 1. Chemical Structure of Cobimetinib Hemifumarate



Cobimetinib is soluble (dose/250 mL=0.24 mg/mL) in aqueous media with measured pH range of 1.9 to 7.5 in vitro, exhibiting 100-fold less solubility at measured pH=6.4 as compared with measured pH=1.9 (**Table 1**). Although the lowest solubility at high pH is greater than the value of the clinical dose (60 mg)/250 mL, an in vivo interaction study with a proton pump inhibitor was conducted and results showed no effect on systemic exposure of cobimetinib (refer to **Section 2.4.2.8**).

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Table 1. Aqueous Solubility of Cobimetinib

pH	Buffer	Solubility (mg/mL)	pH Measured
Neutral	Water	0.72	7.5
6.5	FaSSIF	0.48	6.4
5.0	FeSSIF	4.13	5.0
1.1	0.1 M HCl	48.21	1.9
4.5	50 mM Acetate	1.08	4.5
6.8	50 mM Phosphate	0.78	6.8
7.5	50 mM Phosphate	0.73	7.5

Note: Solubility after 24 h at 37°C.
FaSSIF = fasted-state simulated intestinal fluid; FeSSIF = fed-state simulated intestinal fluid.

Source: Module 3.2.S.1.3 General Properties, Table S.1.3-2, Page 3.

Cobimetinib showed moderate to high permeability across madin-darby canine kidney (MDCKII) and Caco-2 cells (refer to **Section 2.5.1**). The Applicant claims that cobimetinib is a (b) (4) compound with high permeability and high solubility; however, the mean absolute bioavailability of a single 20 mg oral dose of cobimetinib was 46%.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Cobimetinib is an inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). BRAF V600 mutations result in constitutive activation of the BRAF pathway, which includes downstream proteins MEK1 and MEK2. Inhibition of BRAF catalyzed MEK activation and kinase activity of phosphorylated MEK leads to decreased cellular proliferation in tumors with BRAF V600 mutations. Acquired resistance to vemurafenib, a BRAF inhibitor, can occur by MAPK reactivation through MEK. Simultaneous inhibition of MEK and BRAF blocks paradoxical activation of the MAPK pathway from RAF inhibition and reduces the incidence of hyperproliferative lesions.

The proposed indication is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations in combination with vemurafenib.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The Applicant's proposed dosing regimen is 60 mg orally once daily (QD) for 21 days followed by a 7-day rest period with or without food in each 28-day cycle until disease progression or unacceptable toxicity.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 2 lists the relevant clinical pharmacology and clinical studies included in the application.

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Table 2. Summary of Clinical Pharmacology and Clinical Studies

Study Number	Study Design	Study Population	Assessment	Dosing regimen
GP28369	Open label, single dose	Healthy subjects (n=5)	ADME	20 mg [^{14}C]-cobimetinib oral solution containing 200 µCi radioactivity
GP28370	Open label, single dose, randomized, crossover with 14-day washout	Healthy subjects (n=28)	Relative BA	Cobimetinib 20 mg as a 20 mg tablet (to-be-marketed formulation) and four × 5 mg capsules
GP28620	Open label, single dose	Healthy subjects (n=15)	DDI	Cobimetinib 10 mg and coadministration with itraconazole
MEK4952g	Open label, single dose, randomized, crossover with 10-day washout	Healthy subjects (n=13)	Absolute BA	Cobimetinib 2 mg administered intravenously over 30 minutes and cobimetinib 20 mg administered orally
MEK4953g	Open label, single dose, randomized, crossover with 10-day washout	Healthy subjects (n=19)	Relative BA and food effect	Cobimetinib 20 mg as a 20 mg prototype tablet and four × 5 mg capsules in the fasted state and cobimetinib 20 mg prototype tablet with a high-fat meal
MEK4954g	Open label, single dose	Healthy subjects (n=20)	DDI	Cobimetinib 20 mg and coadministration with rabeprazole
MEK4592g (Stage III)	Open label, multiple doses	Solid tumor patients (n=20)	DDI	Cobimetinib 60 mg QD 21/7 and coadministration with midazolam and dextromethorphan
MEK4592g (Stages I, IA, II, IIa)	Open label, 3+3 dose escalation and expansion	Solid tumor patients (n=97)	MTD/RP2D of cobimetinib, safety, PK, antitumor activity	<u>Dose escalation</u> • Stage I: 21/7 Cohort 01: C 0.05 mg/kg; Cohort 02: C 0.10 mg/kg; Cohort 03: C 0.20 mg/kg; Cohort 04: C 10 mg; Cohort 05: C 20 mg; Cohort 06: C 40 mg; Cohort 07: C 60 mg; Cohort 08: C 80 mg • Stage IA: 14/14 Cohort 01A: C 60 mg; Cohort 02A: C 80 mg; Cohort 03A: C 100 mg; Cohort 04A: C 125 mg <u>Expansion</u> • Stage II: 21/7 Cohort 20: C 60 mg • Stage IIA: 14/14 Cohort 30: C 100 mg

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Study Number	Study Design	Study Population	Assessment	Dosing regimen
NO25395	Open label, 3+3 dose escalation and expansion	BRAF V600E mutation-positive metastatic melanoma patients (n=129 C+V, n=2 C)	MTD/RP2D of cobimetinib + vemurafenib, safety, PK	<u>Dose escalation</u> • 14/14 Cohort 1: C 60 mg + V 720 mg; Cohort 2: C 80 mg + V 720 mg; Cohort 2A: C 100 mg + V 720 mg; Cohort 3: C 60 mg + V 960 mg; Cohort 4: C 80 mg + V 960 mg • 21/7 Cohort 1A: C 60 mg + V 720 mg; Cohort 1B: C 60 mg + V 960 mg • 28/0 Cohort 1C: C 60 mg + V 720 mg; Cohort 1D: C 60 mg + V 960 mg <u>Expansion</u> • 21/7 Exp2112: C 60 mg + V 720 mg; Exp2122: C 60 mg + V 960 mg <u>Single agent</u> C 60 mg 21/7 or C 100 mg 14/14
GO28141	Double-blind, randomized (1:1), active-controlled, cobimetinib + vemurafenib vs. vemurafenib	BRAF V600 mutation-positive metastatic melanoma patients (n=249 C+V, n=248 V+P)	Efficacy, safety, popPK, E-R, HRQL	Cobimetinib 60 mg QD 21/7 + vemurafenib 960 mg BID vs. vemurafenib 960 mg BID + placebo

ADME: Absorption, distribution, metabolism, excretion; BA: Bioavailability; BID: Twice daily; C: Cobimetinib administered daily in 14/14, 21/7, or 28/0 dosing schedules; DDI: Drug-drug interaction; E-R: Exposure-response; HRQL: Health-related quality of life; MTD: Maximum tolerated dose; P: Placebo; PK: Pharmacokinetics; PopPK: Population pharmacokinetics; QD: Once daily; RP2D: Recommended Phase 2 dose; V: Vemurafenib administered twice daily continuously

In addition, cobimetinib plasma concentration data from Studies MEK4592g (n=114), NO25395 (n=131), and GO28141 (n=490) were used to develop a PopPK model to assess the potential influence of covariates on inter-patient variability in cobimetinib PK parameters, and to explore exposure-response relationships for efficacy and safety endpoints.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy outcome measure of the registration trial GO28141 was progression-free survival (PFS) by Investigator assessment. Additional outcome measures included overall

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survival (OS), objective response rate (ORR), duration of response (DOR), and PFS by Independent Review Committee (IRC) assessment.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

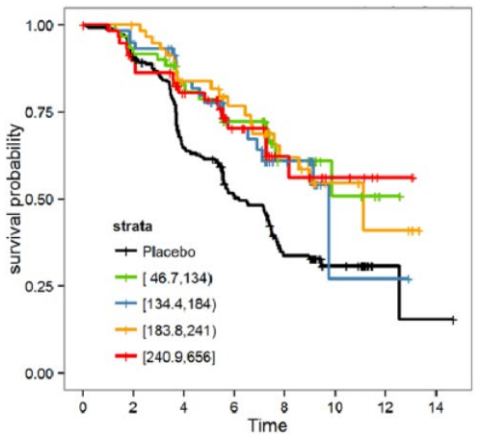
Yes. Cobimetinib was the major component in human plasma after oral administration and it was appropriately identified and measured to assess PK parameters (refer to **Section 2.6**).

2.2.4 Exposure-response

2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

There were no significant exposure-response (E-R) relationships for the primary efficacy endpoint of PFS by Investigator assessment (**Figure 2**) based on data from Study GO28141 in patients with BRAF V600 mutation-positive metastatic melanoma (refer to Pharmacometrics review in **Section 4.1**).

Figure 2. Relationship Between Cobimetinib AUC_{ss} and Probability of PFS Stratified by AUC_{ss} Quartiles in BRAF V600 Mutation-Positive Metastatic Melanoma Patients in Study GO28141



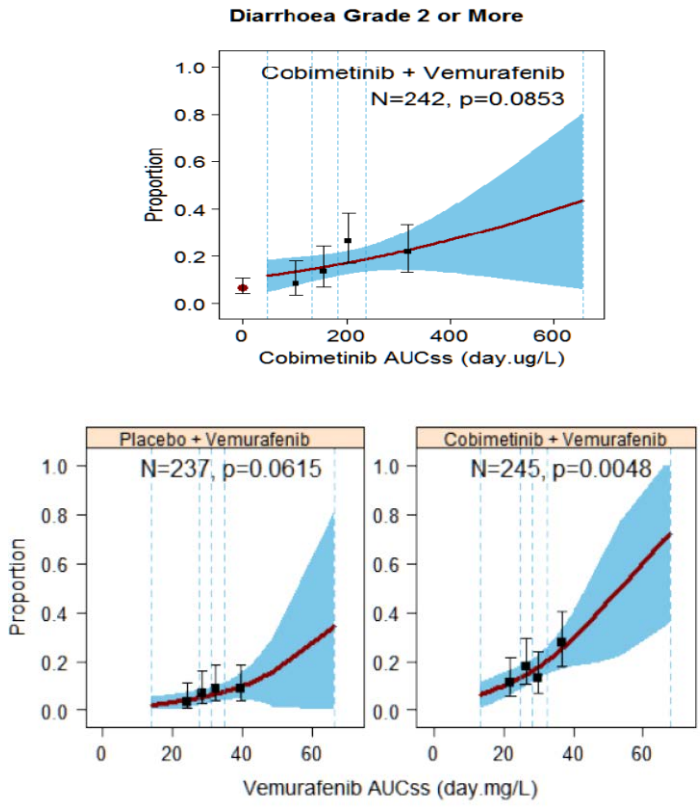
The figure shows a Kaplan-Meier plot of PFS by cobimetinib steady-state AUC quartiles.

Source: Pharmacometrics review, Figure 1.

2.2.4.2 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

Exploratory E-R analysis for safety identified a trend for increase in Grade ≥ 2 diarrhea with increasing cobimetinib and vemurafenib exposure **(Figure 3).** The relationship appeared to be steepest with vemurafenib exposure in the cobimetinib plus vemurafenib arm. The incidence of Grade ≥ 2 diarrhea in the cobimetinib plus vemurafenib arm was 17.1% and 6.7% in the vemurafenib alone arm.

Figure 3. Relationship between Cobimetinib or Vemurafenib AUC_{ss} and Grade 2 or Worse Diarrhea in Patients with BRAF V600 Mutation-Positive Metastatic Melanoma



Source: Pharmacometrics review, Figure 2.

There were no significant E-R relationships for safety including adverse events (AEs) of rash (Grade ≥3), diarrhea (Grade ≥3), retinal detachment or serous retinopathy (any grade), creatine phosphokinase elevation (Grade ≥2), photosensitivity (Grade ≥2), or laboratory elevations in ALT, AST, alkaline phosphatase and total bilirubin (Grade ≥2).

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2.2.4.3 *Does this drug prolong the QT or QTc interval?*

A population concentration-QTc analysis was conducted using PK and ECG data from Studies MEK4592g (n=57), NO25395 (n=123), and GO28141 (n=433) (**Table 3**).

Table 3. Summary of ECG Monitoring and PK Sampling Plan

Study	ECG Monitoring	PK Sampling
MEK4592g	• Stage I - Day 1: Pre-dose, 4 hours post-dose - Days 8, 15, 21: Pre-dose • Stages II, IA and IIA - Day 1: Pre-dose, 1.5, 3, 6, 24 hours post-dose - Day 8: Pre-dose - Day 14 or 21: Pre-dose, 1.5, 3, 6 hours post-dose	• Stage I - Cycle 1, Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12-18 (optional) hours post-dose - Cycle 1, Days 2 and 15: Pre-dose - Cycle 1, Day 8: Pre-dose, 2-4 hours post-dose - Cycle 1, Day 21: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12-18 (optional), 24, 48, 72 hours post-dose - Day 1 of each subsequent cycle: Pre-dose • Stage IA - Cycle 1, Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 24 hours post-dose - Cycle 1, Day 8: Pre-dose, 2-4 hours post-dose - Cycle 1, Day 14: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 24 hours post-dose - Day 1 of each subsequent cycle: Pre-dose - Final visit (if within 48 hours of last dose) • Stages II, IIA - Cycle 1, Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 24 hours post-dose - Cycle 1, Days 10-14 and 26-28: At ±3 hours of FDG-PET - Cycle 1, Day 14 (Stage IIA only), Day 21 (Stage II only): Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 24 hours post-dose - Day 1 of each subsequent cycle: Pre-dose - Final visit (if within 48 hours of last dose)
NO25395	• Screening • Cycle 1, Day 1: Pre-dose, 4, 24 hours post-dose • Cycle 1, Day 14: Pre-dose, 2, 4, 8 hours post-dose • Cycle 1, Day 22: Pre-dose • Day 1 of Cycles 2, 3, 4 • Day 1 of every three cycles thereafter • Disease progression (or final visit)	• Cycle 1, Day 1: Pre-dose, 0.5, 1, 2, 4, 6 hours post-dose • Cycle 1, Day 14: Pre-dose, 0.5, 1, 2, 4, 6, 8 hours post-dose • Cycle 1, Days 2, 8, and 15: Pre-dose • Cycle 2, Days 1 and 8: Pre-dose • Cycle 3, Day 8: Pre-dose • Disease progression (or final visit) • At time of DLT, dose reduction or interruption due to AEs, as feasible
GO28141	• Screening • Cycle 1, Day 15±3: Pre-dose, 2, 4 hours post-dose • Day 15±3 of Cycles 2, 3, and every 3 treatment cycles thereafter (Cycles 6, 9, 12, etc.)	• Cycle 1, Day 1: Pre-dose, 1-4 hours post-dose • Cycle 1, Day 15: Pre-dose, 2-4 hours post-dose • Cycle 2, Day 15: Pre-dose

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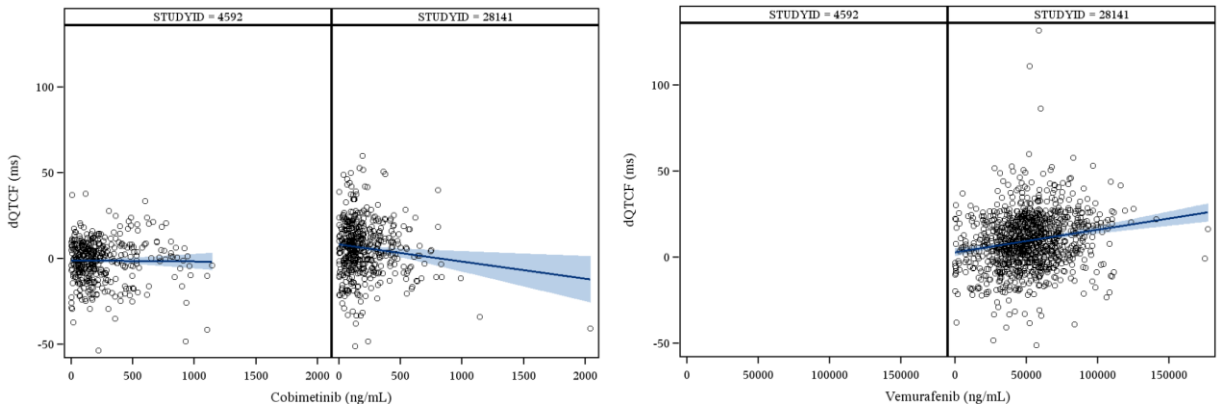
The QT-IRT review found that there was no evident concentration-QTc relationship for cobimetinib as a single agent and concentration-ΔQTcF analysis for vemurafenib confirms the known positive relationship between vemurafenib exposure and increase in QT interval (**Figure 4**).

Figure 4. Concentration-ΔQTcF Relationship for Cobimetinib and Vemurafenib (Studies MEK4592g and GO28141)



Source: QT-IRT review, Figure 3.

QT-IRT analysis of data from Study NO25395 confirmed the significant relationship between vemurafenib concentration and QT prolongation. The analysis also showed that there was a significant slope between cobimetinib exposure and ΔQTcF in Study NO25395; although the QT effect of cobimetinib appears small (ΔQTcF predicted to be 6.7 [95% CI: 3.1, 10.3] ms at cobimetinib steady-state C_{max} of 273 ng/mL). QT-IRT concludes that there are limitations of concentration-QTc analysis for drugs used in combination because of the correlation between the concentrations of the two drugs and the exploratory analysis cannot fully rule out the QT prolongation risk of cobimetinib.

No large changes (i.e., > 20 ms) in QTcF intervals were detected with cobimetinib as a single agent at doses up to 125 mg. Clinically relevant QT prolongation has been reported with vemurafenib as a single agent; however, substantial further increase in QTc was not observed with cobimetinib 60 mg in combination with vemurafenib. Following administration of cobimetinib 60 mg in combination with vemurafenib 960 mg, the mean change from baseline (ΔQTcF) was 7.8 ms with the upper bound of the 2-sided 90% confidence interval (CI) of 8.6 ms (**Table 4**).

Reference ID: 3751393

Table 4. ΔQTcF for Cobimetinib as a Single Agent and in Combination with Vemurafenib

Study	Treatment	ΔQTcF (ms)	Std Dev	90% CI (ms)
MEK4592g	Cobimetinib 60 mg	-2.2	11.0	(-3.7, -0.7)
MEK4592g	Cobimetinib 80 mg	-0.3	13.9	(-4.6, 4.1)
MEK4592g	Cobimetinib 100 mg	2.2	10.4	(0.9, 3.5)
MEK4592g	Cobimetinib 125 mg	-11.2	16.7	(-16.2, -6.3)
GO28141	Vemurafenib 960 mg BID + Placebo	13.1	16.5	(12.2, 13.9)
GO28141	Cobimetinib 60 mg + Vemurafenib 960 mg BID	7.8	16.1	(6.9, 8.6)
NO25395	Cobimetinib 60 mg + Vemurafenib 720 mg BID	6.2	20.8	(4.7, 7.7)
NO25395	Cobimetinib 60 mg + Vemurafenib 960 mg BID	6.8	18.1	(5.8, 7.9)

Source: QT-IRT Review, Table 1.

Refer to **Section 3** for QT-IRT labeling recommendations.

2.2.4.4 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?*

Dosing regimens of 0.05, 0.10, or 0.20 mg/kg, 10, 20, 40, 60, or 80 mg QD on a 21 day on / 7 day off (21/7) dose schedule and dosing regimens of 60, 80, 100, or 125 mg on a 14 day on / 14 day off (14/14) dose schedule were evaluated for cobimetinib as a single agent in Study MEK4592g (refer to **Table 2**). The maximum tolerated dose (MTD) of cobimetinib as a single agent was determined to be 60 mg QD on the 21/7 schedule and 100 mg QD on the 14/14 schedule. Dosing regimens of cobimetinib 60 mg QD on a 21/7 dose schedule plus vemurafenib 720 or 960 mg BID; cobimetinib 60, 80, or 100 mg QD on a 14/14 dose schedule plus vemurafenib 720 mg BID and 60 or 80 mg QD on a 14/14 dose schedule plus vemurafenib 960 mg BID; cobimetinib 60 mg QD continuously in each 28-day cycle plus vemurafenib 720 or 960 mg BID were evaluated in Study NO25395. The Applicant states that the 21/7 dose schedule provides a longer duration of cobimetinib exposure and prolonged suppression of MEK, and is associated with a lower incidence of AEs (including Grade ≥ 3 AEs) than the 14/14 dose schedule.

Based on currently available data, the proposed dosing regimen of 60 mg orally QD for 21 days followed by a 7-day rest period appears acceptable. The results of E-R analyses for efficacy did not show a clear relationship between systemic exposure and PFS (refer to **Section 2.2.4.1**). However, treatment with cobimetinib in combination with vemurafenib resulted in a statistically significant improvement in Investigator-assessed median PFS of 3.7 months (HR 0.51 [95% CI: 0.39, 0.68], p-value < 0.0001) as compared with vemurafenib alone, indicating that the proposed dosing regimen of 60 mg QD for 21 days followed by a 7-day rest period is efficacious. E-R analyses did not show a clear relationship between systemic exposure and safety (refer to **Section 2.2.4.2**). Dose modification (dose interruption or reduction) occurred more frequently in the cobimetinib plus vemurafenib arm as compared with the vemurafenib alone arm in Study GO28141 (**Table 5**); however, addition of cobimetinib to vemurafenib resulted in a similar number of discontinuation as compared with vemurafenib alone.

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Table 5. Percentage of Patients with ≥ 1 Treatment-Emergent Adverse Event that Resulted in ≥ 1 Dose Interruption or Reduction in Study GO28141

Modified Study Treatment	Placebo + Vemurafenib (n = 239)	Cobimetinib + Vemurafenib (n = 254)
Cobimetinib or placebo	83 (34.7%)	129 (50.8%)
Vemurafenib	113 (47.3%)	139 (54.7%)
Both cobimetinib/placebo and vemurafenib*	78 (32.6%)	107 (42.1%)

* Patients who had both drugs interrupted or reduced were also represented in the rows for modification of each individual drug.

Source: GO28141 Final Study Report, Table 40, Page 121.

Additional unresolved dosing and administration issues with cobimetinib to be addressed under a PMR include potential dose adjustment in patients with hepatic impairment.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

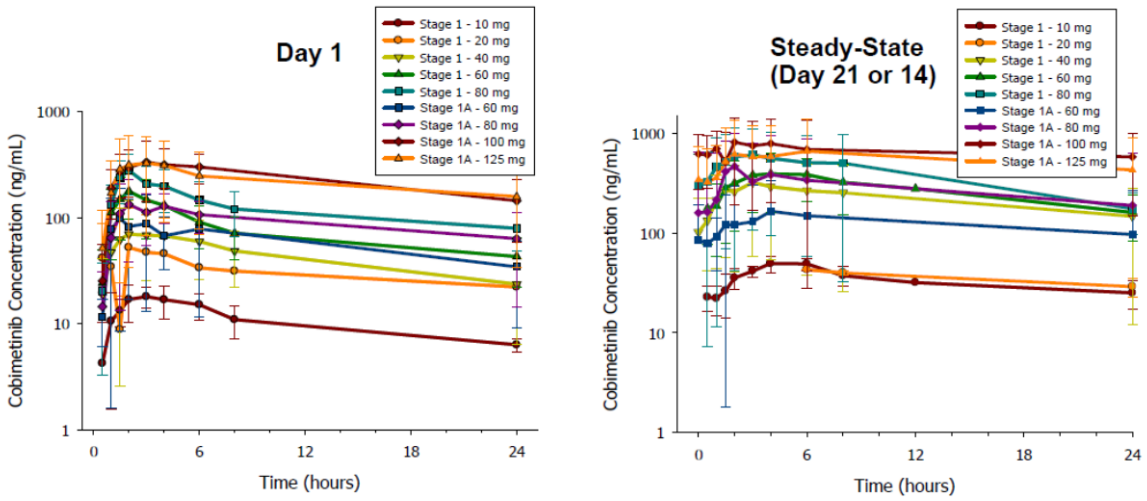
The single dose PK of cobimetinib has been evaluated in 6 clinical pharmacology studies in healthy subjects (refer to **Table 2**). The single and multiple-dose PK of cobimetinib have been evaluated in patients in Studies MEK4592g and NO25395 (refer to **Table 3** for a summary of the PK sampling plans).

Cobimetinib exhibits linear time-independent PK, with exposures that are dose proportional after single and multiple doses in the range of 10 to 100 mg. Following cobimetinib 60 mg QD, steady-state is achieved by approximately 9 days with 2.4-fold accumulation. The mean terminal half-life ($t_{1/2}$) at the 60 mg dose is 44 (23-70) hours.

Mean concentration-time profiles after single and multiple doses of 10 to 125 mg cobimetinib are shown in **Figure 5**.

Reference ID: 3751393

Figure 5. Mean Concentration-Time Profiles After Single Doses (Left) and Multiple Doses (Right) of Cobimetinib



Source: Summary of Clinical Pharmacology Studies, Figure 2, Page 27.

Single dose and multiple dose PK parameters of cobimetinib as a single agent were determined using noncompartmental analysis and summarized in **Table 6** and **Table 7**, respectively.

Table 6. Single Dose PK Parameters of Cobimetinib as Single Agent in Cancer Patients

Stage I

Cohort Numbers (n)	Nominal Dose	Total Dose (mg)	Median t_{max} (range) (hr)	C_{max} (ng/mL) [a]	AUC_{0-24} (h*ng/mL) [a]
1 (n=4)	0.05 mg/kg	3.15 ± 0.91 (29)	2.0 (2.0-8.0)	4.51 ± 5.8 (110)	56.2 ±65 (110)
2 (n=3)	0.1 mg/kg	7.92 ± 2.0 (26)	1.0 (1.0-2.0)	6.92 ± 3.8 (69)	68.0 ± 47 (87)
3 (n=3)	0.2 mg/kg	13.4 ± 2.4 (18)	1.5 (1.0-1.5)	18.3 ± 13 (64)	203 ± 130 (58)
4 (n=3)	10 mg	10	3.0 (1.0-4.0)	18.8 ± 5.1 (29)	242 ± 64 (28)
5 (n=3)	20 mg	20	4.0 (2.0-4.0)	30.8 ±69 (220)	440 ± 870 (190)
6 (n=6)	40 mg	40	2.5 (1.5-6.0)	71.7 ± 57 (89)	785 ± 560 (75)
7 (n=7)	60 mg	60	2.0 (1.0-4.0)	163 ± 79 (52)	1620 ± 830 (49)
8 (n=7)	80 mg	80	2.0 (1.5-2.0)	261 ± 110 (47)	3060 ± 950 (34)

Stage II

Cohort Numbers (n)	Nominal Dose	Total Dose (mg)	Median t_{max} (range) (hr)	C_{max} (ng/mL) [a]	AUC_{0-24} (h*ng/mL) [a]
1 (n=19)	60 mg	60	3.0 (1.0-6.0)	184 ± 160 (87)	2440 ±2100 (80)

Cobimetinib was administered daily on a 21-on/7-off schedule in Stage I (Dose Escalation stage) of the study.

[a] C_{max} and AUC_{0-24} are reported as Geometric Mean ± SD (%CV).

Source: MEK4592g Final Study Report, Tables 1 and 3, Page 5.

Reference ID: 3751393

Table 7. Steady-State PK Parameters of Cobimetinib as Single Agent in Cancer Patients

Study No./Design/ Population/Stage/ Objective/ Regimen	Dosage, Form	Product Lot No.	[a]t_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	R_{acc}	[a]$t_{1/2}$ (h)	CL/F (L/h)
MEK4592g Open-label, dose escalation 47M/50F Age:59.5 (30-82) yrs Stage I Safety, MTD, PK MD, 21/7, oral	0.05 mg/kg, PiB (n=3)	See MEK4592g; Sec. 16.1.6	4.0 (2.0–4.0)	11.2 (92)	164 (94)	3.3 (449)	80.0	18.6 (83)
	0.1 mg/kg PiB (n=3)		1.0 (1.0–2.0)	16.4 (84)	244 (83)	3.6 (28)	62.2 (51.5–73.0)	31.7 (50)
	0.2 mg/kg PiB (n=2)		2.25 (1.5–3.0)	28.0 (31)	387 (54)	2.6 (35)	47.7 (46.5–49.1)	36.2 (31)
	10 mg PiC (n=3)		4.0 (3.0–4.0)	52.9 (10)	752 (21)	3.1 (37)	53.3 (34.0–67.5)	13.3 (21)
	20 mg PiC (n=1)		3.0	57.4	886	3.0	50.5	22.6
	40 mg PiC "(n=5)		2.0 (1.5–3.0)	272 (88)	3840 (120)	2.9 (36)	43.8 (34.2–62.4)	10.4 (120)
	60 mg PiC (n=4)		3.0 (1.5–4.0)	364 (53)	5600 (57)	2.8 (32)	43.6 (23.1–61.4)	10.7 (57)
	80 mg PiC (n=6)		2.5 (2.0–4.0)	525 (72)	8060 (81)	2.8 (67)	48.9 (33.5–65.4)	9.9 (81)
Stage II MD, 21/7, oral	60 mg PiC (n=15)		3.0 (1.0–6.0)	315 (57)	5090 (50)	2.3 (50)	42.7 (27.8–69.6)	11.8 (50)
Stage IA Safety, MTD, PK MD,14/14, oral	60 mg PiC (n=3)		2.0 (1.5–4.0)	163 (60)	2670 (64)	2.3 (21)	59.4 (NA)	22.5 (64)
	80 mg PiC (n=3)		2.0 (2.0–6.0)	470 (41)	6020 (64)	2.8 (62)	44.1 (NA)	13.3 (64)
	100 mg PiC (n=5)		3.0 (1.5–4.0)	470 (115)	7270 (165)	1.8 (134)	56.1 (48.1–71.1)	13.7 (165)
	125 mg PiC (n=3)		6.0 (2.0–6.0)	1070 (54)	19, 700 (55)	4.9 (45)	47.7 (NA)	6.4 (3.2)
Stage IIA MD, 14/14, oral	100 mg PiC (n=13)		4.0 (1.5–6.0)	566 (70)	10200 (69)	2.5 (32)	53.4 (45.3–68.3)	9.8 (69)

AUC_{0-24} = area under the plasma concentration-time profile over a 24-hour sampling interval; C_{max} = maximum observed plasma concentration; CL/F = apparent clearance; F = females; M = males; MD = multiple dose; MTD = maximum tolerated dose; NA = not available; PiB = powder in bottle; PiC = powder in capsule; PK = pharmacokinetic; R_{acc} = accumulation ratio (Day 21 AUC_{0-24}/Day 1 AUC_{0-24}); SD = single dose; $t_{1/2}$ = elimination half-life; t_{max} = time to C_{max}.

[a] Median (min-max).

Source: Summary of Clinical Pharmacology Studies, Appendix 2, Pages 72-73.

Single dose and multiple dose PK parameters of cobimetinib in combination with vemurafenib were determined using noncompartmental analysis and summarized in **Table 8** and **Table 9**, respectively.

Table 8. Single Dose PK Parameters of Cobimetinib in Combination with Vemurafenib in Cancer Patients

Cohort	Cobimetinib Dose/Regimen	Vemurafenib Dose/Regimen	t_{max} (h)[a]	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)
1 n=5	60 mg QD 14/14	720 mg BID 28/0	4.00 (2.0–5.5)	159 (110)	2280 (90)
2 n=4	80 mg QD 14/14	720 mg BID 28/0	4.02 (4.0–4.1)	133 (37)	1600 (29)
2A n=4	100mg QD 14/14	720 mg BID 28/0	4.03 (4.0–4.3)	146 (79)	2300 (100)
3 n=2	60 mg QD 14/14	960 mg BID 28/0	2.0, 4.1	16.1, 87.0	334, 1120
4 n=5	80 mg QD 14/14	960 mg BID 28/0	4.00 (2.0–6.0)	93.6 (26)	1410 (29)
1A n=8	60 mg QD 21/7	720 mg BID 28/0	4.00 (2.0–27)	146 (100)	1990 (99)
1B n=26	60 mg QD 21/7	960 mg BID 28/0	4.00 (1.0–25)	121 (96)	1790 (88)
1C n=3	60 mg QD 28/0	720 mg BID 28/0	2.03 (2.0–24)	136 (81)	1300 (35)
1D n=4	60 mg QD 28/0	960 mg BID 28/0	3.99 (1.0–6.2)	130 (53)	1850 (35)
1A Expansion n=27	60 mg QD 21/7	720 mg BID 28/0	4.00 (0.5–6.0)	84.3 (67)	1220 (63)
1B Expansion n=38	60 mg QD 21/7	960 mg BID 28/0	4.00 (1.0–24)	105 (64)	1530 (65)

AUC_{0-24} = area under the plasma concentration-time profile over a 24-hour sampling interval; BID = twice a day; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; QD = once a day; $t_{1/2}$ = elimination half-life; t_{max} = time to C_{max}.

[a] Median (min-max).

AUC_{0-24} and C_{max} presented as geometric mean (%CV)

Source: Summary of Clinical Pharmacology Studies, Appendix 4, Page 76.

Table 9. Steady-State PK Parameters of Cobimetinib in Combination with Vemurafenib in Cancer Patients

Cohort	Cobimetinib Dose/Regimen	Vemurafenib Dose/Regimen	t_{max} (h)[a]	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	R_{acc}	CL/F (L/h)
1 n=5	60 mg QD 14/14	720 mg BID 28/0	2.0 (0.98–4.0)	342 (130)	5180 (170)	2.27 (180)	11.6 (170)
2 n=3	80 mg QD 14/14	720 mg BID 28/0	6.0 (2.0–6.0)	195 (48)	3820 (48)	2.39 (37)	21.0 (48)
2A n=4	100mg QD 14/14	720 mg BID 28/0	4.03 (2.2–6.1)	383 (50)	6360 (46)	2.86 (40)	15.7 (46)
3 n=3	60 mg QD 14/14	960 mg BID 28/0	4.08 (4.0–6.1)	215 (19)	3520 (35)	6.71 (170)	17.0 (35)
4 n=3	80 mg QD 14/14	960 mg BID 28/0	4.00 (3.9–4.1)	350 (37)	5790 (36)	3.76 (36)	13.8 (36)
1A n=8	60 mg QD 21/7	720 mg BID 28/0	3.98 (2.0–7.0)	307 (75)	4800 (76)	2.41 (46)	12.5 (76)
1B n=25	60 mg QD 21/7	960 mg BID 28/0	4.02 (0.5–8.0)	232 (80)	3540 (83)	2.01 (7)	17.0 (83)
1C n=3	60 mg QD 28/0	720 mg BID 28/0	4.00 (4.0–4.1)	239 (14)	4500 (17)	3.49 (11)	13.3 (17)
1D n=3	60 mg QD 28/0	960 mg BID 28/0	6.00 (4.9–6.1)	414 (16)	7020 (27)	4.10 (51)	8.55 (27)
1A Expansion n=25	60 mg QD 21/7	720 mg BID 28/0	4.04 (2.0–8.0)	177 (74)	2540 (84)	1.95 (47)	23.6 (84)
1B Expansion n=32	60 mg QD 21/7	960 mg BID 28/0	4.00 (0.0-8.0)	200 (91)	3220 (124)	1.99 (95)	18.6 (124)

AUC_{0-24} = area under the plasma concentration-time profile over a 24-hour sampling interval; BID = twice a day; CL/F = apparent plasma clearance; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; R_{acc} = accumulation ratio (Day 14 AUC_{0-24}/Day 1 AUC_{0-24}); QD = once a day; t_{max} = time to C_{max}.

[a] Median (min-max).

AUC_{0-24} and C_{max} presented as geometric mean (%CV)

Source: Summary of Clinical Pharmacology Studies, Appendix 4, Page 76.

Reference ID: 3751393

2.2.5.2 *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

Dose-normalized AUC was approximately 2-fold higher in cancer patients than in healthy subjects (**Table 10**). The Applicant states that the higher cobimetinib exposure in cancer patients may be due to reduction of first pass gut metabolism, resulting in higher F_g, and literature has suggested that cancer patients may have reduced expression of CYP3A4 [PMID: 18248309].

Table 10. Comparison of Dose-Normalized PK Parameters in Healthy Subjects and Cancer Patients

	Geometric Mean (%CV)	
	Healthy Volunteer	Patients with Cancer
Parameter	MEK4952g	MEK4592g
$AUC_{0\text{-}inf}$ (ng•hr/mL) or AUC_{ss} (ng•hr/mL)	39.2 (29.5)	72.4 (61)
t_{max} (h)[a]	4.00 (2.00–8.00)	2.4 (1.0–23.75)
CL/F (L/h)	23.0 (29.5)	13.8 (61)
$t_{1/2}$ (h)	66.2 (18.2)	43.6 (27.8)

AUC_{ss} = area under the concentration-time curve over a 24-hour sampling interval at steady-state; $AUC_{0\text{-}inf}$ = AUC from time 0 extrapolated to infinity; CL/F = apparent plasma clearance; CV = coefficient of variation; t_{max} = time of maximum concentration; $t_{1/2}$ = elimination half-life

[a] Median (Min-Max).

N=10 healthy subjects; N=39 patients with cancer

Source: Summary of Clinical Pharmacology, Table 14, Page 51.

2.2.5.3 *What are the characteristics of drug absorption?*

In the absolute bioavailability study (Study MEK4952g), healthy subjects were randomized to receive cobimetinib 2 mg intravenously (IV) over 30 minutes and cobimetinib 20 mg orally with a 10-day washout between the two doses. PK samples were collected up to 192 hours post-dose. The mean absolute bioavailability of cobimetinib was 46% (90% CI: 40%, 53%) as determined by the ratio of dose-normalized $AUC_{0\text{-}inf}$ observed after a 20 mg oral dose of cobimetinib (test) and a 2 mg IV dose of cobimetinib (reference) (n=11). Based on the results from the mass balance study (Study GP28369) showing 76.5% of the dose (6.6% as unchanged drug) recovered in the feces and 17.8% (1.6% as unchanged drug) recovered in the urine with the assumption that all metabolism occurred post-absorption and not accounting for biliary excretion of unchanged cobimetinib, the estimated fraction absorbed (f_a) was 88%.

Administration of a single 20 mg dose of cobimetinib with a high-fat meal in healthy subjects resulted in a 10% increase in AUC and 7% increase in C_{max} as compared with fasted conditions (refer to **Section 2.5.3**).

2.2.5.4 *What are the characteristics of drug distribution?*

The volume of distribution at steady-state ($V_{d,ss}$) for cobimetinib was 1052 L after a single IV dose of 2 mg in healthy subjects (Study MEK4952g). Based on population PK analyses, the apparent volume of distribution (V_d/F) was 806 L in patients with cancer.

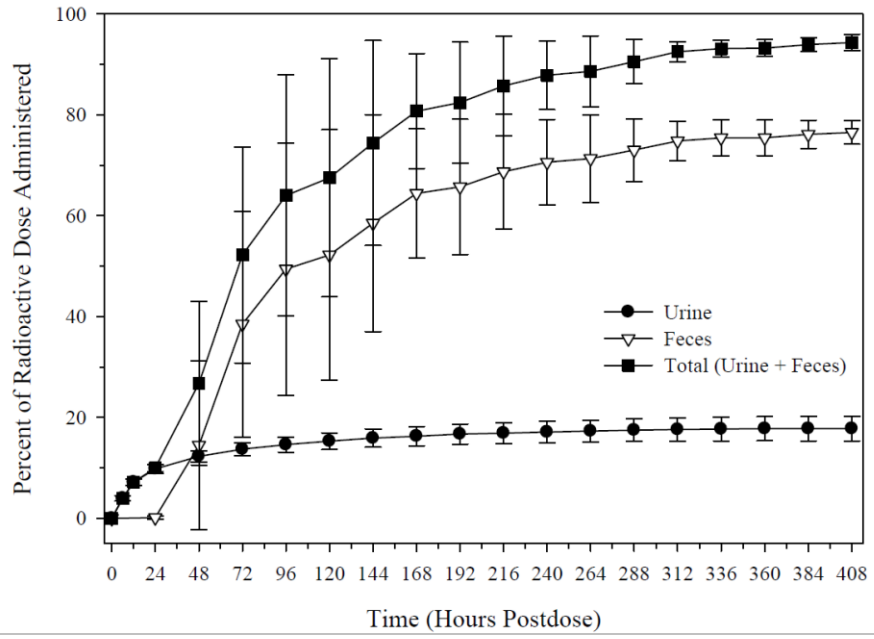
Reference ID: 3751393

Cobimetinib is 95% bound to human plasma proteins (alpha-1 acid glycoprotein) independent of concentration range of 1 to 10 µM [Study 09-0614]. The mean human blood to plasma ratio was approximately 1 over the concentration range of 1 to 10 µM [Study 09-0671].

2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

The ADME study (GP28369) in 5 healthy subjects who received a single oral dose of 20 mg [^{14}C]-cobimetinib with blood, urine, and feces samples collected up to 408 hours post-dose, suggests liver as the major route of elimination. The mean total recovery of the administered dose was 94.3% with 76.5% of the dose (6.6% as unchanged drug) in the feces, and 17.8% (1.6% as unchanged drug) in the urine (**Figure 6**). The majority of circulating radioactivity was associated with metabolites of cobimetinib and unchanged cobimetinib constituted 11% of plasma radioactivity, suggesting that cobimetinib underwent extensive metabolism.

Figure 6. Mean Cumulative Percent of Radioactive Dose Recovered in Urine and Feces After a Single Dose of 20 mg [^{14}C]-Cobimetinib in 5 Healthy Subjects



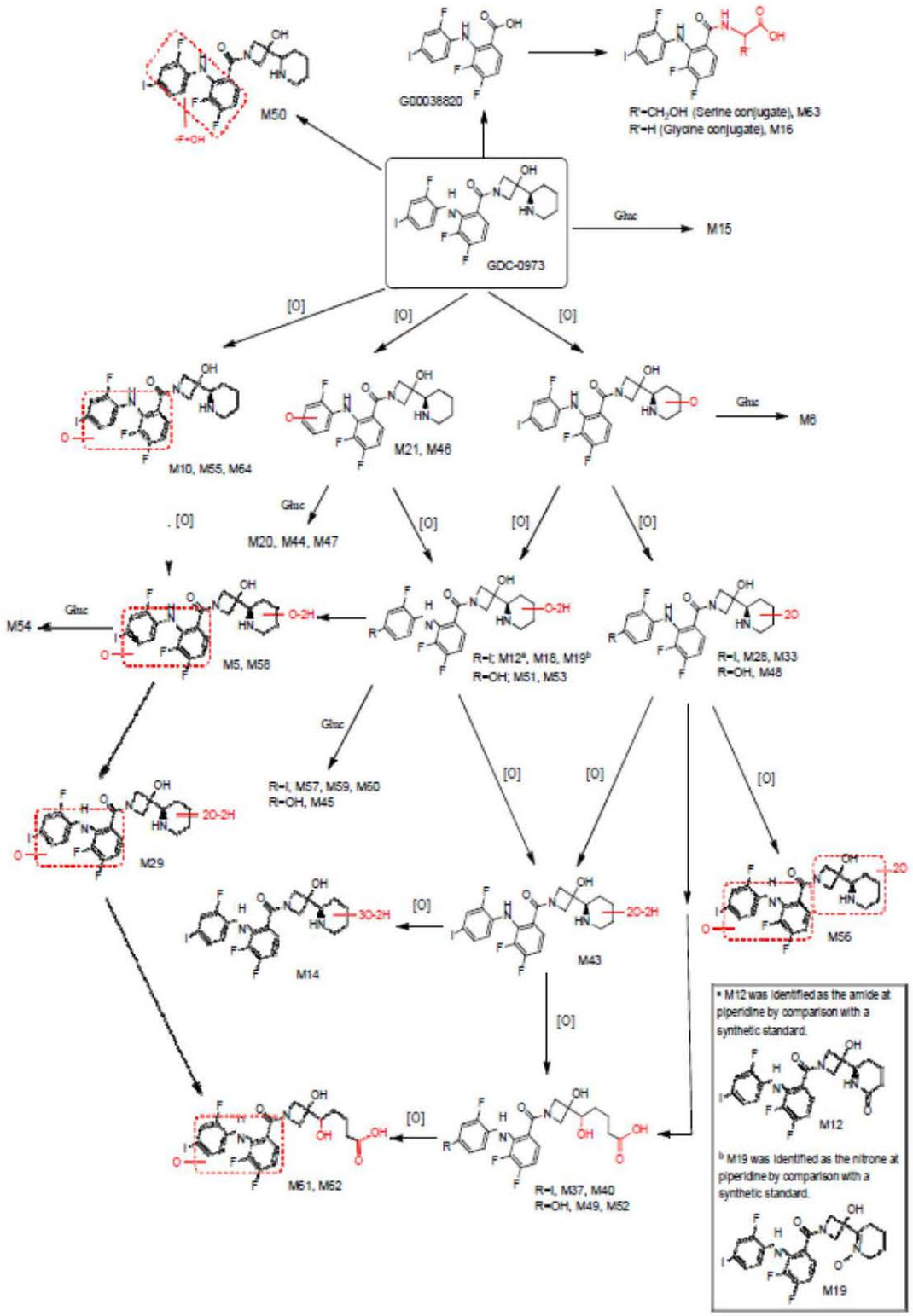
Source: GP28369 Final Study Report, Figure 11-2, Page 36.

2.2.5.6 *What are the characteristics of drug metabolism?*

Cobimetinib is metabolized predominantly via oxidation by CYP3A (>90%) and subsequent glucuronidation, or direct glucuronidation by UGT2B7 in vitro [Study 10-0264]. The metabolic pathway in humans is shown in **Figure 7**.

Reference ID: 3751393

Figure 7. The Metabolism of Cobimetinib after a Single Dose of 20 mg [^{14}C]-Cobimetinib in 5 Healthy Subjects



Source: Report 12-3095, Figure 1, Page 10.

Reference ID: 3751393

The majority of circulating radioactivity was associated with metabolites of cobimetinib and unchanged cobimetinib constituted 11% of plasma radioactivity (mean $AUC_{0\text{-inf}}$ ratio), suggesting that cobimetinib underwent extensive metabolism. The most abundant drug related compounds were unchanged cobimetinib, M15 (glucuronide conjugate), and M16 (glycine conjugate of the hydrolyzed product); No oxidative metabolites were >10% of total circulating radioactivity in plasma (**Table 11**). Cobimetinib appears to undergo high first pass metabolism as results from the mass balance study (Study GP28369) indicated that the estimated f_a of cobimetinib was 88% with mean absolute bioavailability of 46% (Study MEK4952g).

Table 11. Components in Plasma After a Single Dose of 20 mg [^{14}C]-Cobimetinib in Healthy Subjects

Identity[a]	Biotransformation	% of Sample Radioactivity[b]					
		1 hr	2 hr	4 hr	6 hr	24 hr	48 hr
cobimetinib	Parent compound	16.5	17.3	13.9	18.1	32.1	21.2
M44	Oxidative deiodination + Glucuronidation	3.8	3.7	2.0	2.0	ND	ND
M20	Oxidative deiodination + Glucuronidation	0.8	2.0	3.1	1.4	ND	ND
M45	Oxidative deiodination + Oxidation (+14 amu) + Glucuronidation	3.8	3.8	1.4	2.8	ND	ND
M21	Oxidative deiodination	3.0	2.0	2.0	0.9	D	ND
M6	Oxidation (+16 amu) + Glucuronidation	7.9	7.6	7.2	4.9	ND	ND
M15	Glucuronidation	11.1	12.3	12.0	10.9	3.5	6.4
M57	Oxidation (+14 amu) + Glucuronidation	2.2	2.3	3.1	2.7	ND	ND
M59	Oxidation (+14 amu) + Glucuronidation	6.0	2.9	2.8	2.2	ND	ND
M18	Oxidation (+14 amu)	4.9	5.2	5.8	5.2	D	D
M60	Oxidation (+14 amu) + Glucuronidation	3.3	1.5	2.2	1.6	ND	ND
Unknown (63.0 min)	NA	4.6	2.9	2.8	2.4	NA	NA
M40	Oxidation (+32 amu) + Oxidative deamination	4.9	1.9	4.7	2.5	D	ND
M12	Oxidation (+14 amu)	10.0	9.8	6.4	5.7	4.6	D
M19	Oxidation (+14 amu)	3.0	3.5	4.5	2.4	D	D
M16	Hydrolysis + Glycine conjugation	7.6	10.8	12.5	14.6	28.9	28.3
Unextracted Radioactivity[c]		6.8	10.7	13.7	19.6	30.9	44.1

D = metabolite only detected by mass spectrometry; NA = not applicable; ND = not detected.

[a] Metabolites are listed in order of chromatographic elution.

[b] Metabolite distributions were calculated as (% of radioprofile) × (% of sample radioactivity extraction recovery) ÷ 100.

[c] Extractable radioactivity was determined by measuring the radioactivity in the extraction supernatant and in the hydrolyzed post-extraction pellet by LSC and normalizing to 100% for each sample.

Source: GP28369 Final Study Report, Table 11-4, Page 39.

Reference ID: 3751393

Table 12. Components in Urine and Feces After a Single Dose of 20 mg [^{14}C]-Cobimetinib in Healthy Subjects

Identity[a]	Biotransformation	Urine (%)[b]	Feces (%)[b]	Sum of Urine and Feces (%)[b]
cobimetinib	Parent compound	1.6	6.6	8.2
M45	Oxidative deiodination + Oxidation + Glucuronidation	0.8	ND	0.8
M46	Oxidative deiodination	D	1.4	1.4
M47	Oxidative deiodination + Glucuronidation	0.8	ND	0.8
M48	Oxidation deiodination + Oxidation (+32 amu)	D	1.7	1.7
M21	Oxidative deiodination	0.9	2.7	3.6
M49	Oxidation deiodination + Oxidation (+32 amu)	0.7	1.8	2.5
M50	Oxidation defluorination	D	1.3	1.3
M51	Oxidation deiodination + Oxidation (+14 amu)	ND	1.8	1.8
M52	Oxidation deiodination + Oxidation (+32 amu)	D	2.4	2.4
M53	Oxidation deiodination + Oxidation (+14 amu)	D	3.1	3.1
M54	Oxidation (+30 amu) + Glucuronidation	0.6	ND	0.6
M64	Oxidation (+16 amu)	D	1.9	1.9
M55	Oxidation (+16 amu)	D	2.1	2.1
M10	Oxidation (+16 amu)	0.3	10.3	10.6
M15	Glucuronidation	2.1	ND	2.1
M56	Oxidation (+48 amu)	ND	5.3	5.3
M28	Oxidation (+32 amu)	ND	2.7	2.7
M58	Oxidation (+30 amu)	ND	1.2	1.2
M18	Oxidation (+14 amu)	D	1.0	1.0
M33	Oxidation (+32 amu)	ND	1.3	1.3
M61	Oxidation (+48 amu) + Oxidative deamination	0.7	0.8	1.5
M29	Oxidation (+46 amu)	0.3	6.9	7.9
M62	Oxidation (+48 amu) + Oxidative deamination	0.7		
M43	Oxidation (+30 amu)	ND	1.1	1.1
M5	Oxidation (+30 amu)	D	5.2	5.2
M37	Oxidation (+32 amu) + Oxidative deamination	0.3	1.9	2.2
M40	Oxidation (+32 amu) + Oxidative deamination	0.2	3.3	3.5
M12	Oxidation (+14 amu)	D	1.3	1.3
M63	Amide hydrolysis + Serine conjugation	0.7	ND	0.7
M14	Oxidation (+46 amu)	1.1	ND	1.1
M16	Amide hydrolysis + Glycine conjugation	0.5	ND	0.5
% of Administered Dose Eliminated		17.8	76.5	94.3

D = metabolite only detected by mass spectrometry, ND = metabolite not detected.
[a] Metabolites are listed in order of chromatographic elution.
[b] Units represent the % of administered dose eliminated.

Source: GP28369 Final Study Report, Table 11-4, Page 39.

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2.2.5.7 *What are the characteristics of drug excretion?*

The ADME study (GP28369) showed that the mean total recovery of 20 mg [^{14}C]-cobimetinib was 94.3% with 76.5% of the dose (6.6% as unchanged drug) recovered in the feces, and 17.8% (1.6% as unchanged drug) recovered in the urine of healthy subjects (**Table 12**). Biliary excretion of an orally administered [^{14}C]-cobimetinib dose was 80.6% (0.9% as unchanged drug) and 74.5% (1.2% as unchanged drug) in male and female bile-duct cannulated rats, respectively [Study 09-0833].

Elimination

The mean plasma clearance (CL) was 10.7 L/h (16% CV) after a single IV dose of 2 mg in healthy subjects. The mean apparent CL (CL/F) following repeat oral dosing of cobimetinib 60 mg in cancer patients was 13.8 L/h (61% CV). The mean elimination half-life of cobimetinib at the 60 mg dose was 43.6 hours (range: 23.1 to 69.6 hours).

2.2.5.8 *Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?*

Cobimetinib exhibits linear PK in the dose range of 10 to 100 mg. After a single dose of 10 to 100 mg, exposures were approximately dose proportional with an estimated slope of 1.3 (90% CI: 1.1, 1.5) for $AUC_{0\text{-}24h}$ and 1.2 (90% CI: 1.0, 1.4) for C_{max} using a power model (**Figure 8**). After repeat doses of 10 to 100 mg, exposures were approximately dose proportional with an estimated slope of 1.1 (90% CI: 0.86, 1.4) for AUC_{ss} and 1.0 (90% CI: 0.80, 1.3) for $C_{max,ss}$ (**Figure 9**). Exposure of cobimetinib appears to be greater than dose proportional at the dose of 125 mg based on limited data. Of note, the first few cohorts in the dose escalation trial (Study MEK4592g) were weight-based (0.05, 0.1, and 0.2 mg/kg) and a Powder-in-Bottle (PiB) formulation was administered as an oral solution. Therefore PK data from these cohorts were not included in the analysis for dose proportionality.

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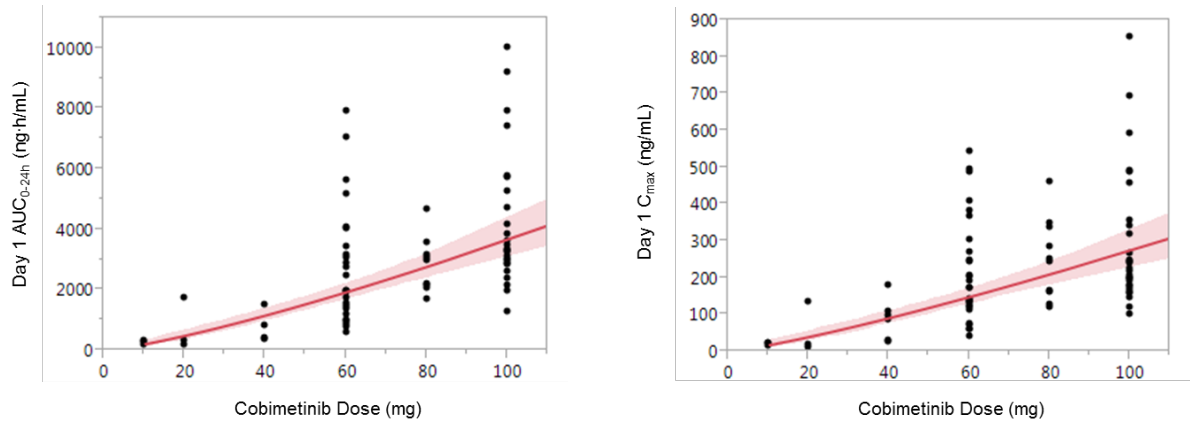
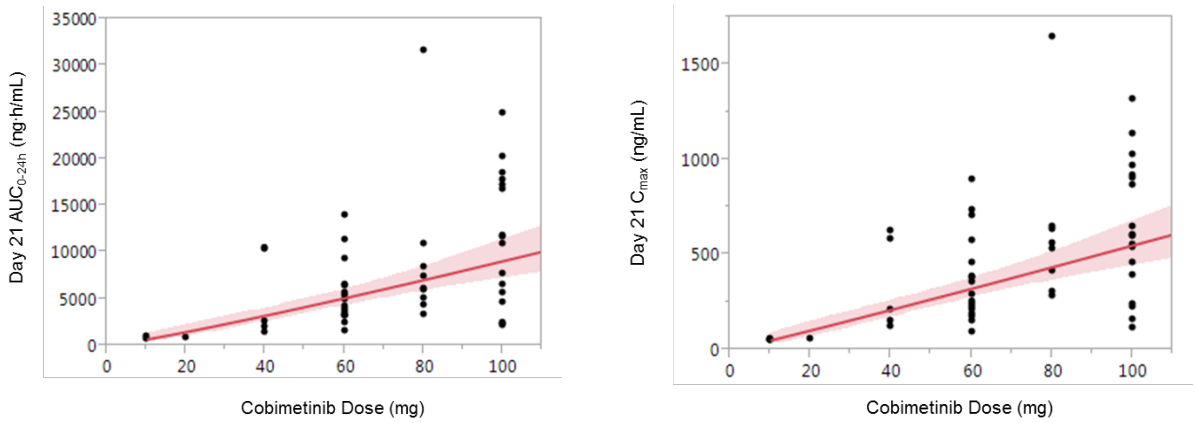
Figure 8. Dose Proportionality Following Single Doses of Cobimetinib 10 to 100 mg



The shaded area is the 90% confidence interval of the slope.

Source: apatpk.xpt.

Figure 9. Dose Proportionality Following Repeat Daily Doses of Cobimetinib 10 to 100 mg



The shaded area is the 90% confidence interval of the slope.

Source: apatpk.xpt.

2.2.5.9 *How do the PK parameters change with time following chronic dosing?*

The mean accumulation ratio for $AUC_{0\text{-}24h}$ is 2.4-fold. Cobimetinib exhibits time-independent PK. Refer to **Table 6** and **Table 7** for single and multiple dose PK parameters, respectively.

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2.2.5.10 *What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the major causes of variability?*

The inter-subject variability as estimated by geometric mean CV% in healthy subjects is 26-52% for AUC_{inf} and C_{max}. Inter-patient variability following repeat doses of 60 mg cobimetinib is 61% for steady-state AUC and 60% for C_{max}.

The population PK (popPK) analysis assessed the influence of covariates including body weight, gender, race, age, hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and total bilirubin), renal function (creatinine clearance), albumin, Eastern Cooperative Oncology Group (ECOG) performance status, disease (melanoma vs. non-melanoma), and formulation (tablet, capsule, solution). Age and body weight were found to be statistically significant covariates impacting CL/F and V_d/F of cobimetinib; however, the effects of these covariates on cobimetinib steady-state exposure were not considered to be clinically important.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

No formal studies have been conducted to assess the effect of age, race, weight, height, or organ dysfunction on exposure and response to cobimetinib. The Applicant's popPK analysis, verified by our pharmacometrics review, did not identify clinically important effects of body weight, age, gender, mild and moderate renal impairment, and mild hepatic impairment as covariates on clearance or volume of distribution of cobimetinib (refer to Pharmacometrics review in **Section 4.1**).

Relationship between Age and Exposure

The popPK analysis showed that age (< 65 years [n=354, 73%]; 65-75 years [n=104, 21%]; and > 75 years [n=29, 6%]) is a statistically significant covariate influencing cobimetinib CL/F. Exposures (AUC_{ss}) of cobimetinib in patients > 75 years of age were 22% higher than that observed in patients < 65 years of age, which is not considered to be a clinically important difference requiring dose modification. Confounding factors such as body weight may contribute in part to this observed exposure difference.

Relationship between Gender and Exposure

The effect of gender was evaluated in men (n=277, 57%) and women (n=210, 43%). The popPK analysis did not identify gender as a significant covariate influencing cobimetinib PK.

Relationship between Race and Exposure

The effect of race on cobimetinib PK could not be evaluated given that the majority of patients were Caucasian (Caucasian n=448, 92%; non-Caucasian (n=39, 8%).

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Relationship between Weight and Exposure

PopPK analyses identified body weight (ranging from 43 to 185 kg) as a significant covariate influencing cobimetinib central volume of distribution (V2/F). There was < 16% variation between the 5th and 95th percentile of body weight, which is not considered to be a clinically important difference requiring dose modification.

Relationship between Renal Impairment and Exposure

The Applicant did not conduct a dedicated renal impairment study. The popPK analysis suggested that creatinine clearance (CLcr) (7.3-325 mL/min) and estimated Glomerular Filtration Rate (eGFR) (6.4-176 mL/min/1.73 m^2) are not statistically significant covariates influencing cobimetinib PK. Cobimetinib exposures were comparable among patients with normal renal function and mild and moderate renal impairment (**Table 13**). Therefore, no dose adjustment in patients with mild and moderate renal impairment is recommended.

Cobimetinib exposure (AUC_{ss}) was available in two patients with severe renal impairment and higher exposure was observed in one patient. A definitive conclusion regarding the effect of severe renal impairment on cobimetinib exposure cannot be drawn. Additional analyses suggested that there was a trend for increased incidence of Grade 3-4 AEs and dose modifications with worsening renal function (**Table 14**), which may be explained by other factors besides PK (e.g., disease or PD).

Table 13. Population-PK Derived Steady-State Cobimetinib Exposure Based on Renal Function

Parameter	Renal Function			
	Normal (n=286)	Mild (n=151)	Moderate (n=48)	Severe (n=2)
CrCL (mL/min)	127 (124; 131)	76.7 (75.4; 77.9)	50.5 (48.6; 52.3)	17.5 (NA)
$C_{max,ss}$ (ng/mL)	246 (234; 258)	280 (259; 301)	291 (261; 321)	392 (NA)
$C_{min,ss}$ (ng/mL)	154 (145; 163)	165 (150; 180)	176 (154; 198)	254 (NA)
AUC_{ss} (µg.day/L)	198 (188; 209)	217 (200; 234)	229 (203; 254)	331 (NA)

Source: Summary of Clinical Pharmacology, Table 15, Page 52.

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Table 14. Incidence of Grade 3-4 AEs and Dose Modification and Population-PK Derived Steady-State Cobimetinib Exposure Based on Renal Function in Patients Receiving Cobimetinib 60 mg QD 21/7

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment
Grade 3-4 AEs	65/197 (33%)	35/85 (41%)	13/26 (50%)
AUC_{ss}			
Geomean (%CV)	186 (50.5%)	209 (51.9%)	219 (25.6%)
90% CI	(84, 412)	(91, 476)	(140, 343)
CL/F			
Geomean (%CV)	317 (50.7%)	285 (51.4%)	259 (30.1%)
90% CI	(143, 705)	(126, 647)	(153, 438)
$C_{min,ss}$			
Geomean (%CV)	141 (54.7%)	164 (56.7%)	167 (30.0%)
90% CI	(60, 332)	(67, 399)	(99, 281)
Dose Modification	39/197 (20%)	20/85 (24%)	9/26 (35%)
AUC_{ss}			
Geomean (%CV)	247 (53.0%)	215 (45.0%)	289 (15.4%)
90% CI	(107, 573)	(102, 452)	(217, 384)
CL/F			
Geomean (%CV)	296 (53.6%)	343 (44.0%)	243 (27.6%)
90% CI	(127, 691)	(166, 711)	(147, 402)
$C_{min,ss}$			
Geomean (%CV)	198 (53.2%)	173 (45.9%)	228 (22.2%)
90% CI	(85, 459)	(81, 368)	(152, 343)
Source: erexpg.xpt, poolnmg.xpt, adae.xpt, adex.xpt			

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Relationship between Hepatic Impairment and Exposure

Because ADME study results showed that 76.5% of the oral administered dose was recovered in the feces with 6.6% unchanged drug, hepatic impairment is likely to increase the systemic exposure of cobimetinib. Therefore, a PMR will be requested to submit the results from the ongoing single dose hepatic impairment study. AST, ALT, alkaline phosphatase, total bilirubin, and albumin were not statistically significant covariates influencing cobimetinib PK. PopPK analyses showed similar cobimetinib exposures between patients with mild hepatic impairment as defined by National Cancer Institute (NCI) liver dysfunction criteria (total bilirubin ≤ULN and AST >ULN or total bilirubin >1-1.5 × ULN and AST any value, n=80) and patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ULN, n=388) (**Table 15**). Dose adjustment in patients with mild hepatic impairment is not recommended. Dose recommendations have not been determined in patients with moderate and severe hepatic impairment. A definitive conclusion regarding the effect of moderate hepatic impairment on cobimetinib exposure cannot be drawn based on limited data in only two patients.

Table 15. Population-PK Derived Steady-State Cobimetinib Exposure Based on Hepatic Function

	Normal Hepatic Function (n=388)	Mild Hepatic Impairment (n=80)	Moderate Hepatic Impairment (n=2)
AUC_{ss}	169 (80.4%)	187 (80.9%)	187 (50.3%)
$C_{max,ss}$	216 (76.3%)	244 (80.0%)	222 (39.1%)
$C_{min,ss}$	127 (87.0%)	139 (87.5%)	147 (61.9%)
Data presented as geometric mean (%CV). Source: erexpg.xpt, achem.xpt, adlb.xpt,			

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

No clinically important PK differences have been identified in specific patient populations. Therefore, no dosage regimen adjustments are currently recommended for specific patient populations. The Applicant is requested to conduct a hepatic impairment study under a PMR to determine the recommended dose in patients with hepatic impairment (refer to **Section 1.2.1**).

2.3.2.1 *Elderly*

Age (< 65 years [n=354, 73%]; 65-75 years [n=104, 21%]; and > 75 years [n=29, 6%]) was identified as a significant covariate influencing cobimetinib PK. Exposures (AUC_{ss}) of cobimetinib in patients > 75 years of age were 22% higher than that observed in patients < 65

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years of age, which is not considered to be a clinically important difference requiring dose modification. Confounding factors such as body weight may contribute in part to this observed exposure difference.

2.3.2.2 *Pediatric*

A study has not been conducted in pediatric patients. As cobimetinib received orphan drug designation for the treatment of patients with Stage IIb, IIc, III and IV melanoma with BRAF V600 mutation, a study in pediatric patients is not required for this indication.

2.3.2.3 *Gender*

The popPK analysis showed that gender was not a statistically significant covariate influencing cobimetinib PK.

2.3.2.4 *Race/Ethnicity*

The effect of race on cobimetinib PK could not be evaluated given that the majority of patients were Caucasian (92%).

2.3.2.5 *Renal Impairment*

Refer to **Section 2.3.1**. PopPK analyses showed 10% and 16% higher cobimetinib exposures (AUC_{ss}) in patients with mild renal impairment (CLcr 60 to < 90 mL/min, n=151) and moderate renal impairment (CLcr 30 to < 60 mL/min, n=48), respectively, as compared to those with normal renal function (CLcr ≥ 90 mL/min, n=286). These exposure differences are not considered to be clinically important; therefore patients with mild and moderate renal impairment do not require dose modification (refer to **Section 3**). A definitive conclusion regarding the effect of severe renal impairment on cobimetinib exposure cannot be drawn based on limited data in only two patients.

2.3.2.6 *Hepatic Impairment*

Refer to **Section 2.3.1**. PopPK analyses showed that cobimetinib exposures were similar between patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1-1.5 × ULN and AST any value, n=80) and patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ ULN, n=388). No dose modification of cobimetinib in patients with mild hepatic impairment is recommended. The Applicant is requested to conduct a pharmacokinetic study under a PMR to determine the appropriate cobimetinib dose in patients with hepatic impairment.

2.3.2.7 *What pregnancy and lactation use information is there in the application?*

The proposed labeling states that cobimetinib can cause fetal harm when administered to a pregnant woman based on findings in animal studies, and lists cobimetinib under pregnancy category (b) (4).

It is not known whether cobimetinib is excreted in human milk. The proposed labeling states that (b) (4)

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2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or dose-response and what is the impact of any differences in exposure on response?

The effect of extrinsic factors including concomitant medications (a strong CYP3A inhibitor) was evaluated in vivo and a strong CYP3A inducer and moderate CYP3A modulators were evaluated using physiologically-based pharmacokinetic (PBPK) analyses.

2.4.2 Drug-drug interactions?

2.4.2.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

Yes. See below.

2.4.2.2 *Is the drug a substrate of CYP enzymes?*

Yes. CYP3A4 was identified as the primary CYP enzyme (>90%) responsible for the hepatic oxidative metabolism of cobimetinib in human liver microsomes (**Table 16**).

Table 16. Inhibition of Cobimetinib Metabolism by 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

ABT=1-aminobenzotriazole; CYP=cytochrome P450; HLM=human liver microsome; +N=plus NADPH; –N=without NADPH; NA=not applicable; NADPH=β-nicotinamide adenine dinucleotide phosphate tetrasodium salt; TAO=troleandomycin; TCP=tranylcypromine.

[a] Percentages (n=3; ±SD) were calculated by setting the amount present at time 0-minute at 100%.

[b] ABT, furafylline, and TAO were pre-incubated for 15 minutes.

Source: Report 10-0264, Table 2, Page 9.

2.4.2.3 *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Inhibitor

Yes. Cobimetinib reversibly inhibits CYP3A4 and CYP2D6 [Studies 09-0218, 09-0390] and is also a time-dependent inhibitor of CYP3A4 in vitro [Study 09-1343].

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The potential of cobimetinib (0.016-50 µM) to inhibit CYP enzymes was evaluated using human liver microsomes [Study 09-0218]. As shown by the R_1 values >1.1 calculated assuming clinical concentrations (maximal steady-state concentration of 273 ng/mL or 0.5 µM) (**Table 17**), cobimetinib reversibly inhibits CYP3A4 and CYP2D6 in vitro. An in vivo study (MEK4592g) to evaluate the drug interaction potential of cobimetinib with coadministered drugs that are CYP3A4 and CYP2D6 sensitive substrates was conducted (refer to **Section 2.4.2.8**).

Table 17. IC_{50} and Calculated R_1 values for Cobimetinib Inhibition of CYP activities in Human Liver Microsomes

CYP Enzyme	Substrate	Cobimetinib IC_{50} µM	Ki value (unbound) µM	R_1 value $(1+I/K_i)$
CYP1A2	Phenacetin	> 50	-	1.0
CYP2B6	Bupropion	> 50	-	1.0
CYP2C8	Paclitaxel	> 50	-	1.0
CYP2C9	Diclofenac	> 50	-	1.0
CYP2C19	S-Mephenytoin	> 50	-	1.0
CYP2D6	Bufuralol	1.8	1.1	1.5
CYP3A4/5	Midazolam	17	7.6	1.1
CYP3A4/5	Testosterone	5.9	-	1.2

Calculation of R_1 values based on maximal steady-state concentration of 273 ng/mL or 0.5 µM [I]
K_i assumed to be $IC_{50}/2$ for competitive inhibition for those CYP enzymes without an experimental K_i value

Inducer

Yes, there was induction of CYP3A4 mRNA in vitro. The potential of cobimetinib (0.1-25 µM) to induce CYP enzymes was evaluated using human hepatocytes from three donors [Study 10-1929]. Results showed that there was concentration-dependent induction of CYP3A4 mRNA up to 9.1-fold at 10 µM relative to vehicle control, but no induction of CYP1A2 or CYP2B6 mRNA (**Table 18**). Cobimetinib did not induce CYP1A2, CYP2B6, and CYP3A4 activity relative to vehicle control. Results from the PXR binding assay indicated that cobimetinib up to 25 µM does not activate PXR.

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Table 18. Cobimetinib Induction of Mean mRNA and Activity Levels of CYP enzymes

CYP Isoform	Substrate	Test Material	Concentration (μM)	Mean Percent mRNA Level (±SD)		Mean Percent Activity (±SD)	
				Vehicle Control [a]	Positive Control [b]	Vehicle Control [a]	Positive Control [b]
CYP1A2	Phenacetin	GDC-0973	0.1	142±34	10.6±4.7	118±20	0.766±2.568
			1	104±18	0.858±7.529	116±20	0.724±1.639
			10	165±34	27.2±8.0	69.7±58.1	–11.2±16.3
			25	59.7±38.3	–14.9±14.2	6.24±7.06	–18.1±19.1
		0.1% DMSO [a]	NA	100±0.00	0.00±0.00	100±NA	0.00±0.00
		3-Methylcholanthrene [b]	2	469±242	100±0.00	1200±940	100 ±0.00
CYP2B6	Bupropion	GDC-0973	0.1	149±33	11.4±7.3	113±22	1.01±2.01
			1	182±45	19.3±10.1	113±49	–1.17±6.75
			10	205±77	24.5±16.8	103±127	–8.88±19.84
			25	56.3±16.0	–10.5±3.9	8.68±10.28	–19.7± 13.6
		0.1% DMSO [a]	NA	100±0.00	0.00±0.00	100±NA	0.00±0.00
		Phenobarbital [b]	1000	521±24.0	100±0.00	771±477	100±0.00
CYP3A4	Testosterone	GDC-0973	0.1	310±123	19.9±17.4	143±34	8.03±6.76
			1	582±194	43.0±24.0	109±26	1.45±5.63
			10	913±961	54.3±42.7	38.1±21.1	–13.7±8.2
			25	745±148	33.6±7.7	14.5±6.4	–17.4±6.5
		0.1% DMSO [a]	NA	100±0.00	0.00±0.00	100±NA	0.00±0.00
		Rifampicin [b]	25	1350±604	100±0.00	650±247	100±0.00

Source: Report 10-1929, Tables 3, 6, Pages 14, 16.

2.4.2.4 *Is the drug an inhibitor and/or an inducer of transporters?*

In vitro studies suggest that cobimetinib is not an inhibitor of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), Organic Anion Transporting Polypeptide 1B1 (OATP1B1), OATP1B3, or Organic Cation Transporter 1 (OCT1). There are no in vitro studies to evaluate cobimetinib as an inducer of transporters.

Inhibitor

P-gp: The potential for cobimetinib to inhibit P-gp was evaluated by assessing the effect of cobimetinib on the efflux of the P-gp substrate, digoxin, in MDR1-MDCK cells in vitro [Study 08-1902]. Given that the efflux ratio of digoxin were similar in the presence and absence of cobimetinib (95 versus 72, respectively), cobimetinib does not appear to be a P-gp inhibitor.

BCRP: The potential for cobimetinib to inhibit BCRP was evaluated by assessing the effect of cobimetinib on the effect of increasing concentrations of cobimetinib (0.5-50 μM) on the efflux of the BCRP substrate, estrone-3-sulfate (E3S), in CPT-P1 cells in vitro [Study 09-0339]. Efflux ratios of E3S decreased with increasing concentrations of cobimetinib. The estimated IC_{50} value was 3.3 μM ($[I]_1/IC_{50}$ = 0.15), suggesting that cobimetinib appears to be a BCRP inhibitor based on the results of this E3S transport inhibition experiment; however, the potential for cobimetinib to inhibit BCRP was also evaluated by assessing the effect of cobimetinib on the efflux of the BCRP substrate, prazosin, in MDCKII cells in vitro [Study 10-3241]. Cobimetinib had an

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inhibitory effect on the efflux ratio of prazosin with an IC_{50} of 40 µM ($[I]_1/IC_{50}$ = 0.01), suggesting that cobimetinib is not a BCRP inhibitor based on this bi-directional transport assay with a probe substrate in MDCKII cells (assay that is referenced in the 2012 draft FDA DDI Guidance).

OATP1B1 and OATP1B3: The potential for cobimetinib to inhibit OATP1B1 and OATP1B3 transporters were evaluated by assessing the effect of increasing concentrations of cobimetinib (0.41-300 µM) on accumulation of the OATP1B1 substrate (E3S) and OATP1B3 substrate (Fluo-3) and percent inhibition of OATP activity in transporter expressing Chinese hamster ovary (CHO) cells in vitro [Study 10-3241]. Given that the calculated C_{max}/IC_{50} is < 0.1 (**Table 19**), an in vivo DDI study with a sensitive substrate of OATP1B1 or OATP1B3 is considered unnecessary.

Table 19. IC_{50} and Calculated R values for Cobimetinib Inhibition of OATP transporters

Transporter	**Substrate**	**Cobimetinib IC_{50} (µM)**	**C_{max}[a]/IC_{50}**
OATP1B1	Estrone-3-sulfate	118	0.004
OATP1B3	Fluo-3	85	0.006
[a] Plasma maximal steady-state concentration (C_{max}) of 273 ng/mL or 0.5 µM			

OCT1: The potential for cobimetinib to inhibit OCT1 was evaluated by assessing the effect of increasing concentrations of cobimetinib (0.41-300 µM) on accumulation of the OCT1 substrate (tetraethylammonium chloride [TEA]) in transporter expressing CHO cells in vitro [Study 10-3241]. The IC_{50} value was 49 µM. Given that the calculated unbound C_{max}/IC_{50} is < 0.1, an in vivo DDI study with a sensitive substrate of OCT1 is considered unnecessary.

Inducer

In vitro studies to evaluate cobimetinib as an inducer of transporters have not been conducted.

2.4.2.5 *Are there other metabolic/transporter pathways that may be important?*

UGT: Uridine diphosphate-glucuronosyltransferase 2B7 (UGT2B7) was identified as the primary UGT enzyme responsible for the direct glucuronidation of cobimetinib to M15 (**Table 20**). Given that cobimetinib is extensively metabolized to form many metabolites as shown in **Table 11** and **Table 12** and direct glucuronidation of cobimetinib to form M15 is < 25% of total metabolism, the inhibition of UGT2B7 alone is not expected to result in a clinically important DDI with cobimetinib. Furthermore, polymorphisms in UGT2B7 and effect on enzyme activity are not well understood and recommendations for DDI studies with UGT2B7 are not well defined.

Reference ID: 3751393

Table 20. Relative Percentage of M15 Present After Incubation with Human Recombinant UGT (Left) and HLMs or rUGT in the Presence of an UGT2B7 Inhibitor (Right)

UGT Isoforms	Relative Percentage of M15 Present [a]
rUGT1A1	0.370±0.397
rUGT1A3	0.819±0.134
rUGT1A4	0.692±0.385
rUGT1A6	0.254±0.163
rUGT1A7	0.845±0.158
rUGT1A8	0.985±0.307
rUGT1A9	1.04±0.84
rUGT1A10	0.525±0.298
rUGT2B4	1.90±0.59
rUGT2B7	100±4
rUGT2B15	0.704±0.083
rUGT2B17	0.606±0.218

rUGT=recombinant uridine 5'-diphospho-glucuronosyltransferase.
[a] Percentages (n=3;±SD) were calculated by setting the highest amount present at time 60 minutes in the rUGT+U incubation at 100%.

Source: Report 10-0264, Table 4, Page 11.

UGT Inhibitor	Assay Condition	Inhibitor (mM)	Relative Percentage of M15 Present [a] HLM	rUGT
NA	+U	NA	100±9	100±8
NA	–U	NA	0.160±0.124	0.338±0.234
2B7	+U+Fluconazole	2.5	66.3±10.7	56.0±7.6

HLM=human liver microsome; rUGT=recombinant 5'-diphospho-glucuronosyltransferase; NA=not applicable; +U=plus UDPGA; –U=without UDPGA; UDPGA=uridine 5'-diphosphoglucuronic acid trisodium salt.
[a] Percentages (n=3;±SD) were calculated by setting the amount present at time 60-minute in the HLM+U incubation at 100%.

Source: Report 10-0264, Table 5, Page 11.

P-gp and BCRP: Cobimetinib is a P-gp substrate in vitro as the net flux ratio is 40, which is ≥ 2, and Cyclosporine A (CsA, a P-gp inhibitor) reduced the efflux ratio by > 50% to 1.6 in MDR1-MDCK cells [Study 08-1902]. According to the 2012 draft FDA DDI Guidance, intestinal absorption is not a rate-limiting step for drugs that are highly permeable and highly soluble such as cobimetinib; therefore, it is acceptable to not conduct in vivo evaluation of cobimetinib with a P-gp inhibitor.

Cobimetinib is not a BCRP substrate in vitro as the net flux ratio was 0.75 in Caco-2 cells and 1.1 in CPT-B1 (BCRP knockdown) cells [Study 09-0339].

OATP and OCT Transporters: Cobimetinib is not a substrate of hepatic uptake transporters, OATP1B1 and OATP1B3, or OCT1, a renal uptake transporter as shown by < 2-fold uptake in cells expressing transporters as compared to control cells (**Table 21**) [Study 10-3241].

Table 21. Transport of Cobimetinib by OATP1B1, OATP1B3, and OCT1

Substrate	Concentration (μM) / Incubation time (min)	Accumulation in transporter expressing cells (pmol/mg)	Accumulation in control cells (pmol/mg)	Transporter specific accumulation (fold)
OATP1B1	2 / 2	2382 ± 459	2164 ± 192	1.10
	2 / 20	5436 ± 1105	5327 ±1372	1.02
	20 / 2	17793 ± 567	19751 ± 1247	0.90
	20 / 20	32231 ± 1089	41020 ± 2730	0.79
OATP1B3	2 / 2	1227 ± 91	2091 ± 337	0.59
	2 / 20	6070 ± 1358	9587 ± 1144	0.63
	20 / 2	20078 ± 2902	34931 ± 4408	0.57
	20 / 20	36038 ± 14380	56580 ± 6607	0.64
OCT1	2 / 2	1987 ± 208	2259 ± 32	0.88
	2 / 20	5710 ± 509	7616 ± 545	0.75
	20 / 2	10568 ± 2887	8161 ± 421	1.29
	20 / 20	22869 ± 2901	24118 ± 4513	0.95

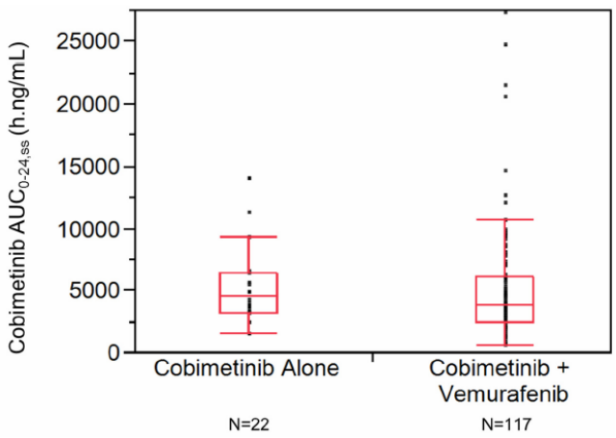
Source: Report 10-3241, Tables 23-25, Pages 50-51.

2.4.2.6 *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

Yes, the labeling specifies administration of cobimetinib in combination with vemurafenib for this marketing application and the PK interaction between cobimetinib and vemurafenib has been evaluated. Vemurafenib is a weak CYP3A inducer (decreased mean AUC of midazolam by 39%) and cobimetinib is a sensitive CYP3A substrate (itraconazole increased its AUC by ≥ 5-fold). In a cross-study comparison, cobimetinib AUC_{ss} was 13% lower in the presence of vemurafenib (Study NO25395) as compared with that of cobimetinib administered as a single agent (Study MEK4592g), which is not considered to be a clinically important difference (**Figure 10**). A cross-study comparison showed that cobimetinib $C_{min,ss}$ were similar in the presence and absence of vemurafenib (**Figure 10**).

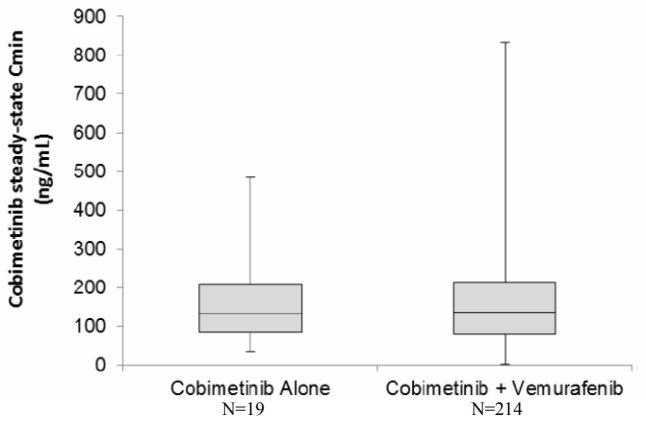
Reference ID: 3751393

Figure 10. Comparison of Steady-State AUC (Left) and C_{min} (Right) of Cobimetinib as a Single Agent and in Combination with Vemurafenib



Cobimetinib 60 mg as a single agent in Study MEK4592g and in combination with vemurafenib 960 mg BID in Study NO25395.

Source: Summary of Clinical Pharmacology, Figure 7, Page 38.



Cobimetinib 60 mg as a single agent in Study MEK4592g, $C_{min,ss}$ observed on cycle 1 day 21; Cobimetinib in combination with vemurafenib 960 mg BID in Study GO28141, $C_{min,ss}$ observed on cycle 1 day 15.

Source: Final Study Report GO28141, Figure 10, Page 105.

It is unlikely that cobimetinib would affect vemurafenib PK via CYP-mediated DDI given that cobimetinib does not affect CYP enzymes at clinical concentrations. Cross-arm comparison in Study GO28141 showed that vemurafenib median C_{min} at cycle 1 day 15 was 20% lower in cobimetinib plus vemurafenib arm versus vemurafenib plus placebo arm. In the population PK analysis, the CL/F and V/F of vemurafenib in the cobimetinib plus vemurafenib arm were 10% higher than in the vemurafenib plus placebo arm. These PK differences are not considered clinically important as efficacy has been established with cobimetinib in combination with vemurafenib in Study GO28141.

2.4.2.7 *What other co-medications are likely to be administered to the target population?*

Concomitant medications used by ≥ 20% of patients in Study GO28141 included systemic and topical steroids (primarily hydrocortisone and prednisone), analgesics (primarily paracetamol), non-steroidal anti-inflammatory drugs (NSAIDs) (primarily ibuprofen), proton pump inhibitors (primarily omeprazole and pantoprazole), and anti-diarrheal therapy (primarily loperamide) (**Table 22**).

Table 22. Summary of Concomitant Medications in Study GO28141

	Vemurafenib + Cobimetinib (n=247)	Vemurafenib (n=248)
Analgesics	42.5%	39.5%
Paracetamol	34.0%	34.7%
Anti-diarrheals	26.3%	8.1%
Loperamide hydrochloride and loperamide	25.5%	7.3%
NSAIDs	37.7%	31.0%
Ibuprofen	21.5%	17.7%
Proton pump inhibitors	36.8%	30.6%
Omeprazole	15.4%	10.1%
Pantoprazole	12.1%	8.5%
Steroids	54.3%	49.6%
Hydrocortisone	8.9%	10.5%
Prednisone	10.1%	8.9%
Source: GO28141 Final Study Report, Concomitant Medications Listing, Pages 531-580.		

2.4.2.8 *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

Yes.

DDI with Strong CYP3A Modulators

The effect of itraconazole (a strong CYP3A inhibitor) on cobimetinib PK was evaluated in a single dose, two period study in 15 healthy subjects under fasted conditions (Study GP28620). Coadministration of itraconazole 200 mg QD for 14 days with a single dose of 10 mg cobimetinib increased cobimetinib AUC by 6.7-fold (90% CI: 5.6, 8.0) and C_{max} by 3.2-fold (90% CI: 2.7, 3.7) as compared with cobimetinib alone (**Table 23**). Clearance (CL/F) of cobimetinib was decreased by 85% from 41.4 L/h to 6.3 L/h with coadministration of itraconazole. Concomitant use of strong CYP3A inhibitors with cobimetinib should be avoided.

Reference ID: 3751393

Table 23. Comparative Analysis of Cobimetinib PK Parameters on Day 1 (Without Itraconazole) and Day 15 (With Itraconazole) (n=15)

	Geometric Mean (%CV)		
Exposure parameter	**Cobimetinib alone (10 mg)**	**Cobimetinib (10 mg) with itraconazole (200 mg QD for 14 days)**	**Geometric Mean Ratio* (90% CI)**
$AUC_{0\text{-}240h}$ (ng·hr/mL)	209 (49.4) n=15	1220 (24.0) n=15	5.84 (4.88-6.98)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	241 (51.5) n=14	1596 (23.0) n=12	6.72 (5.64-8.02)
C_{max} (ng/mL)	5.21 (38.1) n=15	16.5 (27.7) n=15	3.17 (2.68-3.74)

* Cobimetinib 10 mg alone vs. cobimetinib 10 mg and itraconazole 200 mg QD for 14 days

Source: GP28620 Final Study Report, Tables 11-3, 11-4, Pages 53, 55.

Physiologically-based pharmacokinetic modeling (PBPK) predicted that rifampin (a strong CYP3A inducer) can decrease cobimetinib exposure (AUC) by 83% in healthy subjects. Given that labeling for vemurafenib states to avoid concomitant administration with strong CYP3A4 inhibitors and inducers and cobimetinib is administered in combination with vemurafenib, concomitant use of strong CYP3A inducers should also be avoided with cobimetinib.

DDI with Moderate CYP3A Modulators

The 2012 draft FDA DDI Guidance suggests that when there is significant interaction with strong inhibitors/inducers, mechanistic modeling with less strong inhibitors/inducers can be applied. PBPK simulations suggested that erythromycin and diltiazem (moderate CYP3A inhibitors) can increase cobimetinib exposure (AUC) by 3 to 4-fold; efavirenz (moderate CYP3A inducer) can decrease cobimetinib AUC by 73% in healthy subjects (**Table 24**).

Table 24. PBPK Model Predicted AUC and C_{max} Geometric Mean Ratios Following Coadministration of CYP3A Modulators with a Single 60 mg Dose of Cobimetinib in Healthy Subjects

	Interaction mechanism	AUC Ratio	C_{max} Ratio
CYP3A Inhibitor			
Erythromycin (500 mg TID)	Moderate TDI [a]	4.35	2.15
Diltiazem (120 mg BID)	Moderate TDI [a]	3.26	1.85
Fluvoxamine (100 mg QD)	Weak reversible	1.03	1.02
CYP3A Inducer			
Rifampin [b] (600 mg QD)	Strong	0.17	0.37
Rifampin [c] (600 mg QD)	Strong	0.08	0.24
Efavirenz (600 mg QD)	Moderate	0.28	0.36

[a] TDI: Time-dependent inhibitor
[b] Using default perpetrator model (Simcyp V13.1)
[c] Using model with stronger induction effect (Simcyp V14.1)

Source: PBPK Review, Table 2.

The Applicant developed a PBPK model using an oncology population library and reduced gut CYP3A content based on the hypothesis that cancer patients have decreased gut metabolism as compared with healthy subjects. The PBPK review concluded that this model is sufficient to predict steady-state cobimetinib PK in cancer patients. Concomitant use of cobimetinib 60 mg QD with erythromycin increased cobimetinib steady-state exposure by 2-fold in cancer patients (assuming decreased gut CYP3A content to 5% of its abundance in the oncology population library) (**Table 25**). PBPK simulations showed that coadministration of short-term erythromycin treatment with cobimetinib (e.g., reduced cobimetinib dose of 20 mg QD with 14 days of erythromycin treatment) resulted in similar exposures to that of cobimetinib alone (**Figure 11**).

Based on PBPK simulations, the recommendation is avoidance of concurrent chronic use of moderate CYP3A inhibitors and inducers. If avoiding concomitant moderate CYP3A inhibitors is not possible, consider dose reduction of cobimetinib to 20 mg during treatment with a moderate CYP3A inhibitor for 14 days or less. After discontinuation of a moderate CYP3A inhibitor, the cobimetinib dose that was taken prior to initiating the moderate CYP3A4 inhibitor should be resumed.

Reference ID: 3751393

Table 25. PBPK Model Predicted AUC and C_{max} Geometric Mean Ratios Following Coadministration of A Moderate CYP3A Modulator with Cobimetinib 60 mg QD in Healthy Subjects and Patients

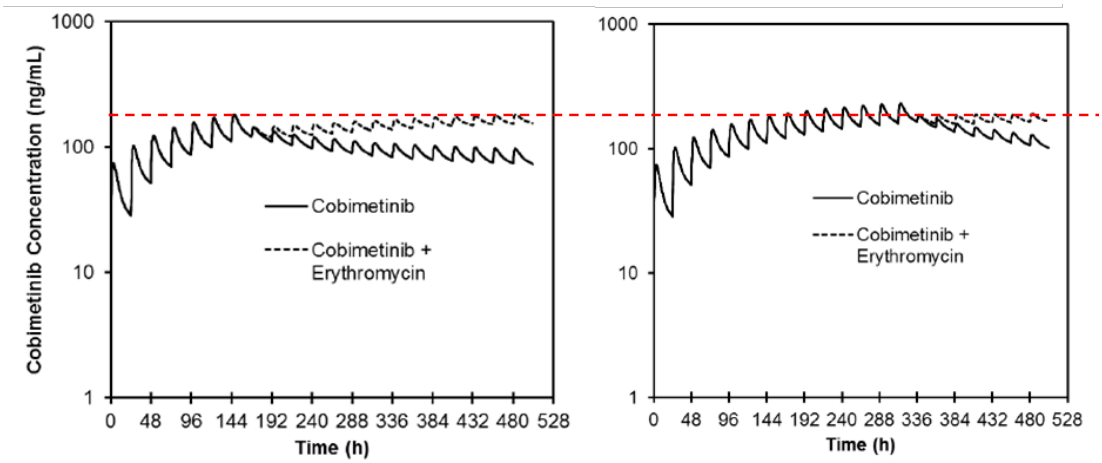
Cobimetinib	Moderate CYP3A Modulator	AUC Ratio	C_{max} Ratio
Healthy Subjects			
60 mg QD × 35 days [a]	Erythromycin 500 mg TID × 35 days	4.27	3.76
60 mg QD × 28 days [b]	Erythromycin 500 mg TID × 14 days, starting on day 15	3.86	3.43
60 mg QD × 21 days [a]	Efavirenz 600 mg QD × 21 days	0.27	0.29
60 mg QD × 28 days [b]	Efavirenz 600 mg QD × 14 days, starting on day 15	0.30	0.32
Patients			
60 mg QD × 21 days [a]	Erythromycin 500 mg TID × 21 days	2.40	2.09
20 mg QD × 21 days [a]	Erythromycin 500 mg TID × 21 days	2.40	2.10
60 mg QD × 21 days [a]	Erythromycin 500 mg TID × 14 days, starting day 8	2.22	1.95
60 mg QD × 7 days, 20 mg QD starting day 8 [a]	Erythromycin 500 mg TID × 14 days, starting day 8	2.34	2.06
60 mg QD × 21 days [a]	Erythromycin 500 mg TID × 7 days, starting day 15	1.79	1.60
60 mg QD × 14 days, 20 mg QD starting day 15 [a]	Erythromycin 500 mg TID × 7 days, starting day 15	1.86	1.67
60 mg QD × 14 days, interrupt on day 15 [a]	Erythromycin 500 mg TID × 7 days, starting day 15	1.24	NA

[a] PK evaluated on day 21
[b] PK evaluated on day 28

Source: PBPK Review, Table 3.

Reference ID: 3751393

Figure 11. PBPK Simulated Mean Cobimetinib Plasma Concentration Time Profiles of Cobimetinib Alone and Coadministration of Cobimetinib and Erythromycin



The left figure shows cobimetinib concentration-time profiles of cobimetinib 60 mg QD alone (solid line) and cobimetinib 20 mg QD with coadministration of erythromycin 500 mg TID starting on day 8 for 14 days (dashed line). The right figure shows cobimetinib concentration-time profiles of cobimetinib 60 mg QD alone (solid line) and cobimetinib 20 mg QD with coadministration of erythromycin 500 mg TID starting on day 15 for 7 days (dashed line). The red dashed line approximates day 21 cobimetinib steady-state trough concentration when cobimetinib 60 mg was administered without a CYP3A inhibitor.

Source: PBPK Review, Figure 4.

DDI with Weak CYP3A Modulators

PBPK simulations predicted that fluvoxamine (weak CYP3A inhibitor) did not change cobimetinib exposure in healthy subjects.

DDI with an Acid Reducing Drug

The effect of rabeprazole (a proton pump inhibitor [PPI]) on cobimetinib PK was evaluated in a single dose, three period study in 20 healthy subjects under fasted and fed conditions (Study MEK4954g). Coadministration of rabeprazole 20 mg QD for 5 days with a single dose of 20 mg cobimetinib increased cobimetinib AUC by 11% and did not affect C_{max} as compared to cobimetinib alone in the fasted state (**Table 26**). Under fed conditions, coadministration of rabeprazole 20 mg QD for 5 days with a single dose of 20 mg cobimetinib increased cobimetinib AUC by 6% and decreased C_{max} by 14% as compared to cobimetinib alone. Based on these results, cobimetinib can be coadministered with acid reducing drugs.

Reference ID: 3751393

Table 26. Comparative Analysis of Cobimetinib PK Parameters on Day 1 (Without Rabeprazole) and Day 14 (With Rabeprazole)

	Geometric Mean (%CV)			Geometric Mean Ratio (90% CI)	
PK Parameter	Cobimetinib (20 mg) with rabeprazole (20 mg QD for 5 days) in a fasted state	Cobimetinib (20 mg) with rabeprazole (20 mg QD for 5 days) with a high-fat meal	Cobimetinib alone (20 mg)	Coadministration of cobimetinib with rabeprazole / cobimetinib alone (fasted state) (B:A)	Coadministration of cobimetinib with rabeprazole / cobimetinib alone (high-fat meal) (C:A)
AUC_{inf} (ng·hr/mL)	864 (39.1) n=16	846 (48.2) n=17	778 (32.8) n=20	1.11 (0.980-1.25)	1.06 (0.945-1.20)
AUC_{0-192h} (ng·hr/mL)	801 (38.1) n=17	758 (48.7) n=17	700 (30.1) n=20	1.13 (0.996-1.28)	1.07 (0.942-1.21)
C_{max} (ng/mL)	17.2 (36.0) n=17	14.8 (51.2) n=17	17.0 (35.3) n=20	1.00 (0.851-1.18)	0.859 (0.729-1.01)
Source: MEK4954g Final Study Report, Tables 11-3, 11-4, Pages 68, 70.					

DDI with Sensitive CYP3A Substrate

The effect of cobimetinib on midazolam PK (sensitive CYP3A substrate) was evaluated in a multiple dose, two period study in 20 patients with solid tumors under fasted conditions (Study MEK4592g, Stage III). Coadministration of cobimetinib 60 mg QD for 15 days with a single dose of midazolam 2 mg did not change midazolam exposure (**Table 27**). Clearance (CL/F) of midazolam with coadministration of cobimetinib was similar to that of midazolam alone.

Table 27. Comparative Analysis of Midazolam PK Parameters on Day 1 (Without Cobimetinib) and Day 15 (With Cobimetinib)

	Geometric Mean (%CV)		
Exposure parameter	**Midazolam alone (2 mg)**	**Midazolam (2 mg) with cobimetinib (60 mg QD for 15 days)**	**Geometric Mean Ratio* (90% CI)**
AUC_{0-24h} (ng·hr/mL)	33.0 (74) n=11	33.4 (88) n=14	1.01 (0.841-1.21)
AUC_{0-inf} (ng·hr/mL)	34.9 (77) n=19	35.7 (91) n=17	1.03 (0.859-1.23)

Reference ID: 3751393

	Geometric Mean (%CV)		
Exposure parameter	**Midazolam alone (2 mg)**	**Midazolam (2 mg) with cobimetinib (60 mg QD for 15 days)**	**Geometric Mean Ratio* (90% CI)**
C_{max} (ng/mL)	10.9 (79) n=20	11.5 (64) n=17	1.06 (0.869-1.29)
* Midazolam 2 mg alone vs. midazolam 2 mg and cobimetinib 60 mg QD for 15 days Source: MEK4592g DDI Updated Final Study Report, Tables 3, 4, Pages 39, 40.			

DDI with Sensitive CYP2D6 Substrate

The effect of cobimetinib on dextromethorphan PK (sensitive CYP2D6 substrate) was evaluated in a multiple dose, two period study in 20 patients with solid tumors under fasted conditions (Study MEK4592g, Stage III). Coadministration of cobimetinib 60 mg QD for 15 days with a single dose of dextromethorphan 2 mg did not change dextromethorphan exposure (**Table 28**). Clearance (CL/F) of dextromethorphan with coadministration of cobimetinib was similar to that of dextromethorphan alone.

Table 28. Comparative Analysis of Dextromethorphan PK Parameters on Day 1 (Without Cobimetinib) and Day 15 (With Cobimetinib)

	Geometric Mean (%CV)		
Exposure parameter	**Dextromethorphan alone (2 mg)**	**Dextromethorphan (2 mg) with cobimetinib (60 mg QD for 15 days)**	**Geometric Mean Ratio* (90% CI)**
AUC_{0-24h} (ng·hr/mL)	25.8 (240) n=19	24.8 (180) n=17	0.93 (0.803-1.07)
AUC_{0-inf} (ng·hr/mL)	29.1 (250) n=19	18.9 (124) n=13	0.99 (0.815-1.19)
C_{max} (ng/mL)	3.44 (150) n=20	3.16 (273) n=17	0.96 (0.742-1.24)
* Dextromethorphan 2 mg alone vs. dextromethorphan 2 mg and cobimetinib 60 mg QD for 15 days Source: Study MEK4592g DDI Updated Final Study Report, Tables 5, 6, Pages 43, 44.			

Of note, midazolam and dextromethorphan were both administered at the same time in Study MEK4592g. Midazolam and dextromethorphan have been utilized in Cooperstown cocktail DDI studies and there are no known PK interactions between midazolam and dextromethorphan.

2.4.2.9 *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?*

No.

2.4.2.10 *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?*

No.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Refer to **Section 2.2.4.4** on unresolved dosing and administration issues with regard to patients with hepatic impairment.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The Applicant classifies cobimetinib (b) (4) based on data showing that cobimetinib has moderate to high permeability in Madin-Darby canine kidney (MDCKII) cells (P_{app} of 5.1×10^{-6} cm/sec) [Study 10-3241] and Caco-2 cells (P_{app} of 18.5×10^{-6} cm/sec) [Study 09-0339] and high aqueous solubility across the physiological pH range (refer to **Section 2.1.1**). Results from the mass balance study (GP28369) suggested that the estimated fraction of cobimetinib absorbed after oral administration (f_a) was approximately 88%, indicating cobimetinib is highly permeable; however, the absolute bioavailability of a single 20 mg dose of cobimetinib is 46%.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

The proposed cobimetinib drug product has been available as a Powder-in-Bottle (PiB) formulation that was administered as an oral solution for weight-based dosing in the first three cohorts in Study MEK4592g, Powder-in-Capsule (PiC) formulation of 5, 25, and 100 mg strengths that was administered in the dose escalation trial (Study NO25395), and the "optimized" to-be-marketed 20 mg tablet formulation that was administered in the registration trial (Study GO28141) (**Table 29**). A "prototype" 20 mg tablet was also used in the food effect study (MEK4953g) and rabeprazole DDI study (MEK4954g). A comparison of the composition of the prototype and optimized tablets is shown in **Table 30**.

Reference ID: 3751393

Table 29. Cobimetinib Oral Dosage Forms used in Clinical Studies

Cobimetinib Formulation [a]	Rationale for Change	Clinical Study Number
Drug substance PiB	First formulation for Phase I to allow dosing flexibility adjusted for body weight	MEK4592g
Drug substance PiC	Change to fixed dosing rather than dosing by body weight	MEK4592g, NO25395, GP28620, MEK4952g, MEK4953g, GP28370
Prototype tablet	Development of a tablet formulation as intended Phase II formulation	MEK4953g, MEK4954g
Commercial tablet	Optimization of disintegration and in vitro dissolution properties	GP28370, GO28141

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 2, Page 7.

Table 30. Comparison of Composition of Cobimetinib 20 mg Tablets

Material	Function	Prototype Tablet (%w/w)	Commercial Tablet (%w/w)	Tablet Change (prototype to commercial)
Cobimetinib Hemifumarate	API	(b) (4)		
Lactose Monohydrate				
Microcrystalline Cellulose[a]				
(b) (4)				
Croscarmellose Sodium				
(b) (4)				
Magnesium Stearate				
(b) (4)				
(b) (4)				

API = active pharmaceutical ingredient.

[a] Microcrystalline cellulose (b) (4) used for prototype tablet/Phase I

(b) (4)

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 3, Page 8.

Reference ID: 3751393

Relative Bioavailability between Capsule and To-Be-Marketed Tablet Formulation: A randomized, two-treatment, two period crossover study with a 14-day washout period was conducted in 28 healthy subjects to evaluate the PK of a single 20 mg dose of cobimetinib administered as a 20 mg tablet or four × 5 mg capsules (Study GP28370). Cobimetinib was administered under fasting conditions. PK samples were collected at pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144, 192, and 216 hours post-dose.

The exposure of cobimetinib (dose normalized AUC and C_{max}) administered as the to-be-marketed tablet formulation was comparable to that following administration as the capsule formulation with geometric mean ratios and 90% CI falling within 0.80-1.25 (**Table 31**). Of note, the upper bound of the 90% CI for C_{max} was 1.29, which was slightly outside of the 0.80-1.25 window, but is not considered clinically important. The median t_{max} for the tablet formulation was 2 (1, 8) hours and 4 (2, 8) hours for the capsule formulation. Study GP28370 provided appropriate bridging between the capsule formulation utilized in Study NO25395 to establish the RP2D of cobimetinib and the tablet formulation administered in Study GO28141 that demonstrated efficacy and safety of cobimetinib.

Reference ID: 3751393

Table 31. Relative Bioavailability of Cobimetinib 20 mg Administered as One 20 mg Tablet (To-Be-Marketed Formulation) and Four × 5 mg Capsules (Formulation Used in Study NO25395 to Establish the RP2D)

Exposure Parameter	Geometric Mean (%CV)		
	One 20 mg tablet	Four × 5 mg capsules	**Geometric Mean Ratio* (90% CI)**
DN $AUC_{0\text{-}216h}$ (ng·hr/mL/mg)	36.7 (39.3) n=27	36.4 (38.4) n=27	1.01 (0.947-1.08)
DN $AUC_{0\text{-}inf}$ (ng·hr/mL/mg)	39.2 (41.0) n=26	39.2 (37.8) n=27	1.01 (0.941-1.07)
DN C_{max} (ng/mL/mg)	0.908 (38.7) n=28	0.806 (47.8) n=27	1.16 (1.05-1.29)

* One 20 mg tablet (optimized tablet, to-be-marketed formulation) vs. four × 5 mg capsules (formulation used in Study NO25395 to establish the RP2D).

Of note, the actual dose of four 5 mg capsules was (b) (4) mg, (b) (4) . Each capsule had 20 mg of the hemifumarate salt of cobimetinib, whereas the tablet formulation, corrected for salt, had 22(b) (4) mg of the hemifumarate salt, which provided 20 mg of free base (cobimetinib). Thus, the statistical analysis was performed on the dose normalized (DN) PK parameters.

Source: GP28370 Final Study Report, Tables 11-2, 11-3, Pages 50-51.

Relative Bioavailability between Capsule and Prototype Tablet Formulation: A randomized, two-treatment, two period crossover study with a 14-day washout period was conducted in 19 healthy subjects to evaluate the PK of a single 20 mg dose of cobimetinib administered as a 20 mg prototype tablet or four × 5 mg capsules (Study MEK4953g). Cobimetinib was administered under fasting conditions. PK samples were collected at pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144, and 192 hours post-dose.

The exposure of cobimetinib (dose normalized AUC and C_{max}) administered as the "prototype" tablet formulation was comparable to that following administration as the capsule formulation with geometric mean ratios and 90% CI falling within 0.80-1.25 (**Table 32**). The median t_{max} for the tablet formulation was 2 (1, 6) hours and 6 (1, 8) hours for the capsule formulation.

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Table 32. Relative Bioavailability of Cobimetinib 20 mg Administered as One 20 mg Prototype Tablet and Four × 5 mg Capsules (Formulation Used in Study NO25395 to Establish the RP2D)

Exposure Parameter	**Geometric Mean (%CV)**		
	One 20 mg tablet	Four × 5 mg capsules	**Geometric Mean Ratio* (90% CI)**
DN $AUC_{0\text{-}192h}$ (ng·hr/mL/mg)	35.3 (33.2) n=19	37.9 (44.8) n=18	0.932 (0.827-1.05)
DN $AUC_{0\text{-}inf}$ (ng·hr/mL/mg)	39.1 (34.7) n=19	41.3 (45.1) n=18	0.947 (0.839-1.07)
DN C_{max} (ng/mL/mg)	0.804 (33.5) n=19	0.829 (45.9) n=18	0.969 (0.842-1.11)

* One 20 mg tablet (prototype tablet, clinical trial formulation) vs. four × 5 mg capsules (formulation used in Study NO25395 to establish the RP2D).

Of note, the actual dose of four 5 mg capsules was (b) (4) mg, (b) (4) . Each capsule had 20 mg of the hemifumarate salt of cobimetinib, whereas the tablet formulation, corrected for salt, had 22(b) (4) mg of the hemifumarate salt, which provided 20 mg of free base (cobimetinib). Thus, the statistical analysis was performed on the dose normalized (DN) PK parameters.

Source: MEK4953g Final Study Report, Tables 11-2, 11-3, Pages 65, 67.

Patients in cohorts 1-3 (0.05, 0.1, and 0.2 mg/kg) of Study MEK4592g received the PiB formulation to enable weight-based dosing. A relative bioavailability study to evaluate the PiB and PiC formulations was not conducted. Dose-normalized AUC and C_{max} appeared to be similar in an exploratory cross-cohort analysis (**Table 33**).

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Table 33. Comparison of Single Dose PK Parameters Following Administration of Cobimetinib as PiB versus PiC Formulations (Study MEK4592g)

Formulation Administered	Geometric Mean (%CV)		
	t_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)
12–16 mg, Powder in Bottle (n=3)	1.5 (1.0–1.5)	18.3 (64%)	203 (58%)
10 mg, Powder in Capsule (n=3)	3.0 (1.0–4.0)	18.8 (29%)	242 (28%)

AUC_{0-24} = area under the plasma concentration-time curve over a 24-hour sampling interval; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; PiB = powder in bottle; PiC = powder in capsule; t_{max} = time to C_{max}.

[a] median (min–max).

Source: Summary of Clinical Pharmacology Studies, Table 7, Page 28.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on cobimetinib PK was evaluated in a single 20 mg dose, randomized, two-treatment, two period crossover study with a 10-day washout period in 20 healthy subjects who received the 20 mg prototype tablet clinical trial formulation (Study MEK4953g). Given that cobimetinib exhibits linear PK in the dose range of 10 to 100 mg following a single dose, the use of a single 20 mg dose that is lower than the clinical dose of 60 mg appears reasonable. The high-fat meal consisted of approximately 900-1000 total calories with a composition of 500-600 calories from fat, 250 calories from carbohydrates, and 150 calories from protein as recommended in the Food Effect FDA Guidance for Industry. PK samples were collected at pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 144, and 192 hours post-dose.

Administration of a single 20 mg dose of cobimetinib with a high-fat, high-calorie meal in healthy subjects resulted in a 10% increase in AUC and 7% increase in C_{max} and increased t_{max} by a median of 4 hours as compared to fasted conditions (**Table 34**). These results support the labeling recommendation of administering cobimetinib with or without food.

The Food Effect FDA Guidance for Industry states that in general, the highest strength of a drug product intended to be marketed should be tested in food effect studies. Study MEK4953g was conducted with the prototype tablet formulation and not the proposed to-be-marketed tablet formulation. The Biopharmaceutics review concluded that the in vitro dissolution profiles of the prototype and optimized tablets are not comparable in vitro (refer to the Biopharmaceutics review). Given that there was no effect of food on cobimetinib exposure and the registration trial that established the safety and efficacy of cobimetinib was conducted using the to-be-marketed formulation without regards to food, a postmarketing food effect study with the to-be-marketed tablet formulation will not be requested.

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Table 34. PK Parameters of a Single Dose of Cobimetinib after a High-Fat Meal as Compared with a Fasted State

Exposure Parameter	Geometric Mean (%CV)		
	High-Fat Meal	Fasted State	Geometric Mean Ratio* (90% CI)
$AUC_{0\text{-}192h}$ (ng·hr/mL)	777 (39.8) n=20	705 (33.2) n=19	1.10 (0.983-1.24)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	858 (42.4) n=20	780 (34.7) n=19	1.10 (0.982-1.24)
C_{max} (ng/mL)	17.2 (43.1) n=20	16.0 (33.5) n=19	1.07 (0.938-1.23)

* Cobimetinib 20 mg (prototype tablet) administered with a high-fat meal (test) vs. a fasted state (reference)

Source: MEK4953g Final Study Report, Tables 11-2, 11-3, Pages 65, 67.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

Refer to Biopharmaceutics review.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

Not applicable as only one strength of 20 mg tablets will be marketed. Refer to Biopharmaceutics review.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

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2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?

Cobimetinib was measured in human plasma using three validated liquid chromatography-mass spectrometry (LC-MS/MS) methods at different stages during drug development [Validated Reports 080490VSMB_GSC_R1; 8251901; BA-VR-030.00, BA-VR-030.01]. In the mass balance study, total radioactivity in blood, plasma, urine, and feces were measured by liquid scintillation counting.

2.6.2 Which metabolites have been selected for analysis and why?

Concentrations of EXEL-0382 (acid metabolite of cobimetinib, M17) were measured only in Study MEK4592g. The mean metabolite AUC_{ss}/unchanged drug AUC_{ss} was < 3% with many samples that were BLQ (below limits of quantification) as consistent with the human mass balance study (GP28369) in which no circulating concentrations of EXEL-0382 were detected. The Applicant states that EXEL-0382 concentrations were not further measured in clinical studies because EXEL-0382 is not active and concentrations in plasma are low.

2.6.3 For all moieties measured is free, bound or total measured?

Given that cobimetinib is 95% bound to human plasma proteins, total plasma concentrations were measured.

2.6.4 What bioanalytical methods are used to assess concentrations?

Cobimetinib concentrations in human plasma were measured by LC-MS/MS using validated methods. The bioanalytical methods and assay validation parameters of cobimetinib in plasma are summarized in **Table 35** and bioanalytical methods used in clinical studies are summarized in **Table 36**.

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Table 35. Summary of Bioanalytical Methods and Assay Validation Parameters of Cobimetinib in Plasma

Laboratory			(b) (4)
Report Number(s) [a]	080490VSMB_GSC_R1	8251901	BA-VR-030.00, BA-VR-030.01
Aliquot Volume	50 µL	50 µL	100 µL
Sample Preparation	Protein precipitation extraction	Supported Liquid Extraction	Protein precipitation extraction
Analysis Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Regression Weighting	Quadratic, $1/x^2$	Quadratic, $1/x^2$	Linear, $1/x^2$
Internal Standard	$^{13}C_6$–cobimetinib	$^{13}C_6$–cobimetinib	$^{13}C_6$–cobimetinib
Sensitivity Range	0.2-100 ng/mL (0.00038-0.19 µM)	0.2-100 ng/mL (0.00038-0.19 µM)	0.183-732 ng/mL (0.00034-1.38 µM)
LLOQ	0.2 ng/mL (0.00038 µM)	0.2 ng/mL (0.00038 µM)	0.183 ng/mL (0.00034 µM)
Analyte Recovery (%)	49.4–60.3	80.3–86.7	95.0–112.6
IS Recovery (%)	93.5	86.5	97.5–100.2
Calibration Standard Inter-Assay Precision (%CV)	2.4–5.0	2.0–5.2	0.9–5.0
Calibration Standard Inter-Assay Accuracy (%RE)	-2.0 to 2.1	-4.2 to 3.0	-3.9 to 2.2
QC Selectivity	2.1–8.2 (LLOQ and ULOQ)	3.1 (LQC)	5.4% (LLOQ)
Precision (%CV)			
Reinjection Reproducibility	103 h at room temperature (RT)	136 h at 2–8°C	48 h at 5°C
Freeze/Thaw Stability	5 cycles	5 cycles	3 cycles
Benchtop Stability	24 h at RT	25 h at RT	6 h at RT
Long-term Stability	336 days at -20°C and 400 days at -70°C	365 days at -10°C to -30°C and -60°C to -80°C	687 days at -70°C
Whole blood Stability	1 h at RT and at wet ice	2 h at RT, at wet ice and at 37°C	NR
Hemolysis	NR	Up to 2%	NR
Hyperlipidaemic	NR	NR	NR
Co-administered medication interference check	Midazolam, dextromethorphan	Itraconazole, vemurafenib	N/A

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QC Samples	0.2, 0.6, 50, 80 ng/mL (0.00038, 0.0011, 0.094, 0.15 μM)	0.2, 0.6, 8.0, 25, 80 ng/mL (0.00038, 0.0011, 0.015, 0.047, 0.15 μM)	0.549, 18.3, 549 ng/mL (0.0010, 0.034, 1.03 μM)
QC Intra-Assay Precision (%CV)	0.8–10.3	1.3–4.3	0.4–7.4
QC Intra-Assay Accuracy (%RE)	-13.7 to 16.7	-6.6 to 4.2	-2.5 to 6.4
QC Inter-Assay Precision (%CV)	6.3–9.5	2.7–4.4	3.6–5.6
QC Inter-Assay Accuracy (%RE)	-4.0 to 0.8	-4.0 to 2.0	2.9–3.4
Dilution Test	2000 ng/mL (DF=25) (3.76 μM)	1000 ng/mL (DF=20) (1.88 μM)	1830 ng/mL (DF=10) (3.44 μM)
Carryover of Analyte and Internal Standard	No carryover to the blank matrix extracts when injected directly after a ULOQ standard	No carryover to the blank matrix extracts when injected directly after a ULOQ standard	No carryover to the blank matrix extracts when injected directly after a ULOQ standard
Method Selectivity	6 lots blank matrix; no significant interference	6 lots blank matrix; no significant interference	6 lots blank matrix; no significant interference
QC Selectivity Accuracy (% theoretical)	94.1–97.0 (LLOQ and ULOQ)	100.7 (LQC)	98.1 (LLOQ)

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Appendix 3, Pages 29-31.

Table 36. Summary of Bioanalytical Methods used in Cobimetinib Clinical Studies

Analyte	Biological Fluid	Validation Study Number	Validation and Sample Analysis Site	Standard Curve Range (ng/mL)	Clinical Study Number
Cobimetinib	Plasma	080490VSMB_GSC_R1	(b) (4)	0.200–100	NO25395, MEK4592g, MEK4952g, MEK4953g, MEK4954g
		BA-VR-030.00, BA-VR-030.01		0.183–732	MEK4592g
		8251901		0.200–100	GO28141, GP28369, GP28620, GP28370
	Urine	BA-VR-067.00		0.200–800	MEK4592g
		090600VHDW_GSC		0.500–100	MEK4952g
EXEL-0382	Plasma	080490VSMB_GSC_R1		0.200–100	MEK4592g
		BA-VR-030.00		0.200–800	MEK4592g
	Urine	BA-VR-066.00		0.200–800	MEK4592g

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4, Page 11.

2.6.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

Refer to **Table 35** for the range of the standard curves and curve fitting techniques. The standard curve ranges are adequate for the purposes of determining plasma concentrations of cobimetinib in the clinical studies.

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2.6.4.2 *What are the lower and upper limits of quantification?*

Refer to **Table 35**.

2.6.4.3 *What are the accuracy, precision and selectivity at these limits?*

The mean %bias and %CV of calibration standards and quality controls for validation of the bioanalytical method were ≤ 15%, and are acceptable based on the 2013 FDA Bioanalytical Method Validation Guidance. Acceptance criteria for QC samples in each run were met (%bias within ±15% of the nominal concentration for at least 2/3 of QC samples and QC samples at a minimum of three concentrations) (**Table 37**).

Table 37. Summary of Accuracy and Precision of Calibration Standards and Quality Controls used in Clinical Studies

		Range of Values			
Clinical Study No.	Calibration Range (ng/mL)	Calibration Standards Accuracy (%RE)	Calibration Standards Precision (%CV)	QC Accuracy (%RE)	QC Precision (%CV)
NO25395	0.200–100	-0.7 to 1.3	3.8 to 6.4	- 2.5 to 1.4	4.3 to 6.6
MEK4592g* (Exelixis)	0.183–732	NR	NR	NR	NR
MEK4592g (Quintiles)	0.200–100	-0.5 to 1.2	2.7 to 5.0	-6.0 to 0.8	4.5 to 8.8
MEK4952g	0.200–100	- 1.3 to 1.2	2.0 to 4.4	- 3.3 to 4.6	5.2 to 6.4
MEK4953g	0.200–100	- 1.2 to 1.2	2.0 to 5.4	- 2.2 to 1.4	2.8 to 10.4
MEK4954g	0.200–100	- 0.9 to 1.6	4.2 to 6.9	- 0.5 to 3.8	5.4 to 6.6
GP28369	0.200–100	- 4.8 to 9.2	3.5 to 8.9	- 5.9 to 5.8	6.4 to 11.4
GP28620	0.200–100	- 2.0 to 2.0	4.0 to 6.4	0.0 to 7.0	4.0 to 8.0
GP28370	0.200–100	-1.7 to 1.4	3.6 to 5.0	-2.9 to 3.8	3.1 to 3.8
GO28141	0.200–100	-0.8 to 1.0	3.5 to 4.8	-3.1 to 0.8	3.0 to 4.1

BAR = bioanalytical report; CV = coefficient of variation; NR = not reported; QC = quality control; RE = relative error. (b) (4) did not provide statistics for the analysis.

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 5, Page 13.

The selectivity/specificity of the method was established using blank plasma from six sources. Selectivity was ensured at the LLOQ.

2.6.4.4 *What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)*

Refer to **Table 35**.

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2.6.4.5 *What is the QC sample plan?*

Refer to **Table 35**. QC samples were prepared in duplicate in each run.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Agency's suggested changes to the proposed labeling are shown in underline blue text and removal of content shown by ~~red strikethroughs~~. Of note, the Agency's labeling modifications have not been agreed upon by the Applicant as of the date of this review.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of COTELLIC is 60 mg (three 20 mg tablets) orally ~~taken~~ once daily.

(b) (4)

(b) (4) COTELLIC with or without a meal (b) (4)

7 DRUG INTERACTIONS

Strong or Moderate CYP3A Inhibitors

Avoid concurrent use of COTELLIC and strong or moderate CYP3A inhibitors. If concomitant short term (14 days or less) use of moderate CYP3A inhibitors including certain antibiotics (e.g., erythromycin, ciprofloxacin) is unavoidable, reduce cobimetinib dose to 20 mg during treatment with a moderate CYP3A inhibitor. After discontinuation of a moderate CYP3A inhibitor, resume the COTELLIC dose that was taken prior to initiating the moderate CYP3A4 inhibitor *[see Clinical Pharmacology (12.3)]*.

Strong or Moderate CYP3A Inducers

Avoid concurrent use of COTELLIC and strong or moderate CYP3A inducers including but not limited to carbamazepine, efavirenz, modafinil, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort *[see Clinical Pharmacology (12.3)]*.

(b) (4)

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(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

(b) (4)

. Dose adjustment is not recommended for patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST) based on results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. Pharmacokinetics of cobimetinib has not been studied in patients with moderate or severe hepatic impairment.

(b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

Used alone, the QT effect of cobimetinib at doses up to 125 mg daily appears to be less than 20 ms. Clinically relevant QT prolongation has been reported with vemurafenib, but substantial further QTc prolongation was not observed when vemurafenib was used in combination with 60 mg cobimetinib. Monitor ECG and electrolytes before initiating treatment and routinely during treatment with cobimetinib in combination with vemurafenib. See vemurafenib's labeling for details.

12.3 Pharmacokinetics

(b) (4)

Absorption ~~***Absorption***~~

Cobimetinib exhibits linear pharmacokinetics in the dose range of 10 to 100 mg.

Following oral dosing of 60 mg once daily in cancer patients, the median time to achieve peak plasma levels (T_{max}) was (b) (4) 2.4 (1, 24) hours, geometric mean steady-state AUC_{0-24h} was 4340 ng·h/mL (61% CV) and (b) (4) C_{max} was 273 ng/mL (60% CV) (b) (4)

The absolute bioavailability of COTELLIC was 46 (b) (4)% (90% CI: (b) (4) 40%, 53 (b) (4)%) in healthy subjects (b) (4) .

A food effect study conducted in healthy subjects with a single 20 mg cobimetinib dose showed that a high fat meal had no effect on cobimetinib AUC and C_{max}. (b) (4)

Distribution ~~***Distribution***~~

Cobimetinib is (b) (4) 95% bound to human plasma proteins in vitro, independent of drug concentration. No preferential binding to human red blood cells was observed (blood to plasma ratio of 0.93). (b) (4) ~~The apparent volume of distribution was 806 L in cancer patients based on population PK analysis.~~

Elimination (b) (4)

The mean elimination half-life ($t_{1/2}$) following oral dosing of COTELLIC was 44 (range: 23-70) hours. The mean apparent clearance (CL/F) was 13.8 L/h (61% CV) following 60 mg orally once daily in cancer patients.

Metabolism: CYP3A oxidation and UGT2B7 glucuronidation appeared to be the major pathways of cobimetinib metabolism in vitro. Following oral administration of a single 20 mg radiolabeled cobimetinib dose, no oxidative metabolites > 10% of total circulating radioactivity were observed.

Excretion: Following oral administration of a single 20 mg radiolabeled cobimetinib dose, 76.5% of the dose was recovered in the feces (with 6.6% as unchanged drug) and 17.8% of the dose was recovered in the urine (with 1.6% as unchanged drug).

(b) (4)

Specific Populations (b) (4)

Age, Gender, Race, and Body Weight: Based on the population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically important effect on the systemic exposure of cobimetinib.

Hepatic Impairment: As cobimetinib is metabolized and eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. (b) (4) Based on a population pharmacokinetic analysis of 80 patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST) and 388 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN), cobimetinib exposures were similar between patients with mild hepatic impairment and patients with normal hepatic function. The pharmacokinetics of cobimetinib has not been studied in patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

Renal Impairment: (b) (4) Cobimetinib with minimal renal elimination (1.6% of a single oral administered dose as unchanged drug found in the urine). A population pharmacokinetic analysis of 151 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 48 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min) and 286 patients with normal renal function (greater than or equal to 90 mL/min) found cobimetinib exposures to be similar in these patients. (b) (4)

(b) (4)

(b) (4)

Drug Interactions

Effect of Strong and Moderate CYP3A Inhibitors on Cobimetinib: In vitro studies show that cobimetinib is a substrate of CYP3A. Coadministration of a single 10 mg cobimetinib dose with itraconazole (a strong CYP3A inhibitor) 200 mg once daily for 14 days increased mean cobimetinib AUC (90% CI) by 6.7-fold (5.6, 8.0) and mean C_{max} (90% CI) by 3.2-fold (2.7, 3.7) in 15 healthy subjects *[see Drug Interactions (7.1)]*. Simulations predicted that exposures of cobimetinib when administered with short-term treatment of a moderate CYP3A inhibitor (e.g., reduced cobimetinib dose of 20 mg once daily with 14 days of a moderate CYP3A inhibitor) were similar to that of cobimetinib when administered alone *[see Drug Interactions (7)]*.

Effect of Strong and Moderate CYP3A Inducers on Cobimetinib: Based on simulations, cobimetinib exposures would decrease by 83% when coadministered with a strong CYP3A inducer and by 73% when coadministered with a moderate CYP3A inducer *[see Drug Interactions (7)]*.

Effect of Cobimetinib on CYP Substrates: In vitro data suggest that cobimetinib may inhibit CYP3A and CYP2D6. Coadministration of cobimetinib 60 mg once daily for 15 days with single 2 mg doses of dextromethorphan (sensitive CYP2D6 substrate) or midazolam (sensitive CYP3A substrate) to 20 patients with solid tumors did not change dextromethorphan or midazolam systemic exposure.

Effect of Transporters on Cobimetinib: Cobimetinib is a substrate of efflux transporter P-glycoprotein (P- gp), but is not a substrate of Breast Cancer Resistance Protein (BCRP), Organic Anion Transporting Polypeptide (OATP1B1 or OATP1B3) or Organic Cation Transporter (OCT1) in vitro. Drugs that inhibit P-gp may increase cobimetinib concentrations.

Effect of Cobimetinib on Transporters: In vitro data suggest that cobimetinib does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, or OCT1 at clinical concentrations.

Effect of Acid Reducing Drugs on Cobimetinib: Coadministration of a proton pump inhibitor, rabeprazole 20 mg once daily for 5 days, with a single dose of 20 mg cobimetinib under fed and fasted conditions did not result in a clinically important change in cobimetinib exposure.

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 206192
Compound	Cobimetinib
Dosing regimen (route of administration)	60 mg orally daily for 21 consecutive days followed by a 7-day rest period in combination with vemurafenib
Indication	Treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation
Clinical Division	Division of Oncology Products 2 (DOP2)
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

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1 SUMMARY OF FINDINGS

1.1 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

1.1.1 Is there an exposure-response relationship for effectiveness?

Exposure response analysis was conducted by the sponsor using data from Phase 3 trial (Study GO28141) in treatment naïve melanoma patients with BRAF V600E mutation where cobimetinib was administered in combination with vemurafenib. Sponsor's analysis included data from all (N=247) patients in the active treatment arm of the phase 3 trial. Based on Kaplan-Meier plots, no trend for increase in progression free survival with cobimetinib exposures (steady state AUC) was identified within the exposures achieved when cobimetinib is administered in combination with vemurafenib (**Figure 12**). AUC was calculated based on the starting dose of the drug. The baseline patient and disease characteristics in various cobimetinib exposure groups are shown in **Table 38**. There appears to be imbalances in these factors across exposure groups. Therefore, a multivariate analysis was conducted by the reviewer to adjust for these imbalances. Region was included in the analysis as region was a stratification factor in the trial. Exposure of vemurafenib was also included in the analysis. The multivariate analysis showed that cobimetinib exposure is not a significant covariate for PFS. Additionally multivariate analysis was conducted by including data from the placebo arm where vemurafenib concentrations were measured. The analysis confirmed that exposure is not a significant covariate for PFS and the results are shown in **Table 44** in **section 3**.

In summary, relationship between PFS and cobimetinib exposure was not identified within the exposures achieved when cobimetinib is administered in combination with vemurafenib.

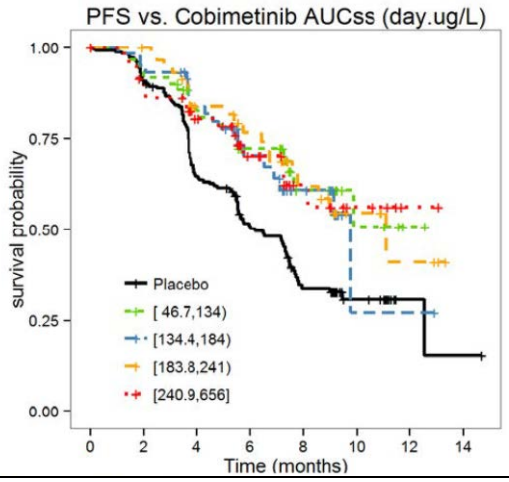

Figure 12: Kaplan-Meier plots of progression free survival for patients in various quartiles (Q1, Q2, Q3 and Q4) based on steady state AUC of Cobimetinib. AUC was calculated based on the starting dose of the drug. Source: Figure 4.2.1.1-1 of sponsor's exposure-response analysis report.

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Table 38: Summary of Continuous Covariates at Baseline in Population PK Analysis

Cobimetinib AUCss (day.ug/L)¶	[46.7,134)	[134.4,184)	[183.8,241)	[240.9,656]
Age (y)				
Mean (CV%)	53.5 22.9)	53.9 (24.4)	56.6 (28.4)	54.9 (25.8)
Sex, N (%)				
Male	39 (63.9)	42 (70.0)	32 (52.5)	30 (50.0)
Female	22 (36.1)	18 (30.0)	29 (47.5)	30 (50.0)
Melanoma Stage, N (%)				
M1a or M1b or IIIc	32 (52.5)	28 (46.7)	22 (36.1)	17 (28.3)
M1c	29 (47.5)	32 (53.3)	39 (63.9)	43 (71.7)
ECOG, N(%)				
Unknown	1 (1.64)	1 (1.67)	0 (0)	1 (1.67)
0	49 (80.3)	49 (81.7)	39 (63.9)	45 (75.0)
1	11 (18.0)	10 (16.7)	21 (34.4)	14 (23.3)
2	0 (0)	0 (0)	1 (1.64)	0 (0)
LDH Status, N(%)				
Normal	36 (59.0)	35 (58.3)	32 (52.5)	24 (40.0)
Elevated	22 (36.1)	25 (41.7)	27 (44.3)	36 (60.0)
Unknown	3 (4.92)	0 (0)	2 (3.28)	0 (0)

N=number of patients; y=year; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; [a,b)=interval notation of exposure metric, a is included and b is excluded, ($a \leq x < b$), "."= information missing. Note: Results represent the number of patients (% of the patient in the group). ¶3 significant digits were used for the upper bound and one decimal for the lower bound

Source: Table 4.1-3 of sponsor's exposure-response analysis report.

Table 39: Results of reviewer's multivariate analysis

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
cobiauc		1	0.0007736	0.00139	0.3112	0.5769	1.001	0.998	1.003	
sex	F	1	-0.50332	0.27014	3.4715	0.0624	0.605	0.356	1.026	sex F
region	Australia/New Zealand/Others	1	-0.51093	0.50460	1.0253	0.3113	0.600	0.223	1.613	region Australia/New Zealand/Others
region	Europe	1	-0.05973	0.39929	0.0224	0.8811	0.942	0.431	2.060	region Europe
mstage	IIIC	1	-0.41247	0.49121	0.7051	0.4011	0.662	0.253	1.734	mstage IIIC
mstage	M1A	1	-0.18623	0.40349	0.2130	0.6444	0.830	0.376	1.831	mstage M1A
mstage	M1B	1	-0.34890	0.35825	0.9485	0.3301	0.705	0.350	1.424	mstage M1B
becog	0	1	10.38587	776.19442	0.0002	0.9893	32398.66	0.000	.	becog 0
becog	1	1	10.43389	776.19444	0.0002	0.9893	33992.23	0.000	.	becog 1
scrnldh	Elevated	1	0.67197	0.26145	6.6059	0.0102	1.958	1.173	3.269	scrnldh Elevated
vemuauc		1	0.00850	0.02432	0.1220	0.7268	1.009	0.962	1.058	

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1.1.2 Is there exposure-response relationship for safety?

Exposure-response analysis for safety endpoints was conducted by the sponsor using data from study GO28141. The safety endpoints included in sponsor's analysis are grade 2 or higher (grade ≥ 2) liver lab abnormalities (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), bilirubin, alkaline phosphatase (ALKP) elevations), creatinine phosphokinase (CPK) elevation (grade ≥ 2), cutaneous squamous cell carcinoma (CuSCC) (any grade), diarrhea (grade ≥ 2), photosensitivity (grade ≥ 2), retinal detachment or serous retinopathy (any grade), visual disturbances (grade ≥ 2), arthralgia (grade ≥ 3), fatigue (grade ≥ 3), rash (grade ≥ 3), basal cell carcinoma (any grade) and reduction in left ventricular ejection fraction (LVEF grade ≥ 2). The cut-off grades for these AEs were selected based on clinical relevance.

ER Analysis for Safety Endpoints with Cobimetinib Exposures: Among all the safety endpoints that were analyzed, a trend for increase in adverse event with cobimetinib exposure was only observed for diarrhea (grade ≥ 2). The probability of diarrhea (grade ≥ 2) tended to increase with cobimetinib exposures (**Figure 13**). It was however noted that the probability of diarrhea (grade ≥ 2) also increased vemurafenib concentrations. In fact, the relationship appeared to be steepest with vemurafenib concentrations in the cobimetinib plus vemurafenib arm. The incidence of diarrhea (grade ≥ 2) in the placebo plus vemurafenib arm was 6.7% and 17.1% in the cobimetinib plus vemurafenib arm. The incidence of diarrhea (grade ≥ 3) in the placebo plus vemurafenib arm was 0% and 6.3% in the cobimetinib plus vemurafenib arm. The incidence of diarrhea (grade ≥ 3) was low to conduct meaningful ER analysis.

ER Analysis for Safety Endpoints with Vemurafenib Exposures: The sponsor conducted additional ER analyses using vemurafenib exposures. The probability of rash (grade ≥3) increased with vemurafenib exposure (**Figure 14**). The frequency of liver lab abnormalities tended to increase with vemurafenib exposure and this effect tended to be more marked in the cobimetinib plus vemurafenib arm (**Figure 15**). Based on the approved label of vemurafenib, it is known that vemurafenib is associated with rash and liver lab abnormalities.

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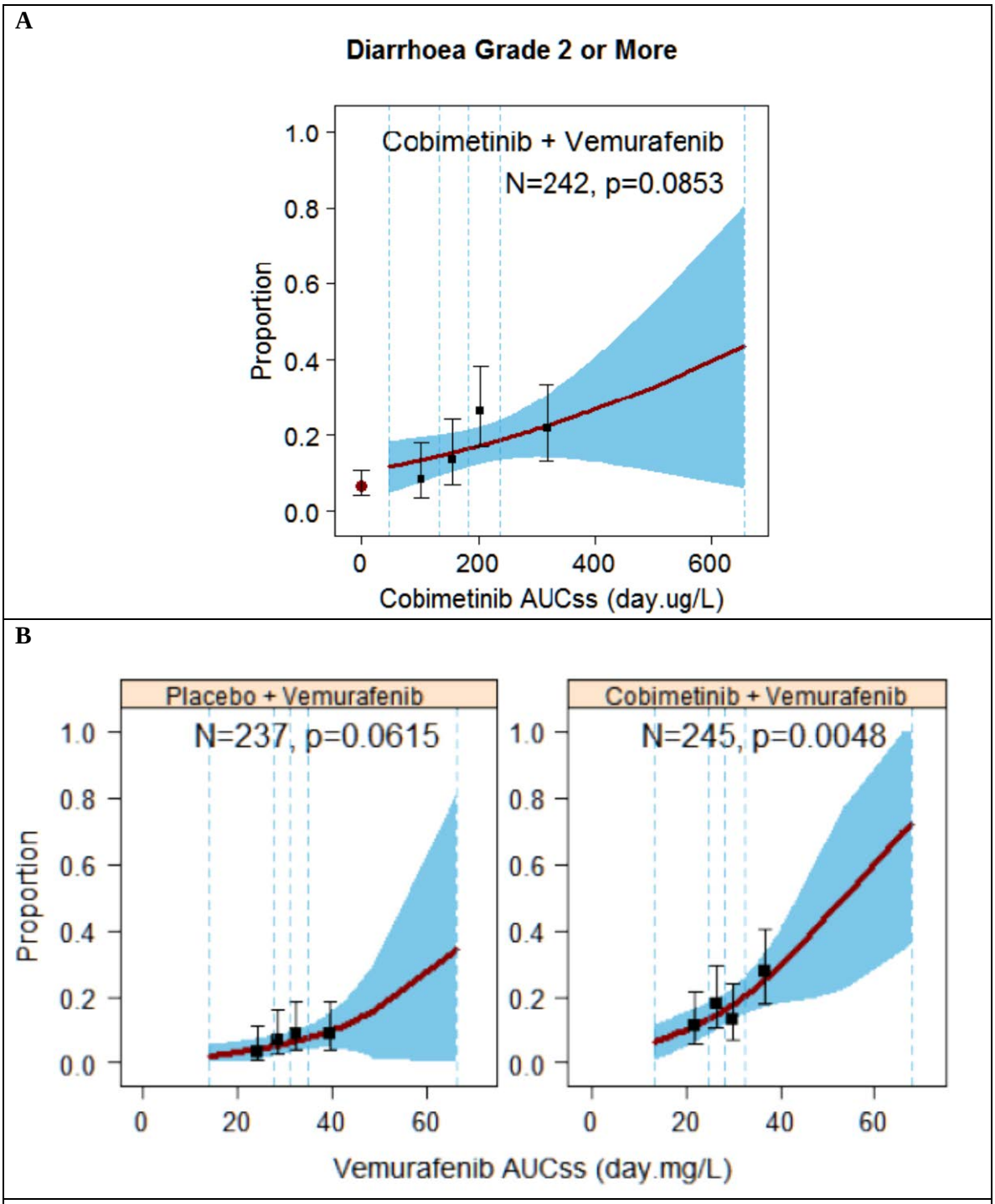


Figure 13: Frequency of Diarrhea (Grade ≥ 2) versus steady state AUC of A) Cobimetinib and B) Vemurafenib. AUC was calculated based on the starting dose of the drug. Source: Figure 4.3.1.4-2 of sponsor's exposure-response analysis report.

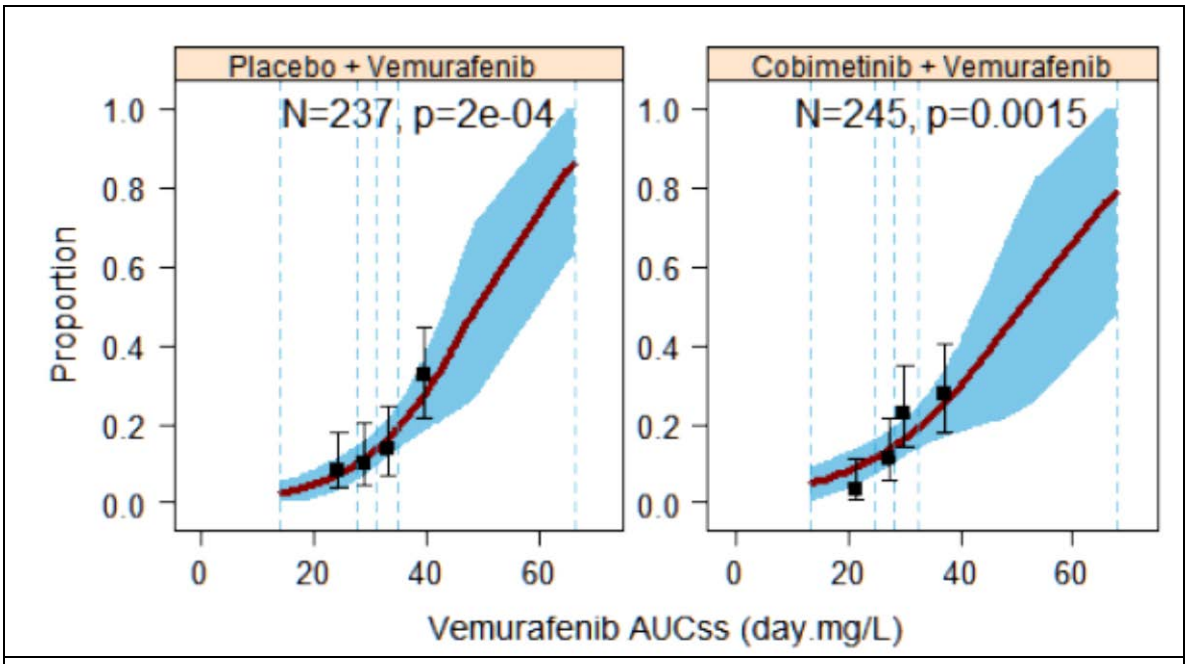
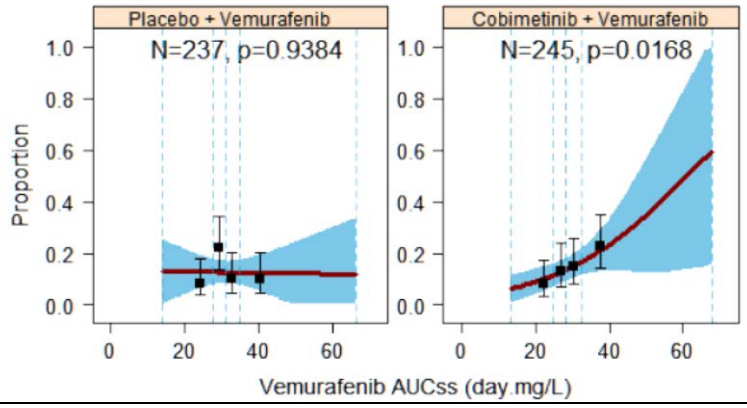
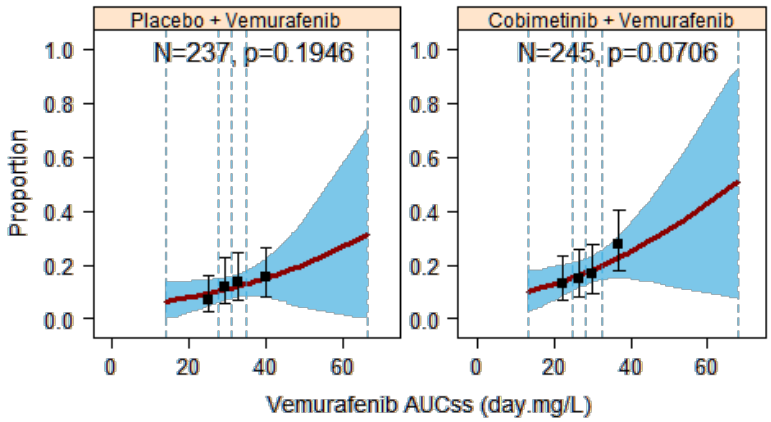


Figure 14: Frequency of Rash (Grade ≥ 2) versus steady state AUC of Vemurafenib. AUC was calculated based on the starting dose of the drug. Source: Figure 4.3.1.10-1 of sponsor's exposure-response analysis report.

A **GGT Elevation**



B **ALT Elevation**



C **AST Elevation**

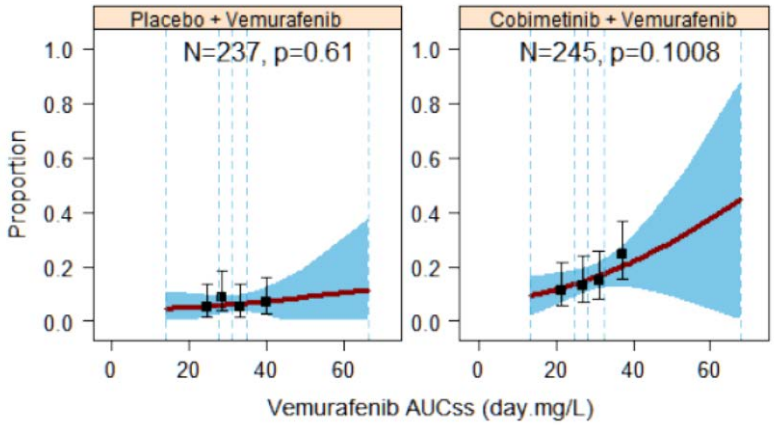


Figure 15: Frequency of A) GGT elevation (Grade ≥ 2), B) ALT elevation (Grade ≥ 2) and C) AST elevation (Grade ≥ 2) versus steady state AUC of vemurafenib. AUC was calculated based on the starting dose of the drug. Source: Figure 4.3.1.1-1, 8.3.1.1 and 8.3.1.2 of sponsor's exposure-response analysis report.

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1.1.3 Is the proposed dose of cobimetinib 60 mg QD for 21 days following 7 days of rest when added to vemurafenib 960 BID reasonable?

The proposed dose is acceptable as ER analysis for efficacy suggested no relationship between cobimetinib exposure and PFS within the exposure range observed at cobimetinib 60 mg QD on a 21/7 schedule (see **section 1.1.1**). The exposure-safety analysis did not show any relationships for selected AEs and cobimetinib exposure within the exposure range observed at cobimetinib 60 mg QD on a 21/7 dosing schedule except for diarrhea, suggesting that the current cobimetinib dose in combination with vemurafenib is adequate (see **section 1.1.2**).

1.1.4 Do intrinsic factors (body weight, age, gender, race, renal function, tumor type) affect the PK of cobimetinib and are dose adjustments needed based on these intrinsic factors?

Body weight and age: Baseline age and baseline body weight were identified as covariates on clearance (CL/F) and volume of distribution (V2/F) respectively. Both identified covariates had a minimal impact on steady-state exposure, suggesting no need for dose adjustments. V2/F was higher in patients with higher body weight; however the impact was less than 16% of change across exposure metrics between the 5th and 95th percentile of body weight distribution (**Figure 16**). CL/F was lower in older patients; between the 5th and 95th percentiles of age distribution, this represented 18% and 24% spreads of variations around the AUCss and Cmin,ss, respectively (**Figure 16**).

Gender, renal function and race: Gender, renal function and race/region had no apparent impact on the clearance of cobimetinib (**Figure 17**). Among the 487 patients included in the analysis, 277 (57%) were male and 210 (43%) were female. In total, 286 patients had normal renal function, 151 patients had mild renal impairment and 48 had moderate renal impairment. No assessment was possible in patients with severe renal impairment as there were only 2 patients with severe renal impairment. Race (Caucasians versus Non-Caucasians) had not impact on the clearance of cobimetinib; however it should be noted that in the dataset majority (>90%) patients were Caucasians.

Melanoma and BRAF V600 mutation subtype: There was no impact of tumor type (melanoma versus non-melanoma) or BRAF V600 mutation (E versus K) on clearance of cobimetinib (**Figure 18**).

ECOG status: There was no impact of ECOG performance status on clearance of cobimetinib (**Figure 19**).

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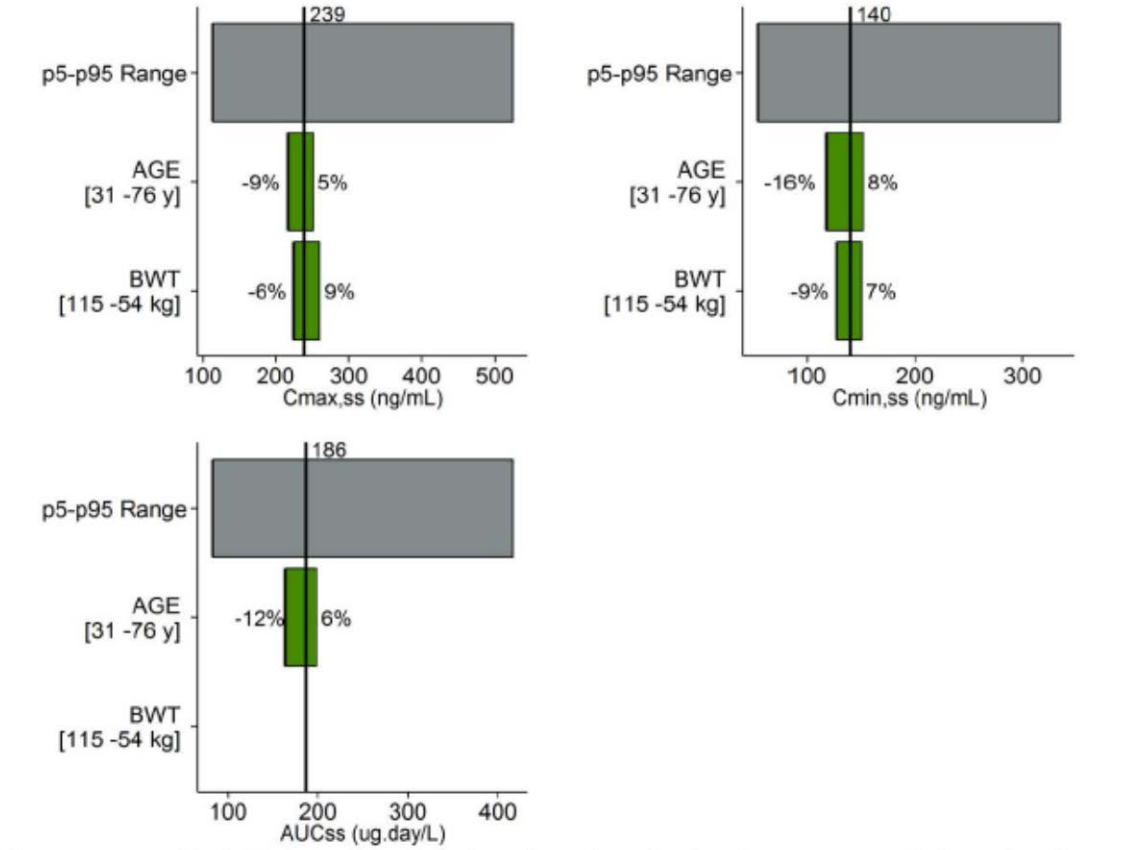

Base, as represented by the black vertical line and value, refers to the predicted steady-state exposure of cobimetinib at 60 mg in a typical patient with body weight of 80 kg and age of 57 years. The gray shaded bar shows the 5th and 95th percentile ([p5-p95]) exposure range across the entire population. Each green shaded bar represents the influence of a single covariate on the steady-state exposure. The label at left end of the bar represents the covariate being evaluated with the upper and lower values of the 5th and 95th percentiles ([p5-p95]) of the covariate distribution for continuous covariates, and the category for categorical covariates. The length of each bar describes the potential impact of that particular covariate on cobimetinib exposure at steady-state, with the percentage value at each end representing the percent change of exposure from the base. AUCss = AUC at steady-state; BWT= body weight; Cmax,ss = Cmax at steady-state; Cmin,ss = Cmin at steady-state; Age= Age in years

Figure 16: Impact of body weight and age on PK of cobimetinib. Figure 4.1.6-1 of population PK report

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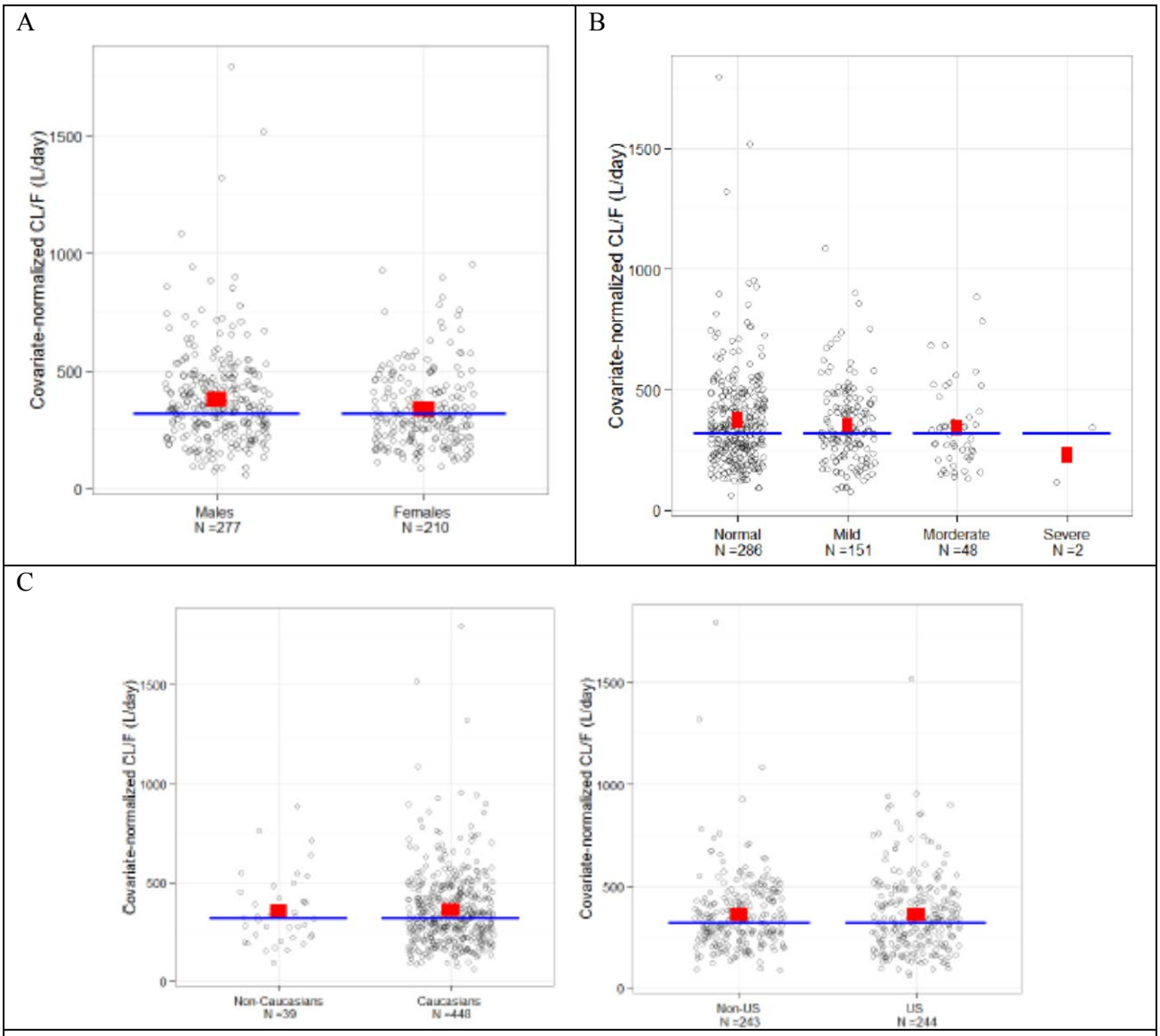

Figure 17: Effect of A) gender, B) renal function and C) race/region on clearance. Circles are the PK parameter estimates from the final population PK model (covariate normalized CL/F). The blue lines represent the typical (population) value and the red squares are the means of the individual estimates. Source: Figure 4.1.6-3, 4.1.6-5 and 4.1.6-4 of population PK report.

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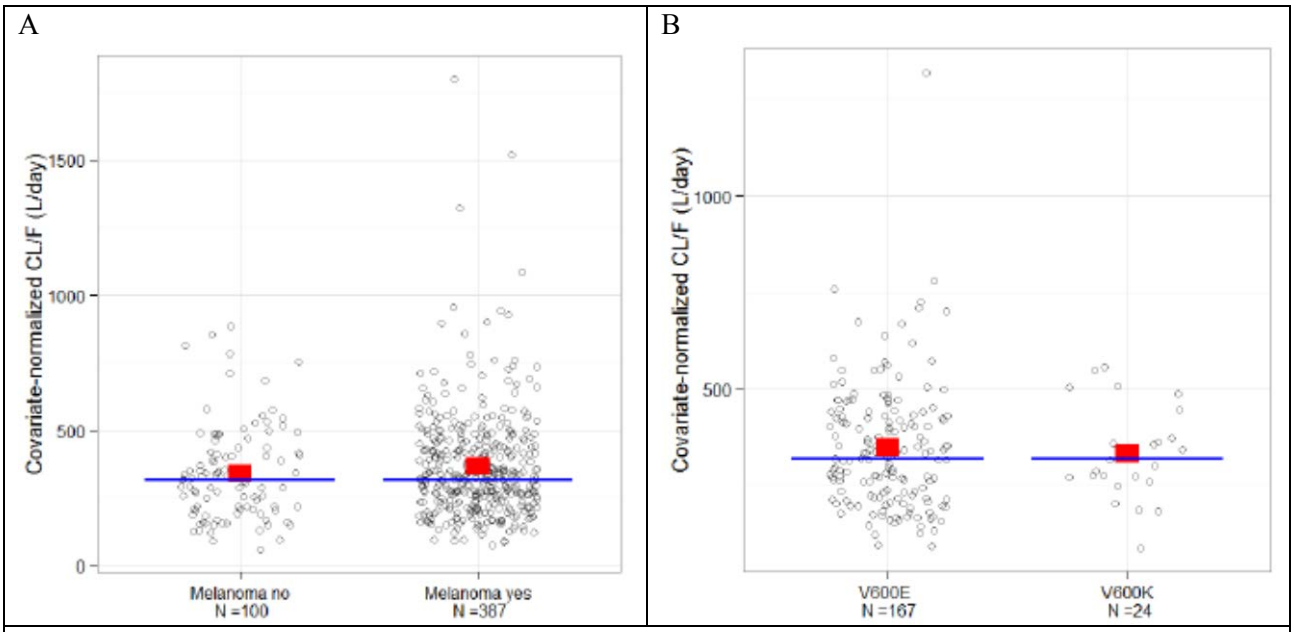

Figure 18: Effect of A) tumor type (melanoma versus non-melanoma) and B) mutation status (V600E versus V600K) on clearance. Circles are the PK parameter estimates from the final population PK model (covariate normalized CL/F). The blue lines represent the typical (population) value and the red squares are the means of the individual estimates. Source: Figure 4.1.6-7 and 4.1.6-8 of population PK report.

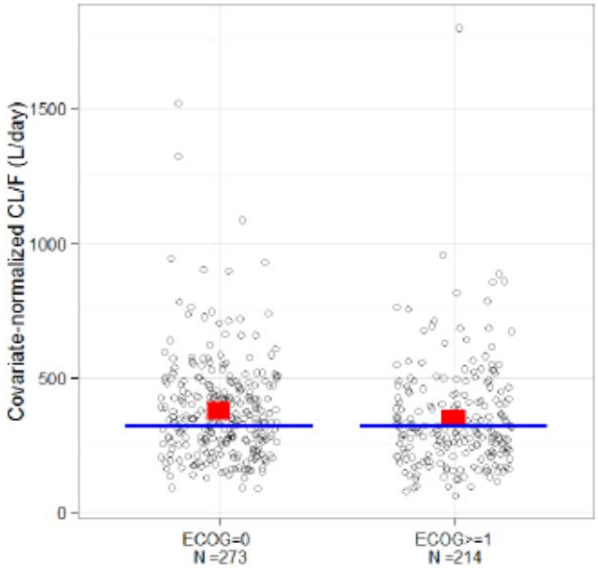

Figure 19: Effect of ECOG status on clearance. Circles are the PK parameter estimates from the final population PK model (covariate normalized CL/F). The blue lines represent the typical (population) value and the red squares are the means of the individual estimates. Source: Figure 4.1.6-6 of population PK report.

1.1.5 Is there an impact of vemurafenib on cobimetinib exposure?

Administration of vemurafenib had no impact on the clearance of cobimetinib (**Figure 20**). A graphical exploration of relationship between individual vemurafenib AUC and individual cobimetinib AUC at steady state is displayed in **Figure 20** suggesting no impact of vemurafenib exposure on cobimetinib exposure.

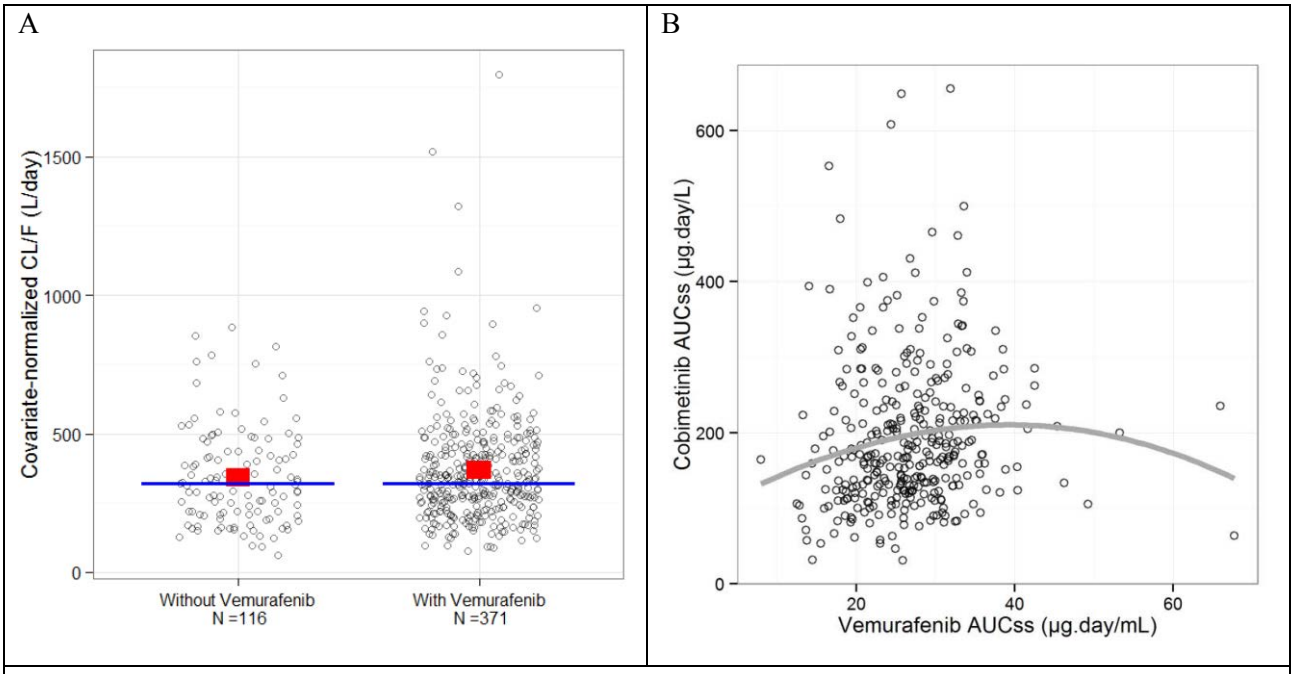

Figure 20: Impact of vemurafenib on cobimetinib PK. A) Comparison of cobimetinib CL/F with and without vemurafenib co-administration. Circles are the PK parameter estimates from the final population PK model (covariate normalized CL/F). The blue lines represent the typical (population) value and the red squares are the means of the individual estimates. B) Graphical exploration of relationship between individual vemurafenib steady state AUC and individual cobimetinib steady state AUC. Data from patients receiving cobimetinib at 60 mg on 21/7 schedule were used (N=343). Grey lines are LOESS (locally weighted scatterplot smoothing). Source: Figure 4.1.6-11 and 4.1.6-12 of population PK report.

1.1.6 Is there an impact of cobimetinib on vemurafenib exposure?

The assessment of cobimetinib effect on vemurafenib PK was performed by comparison of the individual vemurafenib PK parameters between the 2 arms in the Study GO28141. The ratio of geometric means of individual estimates in the two arms was around 1.1 with no or small overlap of the 95% CI of the geometric mean. The CL/F, V/F and Ka of vemurafenib were slightly higher in Arm B (cobimetinib plus vemurafenib) compared to Arm A (placebo plus vemurafenib). However, given the small magnitude of the increase, these are considered to be clinically not significant.

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Table 40: Results of reviewer's multivariate analysis

PK parameter	Arm	N	Mean	SE	Median	P5;P95	Geomean	CI 95% geomean	Ratio Geomean CI 95%
CL/F (L/day)	placebo plus vemurafenib	245	31.5	0.4	30.9	21.9;40.6	30.9	30.14;31.71	1.09 [1.05;1.14]
	cobimetinib plus vemurafenib	245	34.6	0.5	34.0	24.7;48.7	33.8	32.90;34.77	
V/F (L)	placebo plus vemurafenib	245	114.9	3.3	106.4	54.6;212.5	104.9	99.29;110.80	1.10 [1.02; 1.20]
	cobimetinib plus vemurafenib	245	130.8	5.2	115.2	61.3;251.2	115.9	109.23;122.93	
Ka (1/day)	placebo plus vemurafenib	245	6.07	0.3	4.77	2.44;11.8	5.17	4.82;5.54	1.06 [0.95; 1.17]
	cobimetinib plus vemurafenib	245	6.69	0.3	4.83	2.45;14.3	5.47	5.07;5.90	

N= number of patients; Mean= mean of individual estimates; Median= median of individual estimates; P5= 5th percentile of individual estimates; P95= 95th percentile of individual estimates; Geomean= geometric mean of individual estimates; CI 95% geomean = 95% confidence interval of geometric mean of individual estimates; Ratio= geometric mean of individual estimates/ population value; CI 95% = the 95% confidence interval of the ratio

CL/F= Clearance; Ka= first-order absorption rate constant; V/F= Apparent volume of distribution of central compartment

Source: Table 4.2.4-1 of sponsor's population PK report.

1.2 RECOMMENDATIONS

Division of Pharmacometrics finds NDA 206192 acceptable from a clinical pharmacology perspective provided an agreement regarding the label language can be reached between the sponsor and the Agency.

1.3 LABEL STATEMENTS

The following are the labeling recommendations relevant to clinical pharmacology for NDA 206192. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

8.7 RENAL IMPAIRMENT

(b) (4) Dose adjustment is not recommended for mild to moderate renal impairment based on the results of the population pharmacokinetic analysis. (b) (4) *[see Clinical Pharmacology (12.3)]*.

12.3 Pharmacokinetics

(b) (4) Based on a population pharmacokinetic analysis of data from 487 patients with cancer, exposure to [TRADENAME] was not influenced by mild (CrCl: 60 to 90 mL/min; N=151) or moderate (CrCl: 30 to 60 mL/min; N=48) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) was limited (N=2).

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Age, Gender, and Race, (b) (4) Based on the population pharmacokinetic analysis, age, gender, and race, (b) (4) do not have a clinically important effect on the exposure of [TRADENAME]. (b) (4)

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 POPULATION PK ANALYSIS

The objectives of sponsor's population PK analysis were:

- Describe the PK profiles of cobimetinib in cancer patients and to estimate typical values and interpatient variability of PK parameters,
- Evaluate the effects of patient demographics, pathophysiologic factors, renal function, hepatic function, and co-administration with vemurafenib on cobimetinib PK in order to better understand clinical factors that might affect cobimetinib plasma concentrations in individual patients,
- Derive cobimetinib exposure metrics for exploratory exposure-response analysis of cobimetinib,
- Assess the effect of cobimetinib co-administration on vemurafenib PK using historical vemurafenib population PK model and to derive vemurafenib exposure metrics for exploratory exposure-response analysis of vemurafenib.

2.1.1 Data and Method

The population PK analysis for cobimetinib was based on data collected from 3 clinical trials. A brief description of the studies is provided below:

- MEK4592g (N=114): A Phase I dose escalation and expansion study in patients with solid tumors. Cobimetinib doses ranged from 2.1 to 125 mg once daily (QD) on two schedules, 21/7 (21 days on and 7 days off) and 14/14 (14 days on and 14 days off).
- NO25395 (N=131): A Phase Ib dose escalation and expansion study in BRAF V600E mutation-positive advanced melanoma patients in combination with vemurafenib (Zelboraf®). Cobimetinib doses ranged from 60 to 100 mg QD on three schedules, 14/14, 21/7 and 28/0 (28 days on and 0 days off) and vemurafenib doses were 720 and 960 mg twice daily (BID) on a 28/0 schedule .
- GO28141 (N=490): A phase III, double-blind, placebo controlled study of vemurafenib (960 mg BID on a 28/0 schedule) versus vemurafenib (960 mg BID on a 28/0 schedule) plus cobimetinib (60 mg on a 21/7 schedule) in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma.

The PK of cobimetinib in plasma was evaluated in 487 patients with 4886 samples from three studies (NO25395, MEK4592g and GO28141). A nonlinear mixed effects modeling approach was used with the first-order conditional estimation (FOCE) method with interaction in NONMEM 7, version 7.2 (ICON, Maryland).
The impact of covariates, as detailed above, on the PK of cobimetinib was investigated. Covariates were selected using a forward addition and backward elimination method (based on the significance levels of $p<0.05$ and $p<0.001$, respectively). A summary of continuous and categorical covariates in the population PK analysis are summarized in

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Table 41: Summary of Continuous Covariates at Baseline in Population PK Analysis

Covariate (unit)	N Mean (CV%) Median [Minimum - Maximum]			
	All Data	Study MEK4592g	Study NO25395	Study GO28141
Age (years)	487 55.5 (24.7) 57.0 [19.0-88.0]	114 59.3 (20.9) 60.0 [25.0-82.0]	131 53.6 (25.9) 55.0 [19.0-88.0]	242 54.7 (25.5) 56.0 [23.0-88.0]
Weight (kg)	485 81.0 (24.2) 79.2 [42.7-185.0]	113 78.1 (26.3) 74.9 [42.7-157.5]	131 82.9 (24.1) 82.5 [47.0-155.6]	241 81.2 (23.1) 78.8 [48.5-185.0]
BMI (kg/m2)	477 27.6 (23.3) 26.6 [16.0-70.0]	113 27.5 (26.2) 26.2 [17.1-70.0]	127 27.7 (24.0) 27.1 [16.0-58.9]	237 27.7 (21.4) 26.8 [18.4-64.0]
BSA (m2)	477 1.92 (12.2) 1.92 [1.36-2.74]	113 1.87 (13.1) 1.86 [1.36-2.44]	127 1.96 (11.9) 1.98 [1.46-2.53]	237 1.93 (11.7) 1.92 [1.44-2.74]
Serum Creatinine (mg/dL)	466 0.92 (40.1) 0.89 [0.39-7.00]	114 0.98 (62.4) 0.90 [0.50-7.00]	130 0.95 (30.1) 0.90 [0.50-2.05]	222* 0.87 (23.4) 0.85 [0.39-1.73]
Creatinine CL (mL/min)	464 103.7 (39.7) 98.5 [7.3-325.4]	113 92.7 (46.6) 84.8 [7.3-325.4]	130 104.4 (35.8) 101.3 [27.7-264.1]	221** 109.0 (38.0) 104.5 [40.8-299.1]
eGFR (mL/min/1.73m2)	466 82.7 (27.9) 81.2 [6.4-176.3]	114 78.0 (31.3) 74.3 [6.4-143.0]	130 80.6 (27.8) 78.6 [27.5-134.9]	222*** 86.4 (25.8) 84.2 [39.3-176.3]
Albumin (g/L)	461 39.8 (13.8) 40.0 [19.9-53.2]	114 36.4 (13.5) 37.0 [20.0-48.0]	130 40.9 (12.7) 42.0 [24.0-51.0]	217 40.9 (12.8) 41.0 [19.9-53.2]
AST (U/L)	460 26.6 (69.1) 22.0 [6.0-211.0]	114 34.5 (81.5) 26.0 [6.0-211.0]	129 23.1 (35.0) 22.0 [7.0-59.0]	217# 24.5 (60.4) 21.0 [9.0-110.0]
ALT (U/L)	465 27.4 (80.9) 21.0 [5.0-224.0]	114 34.9 (79.5) 27.5 [6.0-205.0]	130 22.1 (59.2) 19.0 [5.0-100.0]	221 26.7 (83.4) 21.0 [5.0-224.0]
Bilirubin (µmol/L)	466 10.4 (50.9) 8.6 [1.7-32.5]	114 8.8 (52.5) 8.6 [1.7-30.8]	130 11.7 (48.2) 10.3 [3.0-29.1]	222## 10.3 (49.8) 9.0 [3.0-32.5]
ALP (U/L)	464 125.6 (91.1) 90.7 [35.0-1058.0]	114 186.8 (96.2) 118.0 [55.0-1058.0]	130 101.8 (57.0) 85.5 [35.0-402.0]	220 108.0 (74.5) 84.5 [36.0-680.0]

*N=number of patients; ALT= alanine aminotransferase (U/L); ALP= alkaline phosphatase (U/L); AST= aspartate aminotransferase (U/L); BMI= body mass index (kg/m2); BSA= body surface area (m^2); Creatinine CL= creatinine clearance (mL/min); eGFR= estimated Glomerular Filtration Rate; CV%= coefficient of variation. * exclusion of 2 aberrant values for the summary statistique (i.e. >600 mg/dL); ** exclusion of 2 aberrant values for the summary statistique (i.e. <1 mL/min);*** exclusion of 2 aberrant values for the summary statistique (i.e. <1 mL/min); # exclusion of 1 aberrant value for the summary statistique. (i.e. >2000 U/L);## exclusion of 1 aberrant value for the summary statistique. (i.e. >153 µmol/L)*

Source: Table 4.1.1-2 of population PK report

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Table 42: Summary of Categorical Covariates at Baseline in Population PK Analysis

Categorical Covariate	Description	All Data N=487 (%)	Study MEK4592g N=114 (%)	Study NO25395 N=131 (%)	Study GO28141 N=242 (%)
Renal impairment Category	Normal	273 (56.1%)	52 (45.6%)	83 (63.4%)	138 (57.0%)
	Mild	141 (29.0%)	39 (34.2%)	37 (28.2%)	65 (26.9%)
	Moderate	48 (9.9%)	21 (18.4%)	9 (6.9%)	18 (7.4%)
	Severe	2 (0.4%)	1 (0.9%)	1 (0.8%)	0 (0.0%)
Sex	Male	277 (56.9%)	56 (49.1%)	78 (59.5%)	143 (59.1%)
	Female	210 (43.1%)	58 (50.9%)	53 (40.5%)	99 (40.9%)
ECOG	missing	3 (0.6%)	0 (0.0%)	0 (0.0%)	3 (1.2%)
	0	270 (55.4%)	23 (20.2%)	65 (49.6%)	182 (75.2%)
	1	206 (42.3%)	84 (73.7%)	66 (50.4%)	56 (23.1%)
	2	8 (1.6%)	7 (6.1%)	0 (0.0%)	1 (0.4%)
Ethnicity	Hispanic	25 (5.1%)	5 (4.4%)	6 (4.6%)	14 (5.8%)
	Not Hispanic	439 (90.1%)	109 (95.6%)	124 (94.7%)	206 (85.1%)
	Not reported	19 (3.9%)	0 (0.0%)	1 (0.8%)	18 (7.4%)
	Unknown	4 (0.8%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
RACE	Caucasian	448 (92.0%)	99 (86.8%)	127 (96.9%)	222 (91.7%)
	Black	7 (1.4%)	7 (6.1%)	0 (0.0%)	0 (0.0%)
	Asian	6 (1.2%)	5 (4.4%)	0 (0.0%)	1 (0.4%)
	Native Hawaiian	1 (0.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
	Other	7 (1.4%)	2 (1.8%)	3 (2.3%)	2 (0.8%)
	Unknown	17 (3.5%)	0 (0.0%)	1 (0.8%)	16 (6.6%)
	Multiple	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Region	US	244 (50.1%)	114 (100.0%)	114 (87.0%)	16 (6.6%)
	GER	22 (4.5%)	0 (0.0%)	0 (0.0%)	22 (9.1%)
	HUN	12 (2.5%)	0 (0.0%)	0 (0.0%)	12 (5.0%)
	ISR	6 (1.2%)	0 (0.0%)	0 (0.0%)	6 (2.5%)
	ITA	44 (9.0%)	0 (0.0%)	0 (0.0%)	44 (18.2%)
	NED	4 (0.8%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
	NOR	3 (0.6%)	0 (0.0%)	0 (0.0%)	3 (1.2%)
	NZL	3 (0.6%)	0 (0.0%)	0 (0.0%)	3 (1.2%)
	RUS	17 (3.5%)	0 (0.0%)	0 (0.0%)	17 (7.0%)
	SUI	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	SWE	9 (1.8%)	0 (0.0%)	0 (0.0%)	9 (3.7%)
	AUS	45 (9.2%)	0 (0.0%)	17 (13.0%)	28 (11.6%)
	AUT	4 (0.8%)	0 (0.0%)	0 (0.0%)	4 (1.7%)
	BEL	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.8%)
	CAN	9 (1.8%)	0 (0.0%)	0 (0.0%)	9 (3.7%)
	CZE	10 (2.1%)	0 (0.0%)	0 (0.0%)	10 (4.1%)
	ESP	15 (3.1%)	0 (0.0%)	0 (0.0%)	15 (6.2%)
	FRA	23 (4.7%)	0 (0.0%)	0 (0.0%)	23 (9.5%)
	GBR	14 (2.9%)	0 (0.0%)	0 (0.0%)	14 (5.8%)

ECOG= Eastern cooperative oncology group performance status; N=number of patients; Renal impairment Category= Normal CRCL ≥90 mL/min; Mild CRCL ≥60 and <90 mL/min; Moderate CRCL ≥30 and <60 mL/min; Severe CRCL <30 mL/min

Source: Table 4.1.1-3 of population PK report

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2.1.2 Results

A linear two-compartment disposition model with first-order absorption with a lag time and a first-order elimination best describes cobimetinib concentration-time data in patients with cancer. The parameters of the final model for cobimetinib are shown in **Table 43**. The goodness-of-fit plots from the cobimetinib final population model are shown in **Figure 21**. Age was identified as a covariate on CL/F and body weight as a covariate on apparent volume of distribution of central compartment; however, none of the identified covariates resulted in clinically meaningful changes to cobimetinib exposure. For details see **section 1.1.4**.
The PK of vemurafenib was described by fixing the parameters from the historical model of vemurafenib. The goodness-of-fit plots from the vemurafenib model are shown in **Figure 22**.

Reviewer's comments:

- *Sponsor population PK model is reasonable based on model diagnostics.*
- *The reviewer agrees with sponsor's assessment that no dose adjustment based on bodyweight, age, race or gender is needed. For details see **section 1.1.4**.*

2.2 EXPOSURE RESPONSE ANALYSIS

Exposure response-relationship for effectiveness and safety endpoints was conducted by the sponsor. See **sections 1.1.1** and **1.1.2** for results from the sponsor's exposure response analysis.

Reviewer's comments:

- *Reviewer agrees with sponsor's assessment that there is no relationship between PFS and cobimetinib exposure as reviewer's multivariate analysis showed that cobimetinib exposure is not a significant covariate for PFS (**Table 39** and **Table 44**).*
- *Sponsor collected samples for measurement of cobimetinib concentrations from all patients in the cobimetinib plus vemurafenib arm. Sponsor also collected samples for measurement of vemurafenib concentrations from both cobimetinib plus vemurafenib arm and placebo plus vemurafenib arm. This allowed for an examination of the impact of cobimetinib and vemurafenib exposure on PFS in multivariate analysis.*

3 RESULTS OF REVIEWER'S ANALYSIS

Multivariate analysis was conducted by the reviewer to assess the relationship between cobimetinib exposure and PFS. The results are shown in **Table 39** in **section 1.1.1**. Additionally multivariate analysis was conducted by including data from the placebo arm where vemurafenib concentrations were measured. The results are shown in **Table 44**.

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Table 43: Parameter estimates of the final population PK model for cobimetinib

Parameter	Unit	Estimate	SE	RSE (%)	95% CI	Variability (%)	Shrinkage (%)
Ka	1/day	35.6	3.33	9.4	[29.1 ; 42.1]		
CL/F	L/day	322	10.2	3.2	[301 ; 342]		
V2/F	L	511	21.1	4.1	[470 ; 553]		
V3/F	L	295	17.2	5.9	[261 ; 328]		
Q/F	L/day	210	37.8	18.0	[136 ; 284]		
Lag time	day	0.0199	0.0000477	0.24	[0.0198 ; 0.0200]		
Age on CL/F		-0.217	0.0682	31.5	[-0.350 ; -0.083]		
BWT on V2/F		0.795	0.0857	10.8	[0.627 ; 0.963]		
IIV Ka		2.76	0.269	9.7	[2.23 ; 3.29]	166	20
IIV CL/F		0.342	0.0344	10.0	[0.275 ; 0.409]	58	16
IIV V2/F		0.237	0.0379	16.0	[0.163 ; 0.311]	49	22
IIV V3/F		0.631	0.235	37.3	[0.170 ; 1.09]	79	44
IIV Q/F		0.808	0.446	55.2	[-0.066 ; 1.68]	90	71
IOV F1		0.211	0.0367	17.4	[0.139 ; 0.283]	46	
correlation CL-V2		0.882					
correlation V2-V3		-0.066					
correlation CL-V3		0.381					
Additive error (SD)		0.423*	0.0183	4.3	[0.387 ; 0.459]		15
Objective function		-46.3					

*corresponds to a proportional error of 53% on normal scale

CL/F= clearance; F1= relative bioavailability ; IIV= inter-individual variability; IOV= inter-occasion variability; Ka= first-order absorption rate constant; Q/F= inter-compartmental clearance; RSE= relative standard error; SD= standard deviation; SE= standard error; V2/F= apparent volume of distribution of central compartment; V3/F= apparent volume of distribution of peripheral compartment; CI= confidence interval; BWT= body weight (normalized by a 80-kg body weight) ;Age= normalized by 57y old

Source: Table 4.1.4-1 of population PK report

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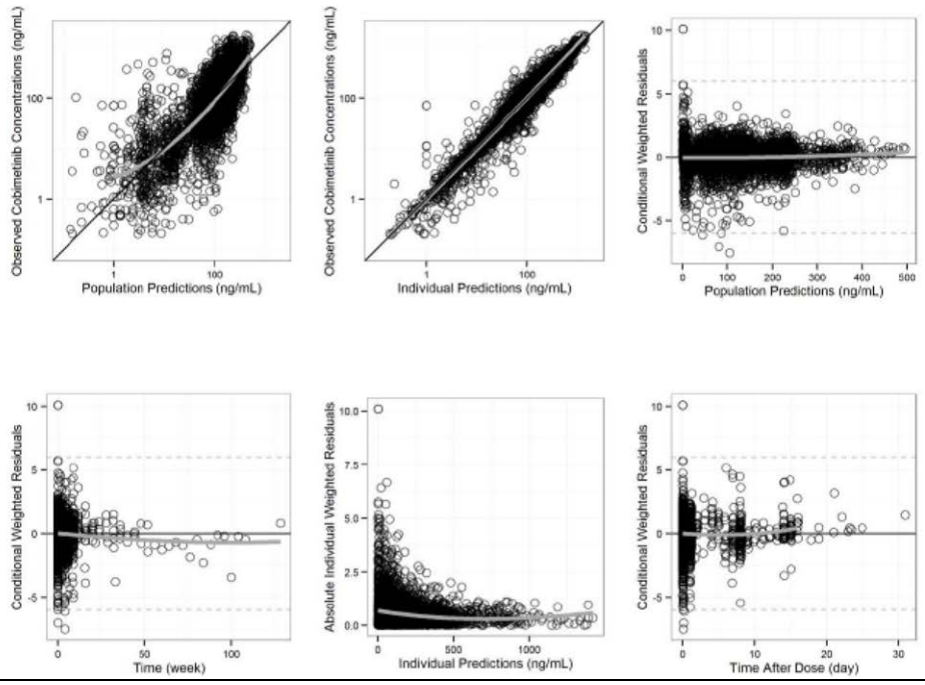

Figure 21: Goodness of fit plots from the final population PK model of cobimetinib. Source: Figure 4.1.4-1 of population PK report

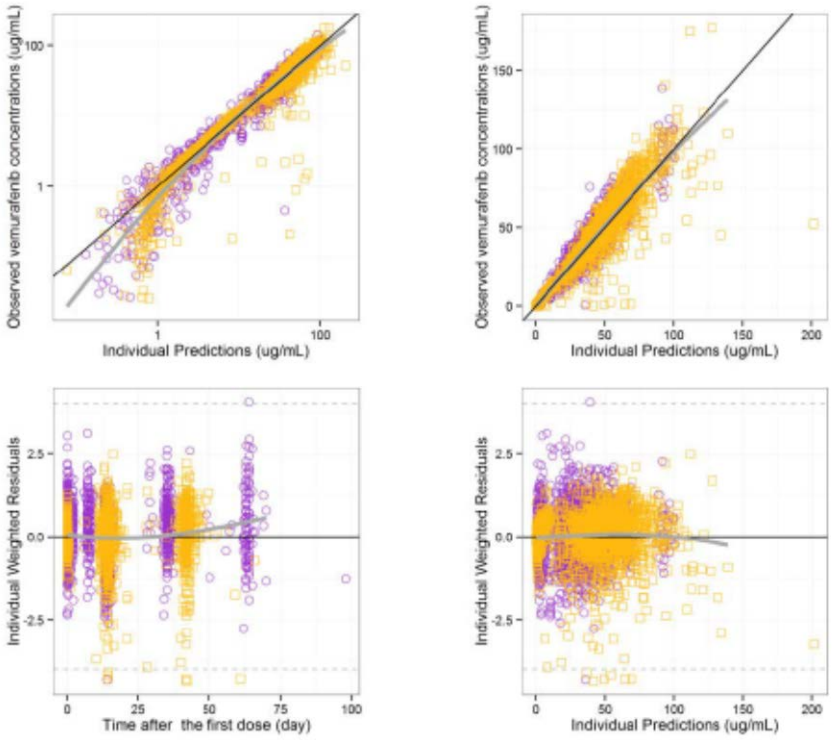

Figure 22: Goodness of fit plots from the final population PK model of vemurafenib. Source: Figure 4.2.2-1 of population PK report

Table 44: Results of reviewer's multivariate analysis including data from both cobimetinib plus vemurafenib and placebo plus vemurafenib arms.

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Label
cobiauc		1	0.0006314	0.00116	0.2957	0.5866	1.001	0.998 1.003	
trta	VEMURAFENIB + GDC0973	1	-0.83223	0.25786	10.4163	0.0012	0.435	0.262 0.721	trta VEMURAFENIB + GDC0973
sex	F	1	-0.41864	0.12976	10.4081	0.0013	0.658	0.510 0.848	sex F
region	Australia/New Zealand/Others	1	-0.49991	0.25352	3.8882	0.0486	0.607	0.369 0.997	region Australia/New Zealand/Others
region	Europe	1	0.12858	0.19891	0.4179	0.5180	1.137	0.770 1.679	region Europe
mstage	IIIC	1	-0.88697	0.31345	8.0070	0.0047	0.412	0.223 0.761	mstage IIIC
mstage	M1A	1	-0.79206	0.19918	15.8137	<.0001	0.453	0.307 0.669	mstage M1A
mstage	M1B	1	-0.64764	0.17995	12.9527	0.0003	0.523	0.368 0.745	mstage M1B
becog	0	1	7.65604	246.25746	0.0010	0.9752	2113.371	0.000 8.7E212	becog 0
becog	1	1	7.90622	246.25747	0.0010	0.9744	2714.109	0.000 1.11E213	becog 1
scrnldh	Elevated	1	0.41666	0.12058	11.9398	0.0005	1.517	1.198 1.921	scrnldh Elevated
vemuauc		1	0.00325	0.01047	0.0964	0.7562	1.003	0.983 1.024	

4.2 PHYSIOLOGICALLY-BASED PHARMACOKINETIC REVIEW

Physiological-based Pharmacokinetic Modeling Review Memo

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 206192
Drug Name	Cobimetinib
Proposed Indication	Unresectable or metastatic melanoma with BRAF V600 mutations in combination with vemurafenib
Clinical Division	DOP2
PBPK Consult Request	Ruby Leong, PharmD
Primary PBPK Reviewer	Ping Zhao, PhD
Secondary PBPK Reviewer	Hong Zhao, PhD
Sponsor	Genentech

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1. OBJECTIVES

The main objective of this review is to evaluate the adequacy of sponsor's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the DDI potential of cobimetinib as a victim of the CYP3A metabolic pathway.

To support its conclusions the sponsor provided the following PBPK modeling and simulation report and updates:

1. Assessment of drug-drug interaction potential between cobimetinib and CYP3A4 inhibitors/inducers using a physiologically-based pharmacokinetic (PBPK) approach [**1**]
2. Response to initial FDA request for information. 13 February 2015 [**2**]
3. Response to FDA request for information. 01 April 2015 [**3**]
4. Response to FDA request for information. 07 April 2015 [**4**]

2. BACKGROUND

2.1. Regulatory history on PBPK submission

Cobimetinib (GDC-0973, XL518 and RO5514041) is an inhibitor of mitogen-activated protein kinases (MEK1 and MEK2) for the treatment of cancers. In the current NDA submission (NDA206192), sponsor seeks approval of combined use of cobimetinib and vemurafenib (Zelboraf®) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations [**5**].

The recommended dose of cobimetinib is 60 mg orally once daily (q.d.) (3 film-coated tablet of 20 mg) for 21 consecutive days followed by a 7-day rest period, in combination with vemurafenib [**6**]. In a drug-drug interaction (DDI) trial, a strong CYP3A inhibitor itraconazole (ITZ) increased cobimetinib AUC by approximately 7-fold. In the absence of additional clinical data, the sponsor predicted the magnitudes of cobimetinib exposure change in the presence of various CYP3A modulators using PBPK (**Figure 23**, [**1**]), and suggested that "cobimetinib may be coadministered with weak inhibitors while caution should be exercised when administering with moderate inducers and inhibitors" [**5**]. In sponsor's proposed product label, it states that "(b) (4) [**6**].

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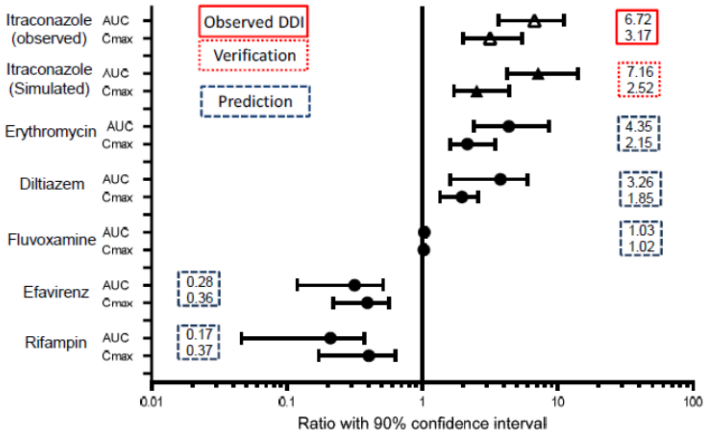
Figure 23. Observed and simulated cobimetinib AUC and Cmax ratios[a] with 90% confidence intervals of various CYP3A4 inhibitors and inducers (Figure 15, ref [1])



[a] AUC or C_{max} Ratios: Geometric mean ratio of $AUC_{144\text{-}1656(h)}$ or C_{max} of victim drug (cobimetinib) in the presence of inhibitor/inducer to $AUC_{144\text{-}1656(h)}$ or C_{max} in the absence of inhibitor/inducer.

On Feb 4, 2015, an information request was sent to the sponsor to conduct additional simulations of untested drug-drug interaction scenarios and to submit model files (02042015IR, **Appendix 6.2.1**). Sponsor submitted model files and response on Feb 17, 2015 (dated Feb 13, 2015) [2]. On March 25, 2015 and Apr 3, 2015, two information requests were sent for the sponsor to address cobimetinib PK differences between healthy subjects and cancer patients, and to conduct simulations to evaluate the effect of chronic and short term use of moderate CYP3A modulators on steady state PK of cobimetinib (03252015IR and 04032015IR, **Appendix 6.2.2** and **6.2.3**). On April 1 and Apr 7, 2015, sponsor submitted responses to these IRs [3,4].

This review evaluates the adequacy of sponsor's cobimetinib PBPK model to predict the DDI potential, and provides dosing recommendations based on the predicted effect of moderate CYP3A inhibitors on cobimetinib PK.

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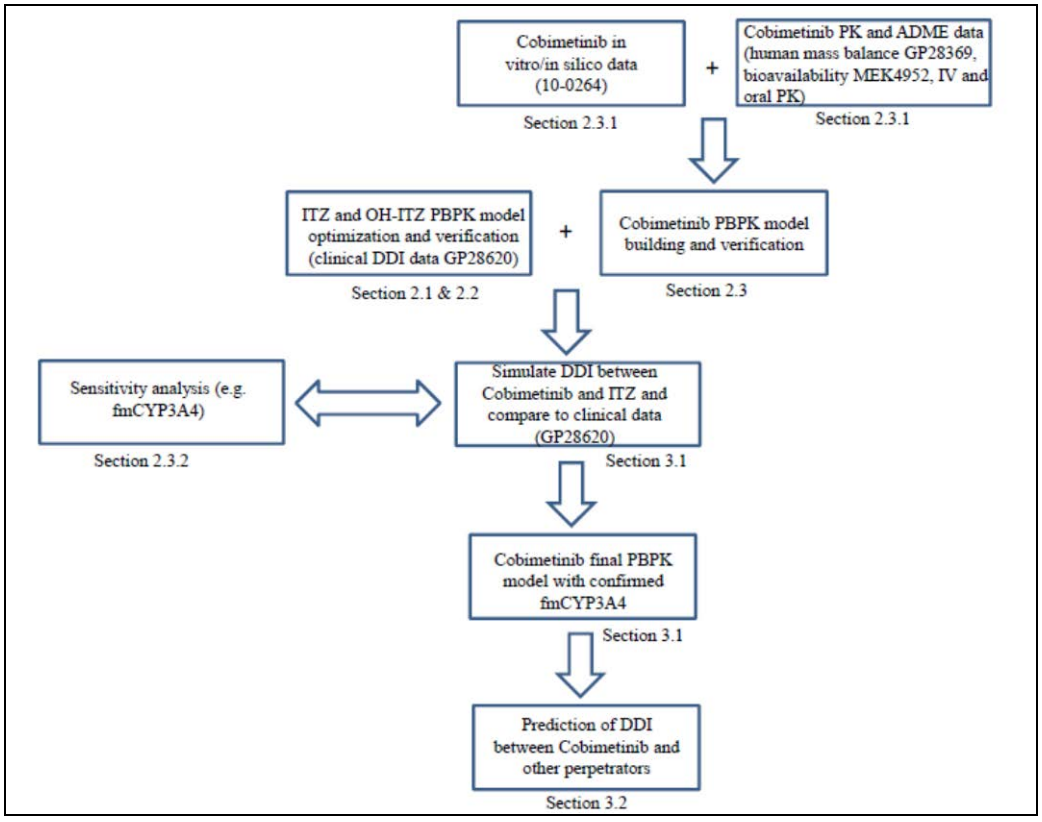
3. *METHODS*

3.1. Model Development

A population based PBPK software Simcyp® (V13, release 1, Sheffield, UK) [7,8] was used by the sponsor to develop cobimetinib PBPK model. Parameters and their sources for cobimetinib are summarized in **Appendix Table 48**. Unless otherwise stated, all simulations were conducted in Software's built-in "Sim-Healthy volunteer" population and ten (10) trials of varying subjects (10 or 15) were simulated for each dosing regimen (age range 18-52 years). Ratio of female subjects in these simulations was reported to be 0.34 in original PBPK study report [1].

Figure 24 shows a workflow of the development and application of PBPK model for cobimetinib. Except for CYP3A contribution ($f_{m,CYP3A4}$), both in vitro data ([9,10]), human PK data from absolute bioavailability study (with intravenous and oral PK data, [11]) and mass balance study [12] were used to construct cobimetinib model in healthy subjects. A full PBPK distribution model was assumed according to Rodgers et al [13], a universal scaler of 3.1 on tissue partitioning coefficient (Kp) was applied to capture observed steady state volume of distribution ($V_{d,ss}$) [10]. In vitro and in vivo results suggested that cobimetinib is extensively metabolized with both CYP3A and UGT2B7 contributing to hepatic metabolism [12, 14]. Sponsor further used results of clinical DDI study [15] to optimize $f_{m,CYP3A4}$ in the model.

Figure 24. Development and application of PBPK model for cobimetinib (Figure 1 of [1])



Before using perpetrator models for ITZ and its inhibitory metabolite hydroxyl-itraconazole (OH-ITZ), sponsor optimized software's default "Sim-Itraconazole.cmp", "Sim-OH-Itraconazole.cmp", as well as probe substrate model for midazolam (**Appendix Table 49** and **Appendix Table 50**, [**16-19**]). These optimization processes intended to capture PK profiles of ITZ and OH-ITZ as well as PK profiles of midazolam. The simulation design followed that of Olkkola et al [**19**] using 10 trials with 10 subjects per trial in healthy subjects (age 19−26 years).

Sensitivity analyses were performed by the sponsor to evaluate a range of values of $f_{m,CYP3A4}$ and a range of values of the hypothetical blood flow in intestine (Q_{gut}, **Appendix Table 48**) on the predicted magnitude of DDI caused by ITZ. The Q_{gut} predicted by the software based on permeability data appears to be reasonable although predicted DDI magnitude is sensitive to this parameter. The value of 0.78 was chosen for $f_{m,CYP3A4}$ in final cobimetinib PBPK model. In response to FDA's 02042015IR, the sponsor provided simulated mean baseline cobimetinib exposure values (Cmax and AUC without ITZ) at different $f_{m,CYP3A4}$ [**2**].

3.2. Model Application

Sponsor used cobimetinib models to predict the effect of CYP3A modulators for scenarios that have not been tested through clinical trials (**Table 45**).

Perpetrator models of moderate (diltiazem and erythromycin) and weak (fluvoxamine) CYP3A inhibitors within software library were directly used ("Sim-diltiazem.cmp", "Sim-desmethyldiltiazem.cmp", 'Sim-erythromycin.cmp", and "SV-fluvoxamine.cmp"). The inhibitors were administered daily for 21 days and a single dose of 60 mg cobimetinib was given on Day 7. The end-time of trial was set to Day 70 to capture AUC infinity of cobimetinib in the simulations. To simulate the effect of rifampin on cobimetinib PK, sponsor used default rifampin model "Sim-rifampicin.cmp" (V13.1, [**1**]) and a model with a higher CYP3A maximal induction effect ($I_{nd,max}$) of 16 (default $I_{nd,max}$ =8) in a newer version of SimCYP software ("Sim-rifampicin.cmp" of V14.1, [**2**]). To simulate the effect of moderate CYP3A inducer efavirenz, sponsor developed efavirenz model using literature-reported parameters [**20**,**21**] (**Appendix Table 51**). Tissue distribution for efavirenz was calculated according to Poulin and Theil [**22**]. Inducers were administered daily for 21 days and a single dose of 60 mg cobimetinib was co-administered with an inducer on Day 7. The end-time of trial was set to Day 70 to capture AUC infinity of cobimetinib in the simulation.

Based on FDA's 04032015IR, sponsor used an alternative system model developed by Cheeti et al. [**23**], and further reduced intestinal CYP3A content by 95% in this model (cancer patient population). Simulation of the effect of moderate CYP3A inhibitor erythromycin on cobimetinib PK after multiple dosing was conducted using cobimetinib PBPK model developed above and virtual cancer patient population.

Sponsor conducted the following simulations of the effect of moderate CYP3A modulators on cobimetinib PK after single or multiple dosing in healthy subjects and cancer patients (**Table 45**).

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Table 45. Simulation study design for drug-drug interaction scenarios with cobimetinib as CYP3A substrate

Simulation	Modulator name	Cobimetinib dosing	Modulator dosing	Reference
In healthy subjects				
1	Erythromycin	60 mg single dose on day 7	500 mg three times a day (t.i.d.)	[1]
2	Diltiazem	60 mg single dose on day 7	120 mg twice daily (b.i.d.)	[1]
3	Fluvoxamine	60 mg single dose on day 7	100 mg once daily (q.d.)	[1]
4	Rifampicin	60 mg single dose on day 7	600 mg q.d.	[1]
5	Efavirenz	60 mg single dose on day 7	600 mg q.d.	[1]
6	Erythromycin	60 mg q.d. for 35 days, PK evaluated on day 21	500 mg t.i.d. for 35 days	[3]
7	Erythromycin	60 mg q.d. for 28 days, PK evaluated on day 28	500 mg t.i.d. for 14 days starting on day 15	[3]
8	Efavirenz	60 mg q.d. for 21 days, PK evaluated on day 21	600 mg q.d. for 21days	[3]
9	Efavirenz	60 mg q.d. for 28 days, PK evaluated on day 28	600 mg q.d. for 14 days starting on day 15	[3]
In cancer patients				
10	Erythromycin (moderate inhibitor), 500 mg b.i.d.	60 mg q.d. 21 days	21 days	[4]
11		20 mg q.d. 21 days	21 days	[4]
12		60 mg q.d. 21 days	14 days staring day 8	[4]
13		60 mg q.d. 7 days, 20 mg q.d. starting day 8	14 days staring day 8	[4]
16		60 mg q.d. 21 days	7 days staring day 15	[4]
		60 mg q.d. 14 days, 20 mg q.d. starting day 15	7 days staring day 15	[4]
		60 mg q.d. 14 days, interrupt on day 15	7 days staring day 15	[4]

4. RESULTS

4.1. Can Cobimetinib PBPK Model Predict The Effect of CYP3A Modulation on Cobimetinib Exposure in Healthy Subjects?

Yes. Two factors are critical for a substrate PBPK model to predict the effect of CYP inhibition or induction on its PK: quantitative determination of the contribution of the CYP pathway that is modulated by co-medication (e.g., assumption of $f_{m,CYP3A}$ for cobimetinib), and capability of the model to predict the PK profile under different dosing regimens.

PBPK model for healthy subjects reasonably describes the observed PK profiles of single dose

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cobimetinib in healthy subjects (**Appendix Figure 54**, [**1**]).

The $f_{m,CYP3A4}$ in final cobimetinib PBPK model is 0.78. The value was obtained via sensitivity analyses based on DDI study with ITZ [**15**]. Therefore, ITZ data did not serve as an independent dataset to verify initial cobimetinib model. This $f_{m,CYP3A}$ value appears to be plausible, because lower values not only under-predicted the magnitude of DDI by ITZ, but also overpredicted cobimetinib exposure, because a greater fraction of the dose would escape gut metabolism (lower magnitude of DDI, higher predicted AUC, Cmax and Fg values, **Appendix Table 52** and **Appendix Table 53**). **Figure 25** shows that the final cobimetinib PBPK model with $f_{m,CYP3A4}$ of 0.78 reasonably describes cobimetinib PK alone or in combination with ITZ.

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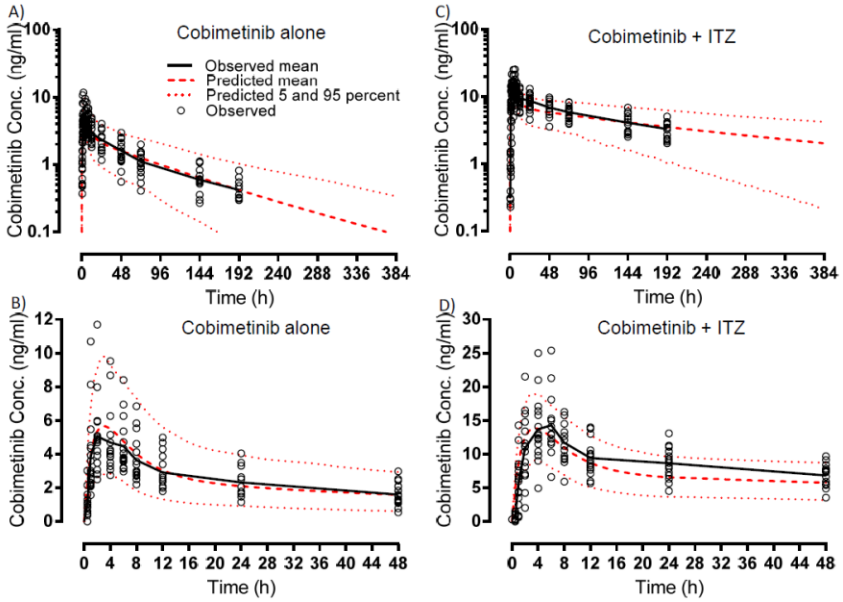
Figure 25. Observed and PBPK simulated plasma concentration-time profile of cobimetinib following oral administration of 200 mg itraconazole solution once daily for 14 days and a single oral dose of 10 mg cobimetinib on day 4. A and C: 0 to 384 hours cobimetinib alone or with co-administration of itraconazole, respectively (semi-log scale); B and D: 0 to 48 hours cobimetinib alone or with co-administration of itraconazole, respectively (linear scale)

Source: Figure 14 of [1]. A total of 10 trials with 15 subjects per trial in the age range of 18−52 years (proportion of female: 0.34)



4.2. Can Cobimetinib PBPK Predictions Be Used to Support Dose Recommendations of Cobimetinib in Cancer Patients Concomitantly Taking a CYP3A Modulator?

Yes. PBPK model of cobimetinib is considered adequate in predicting the effect of CYP3A modulators on cobimetinib PK.

The simulated magnitudes of DDI by various CYP modulators on single oral dose of cobimetinib (60 mg) are summarized in **Table 46**. Moderate CYP3A inhibitors caused 3-4 fold increase in cobimetinib AUC, and a weak inhibitor does not seem to affect cobimetinib exposure. With regard to CYP3A inducers, both strong and moderate inducers may decrease cobimetinib AUC by more than 70%.

Table 46. PBPK predicted geometric mean ratios (AUC and C_{max}, with and without CYP3A modulator) of cobimetinib after single 60 mg oral dose in healthy subjects.

	Interaction mechanism	AUC Ratio	Cmax Ratio	Source
CYP3A inhibitor				
Erythromycin (500 mg t.i.d.)	Moderate TDI [a]	4.35	2.15	Table 8, [1]
Diltiazem (120 mg b.i.d.)	Moderate TDI [a]	3.26	1.85	Table 8, [1]
Fluvoxamine (100 mg q.d.)	Weak reversible	1.03	1.02	Table 8, [1]
CYP3A inducer				
Rifampin[b] (600 mg q.d.)	Strong	0.17	0.37	Table 9, [1]
Rifampin[c] (600 mg q.d.)	Strong	0.08	0.24	[2]
Efavirenz (600 mg q.d.)	Moderate	0.28	0.36	Table 9, [1]

[a] TDI: Time-dependent inhibitor; [b] Using default perpetrator model (V13.1, [1]). [c] Using model with stronger induction effect (V14.1, [2]).

4.3. What Are the Predicted Effect of Short-term and Chronic Dosing of CYP3A Modulator on Cobimetinib PK After Multiple Dosing in Cancer Patients?

The dose-adjusted cobimetinib AUC was approximately 2-fold higher in cancer patients than in healthy subjects, and sponsor hypothesized that a decreased gut metabolism in cancer patients is responsible for the lower apparent CL [**4**,**5**]. This hypothesis is in part supported by similar cobimetinib elimination half-life in patients and healthy subjects (assuming similar distribution as well as systemic elimination between patients and healthy subjects) and a near complete oral absorption of cobimetinib observed in human mass balance study [**5**]. As such, sponsor adopted and modified a system model developed for oncology patients [**23**] by reducing gut CYP3A content. When drug model developed above is directly used, a 95% decrease in gut CYP3A content in this virtual population appears sufficient to describe cobimetinib PK in cancer patients (**Appendix Figure 55**).

Table 47 summarizes PBPK model prediction of the effect of moderate CYP3A modulators on cobimetinib PK after multiple oral dosing. Effects of a short (e.g. 7-14 days) or a long (>14 days) duration of co-administration with a CYP3A modulator in both healthy subjects and cancer patients were simulated. First, the simulated magnitude of DDI was greater when the duration of modulator is longer. Second, the simulated magnitude of DDI was greater in healthy subjects than in patients (e.g., day-21 PK of cobimetinib under conditions when cobimetinib and erythromycin are co-administered for 21 days). Third, in patients receiving short-term erythromycin treatment (7 or 14 days), reducing cobimetinib dose to 20 mg q.d. when erythromycin is initiated, appears to result in a cobimetinib exposure on the last day of erythromycin treatment similar to the condition when cobimetinib is administered alone (**Figure 26**).

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Table 47. PBPK predicted geometric mean ratios (AUC and C_{max}, with and without CYP3A modulator) of cobimetinib after 60 mg oral dose once daily.

Cobimetinib	Modulator	AUC Ratio	Cmax Ratio
In healthy subjects [3]			
60 mg q.d. for 35 days, PK evaluated on day 21	Erythromycin 500 mg t.i.d. for 35 days	4.27	3.76
60 mg q.d. for 28 days, PK evaluated on day 28	Erythromycin 500 mg t.i.d. for 14 days starting on day 15	3.86	3.43
60 mg q.d. for 21 days, PK evaluated on day 21	600 mg q.d. for 21days	0.27	0.29
60 mg q.d. for 28 days, PK evaluated on day 28	600 mg q.d. for 14 days starting on day 15	0.30	0.32
In patients [4] (Cobimetinib PK evaluated on day 21, erythromycin 500 mg t.i.d.)			
60 mg q.d. 21 days	Erythromycin 21 days	2.40	2.09
20 mg q.d. 21 days	Erythromycin 21 days	2.40	2.10
60 mg q.d. 21 days	Erythromycin 14 days staring day 8	2.22	1.95
60 mg q.d. 7 days, 20 mg q.d. starting day 8	Erythromycin 14 days staring day 8	2.34	2.06
60 mg q.d. 21 days	Erythromycin 7 days staring day 15	1.79	1.60
60 mg q.d. 14 days, 20 mg q.d. starting day 15	Erythromycin 7 days staring day 15	1.86	1.67
60 mg q.d. 14 days, interrupt on day 15	Erythromycin 7 days staring day 15	1.24	NA

NA: Not applicable

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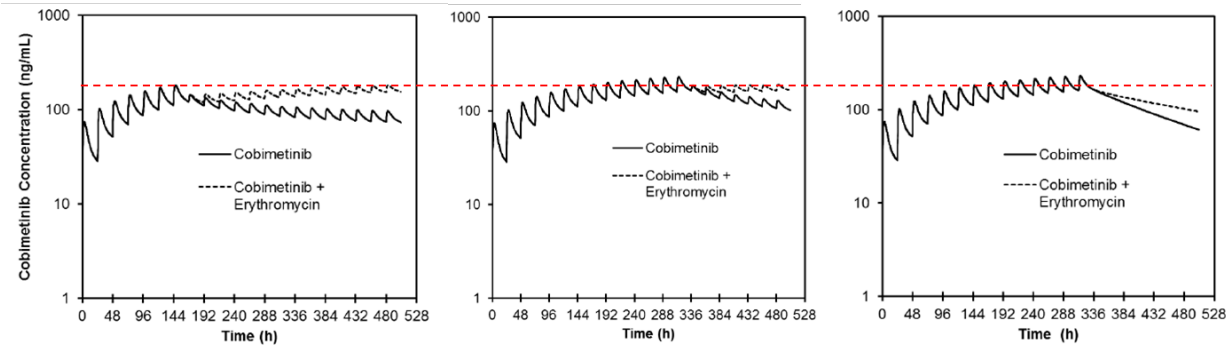
Figure 26. Simulated mean cobimetinib plasma concentration at 60 mg q.d. and erythromycin 500 mg t.i.d. Left, cobimetinib dose is reduced to 20 mg q.d. when erythromycin treatment begins on day 8 for 14 days; middle, cobimetinib dose is reduced to 20 mg q.d. when erythromycin treatment begins on day 15 for 7 days; and right, cobimetinib dose is interrupted on day 15 when erythromycin treatment begins on day 15 for 7 days. Red dashed line approximates trough cobimetinib concentration achieved at steady state (e.g. on day 21) without inhibitor.

Source: Figures 5, 7and 8, reference [4]



5. *CONCLUSION*

Sponsor's PBPK model of cobimetinib is considered sufficient to predict steady state cobimetinib PK in patients co-administered with CYP3A modulators. In healthy subjects, moderate CYP3A inhibitors were predicted to increase cobimetinib exposure (AUC) after single dose by 3- to 4-fold; weak inhibitor has no effect on cobimetinib exposure; strong and moderate inducers can reduce cobimetinib exposure (AUC) by more than 70%. After multiple dosing of cobimetinib in cancer patients, co-administration with moderate CYP3A inhibitor erythromycin was predicted to increase cobimetinib exposure by approximately 4-fold and 2-fold in healthy subjects and cancer patients (assuming significantly reduced gut metabolism), respectively. In patients, the inhibitory effect of short-term use of erythromycin (e.g. 7 or 14 days) can be alleviated by reducing cobimetinib dose to 20 mg q.d. after the initiation of erythromycin treatment.

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6. *APPENDICES*

6.1. Abbreviations

ADAM, Advanced dissolution, absorption, and metabolism model; ADME, absorption, distribution, metabolism, and excretion; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; b.i.d., twice daily dosing; B/P, blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; DDI: drug-drug interaction; F, bioavailability; f_a, fraction absorbed; F_g, fraction that escapes intestinal metabolism; f_{mj}, fraction of total clearance mediated by j CYP isoform or renal elimination; f_{up}, fraction unbound in plasma; $f_{u,gut}$, apparent unbound fraction in enterocytes; GI: gastrointestinal; γ, Hill coefficient; $I_{nd,max}$, maximal fold induction; $I_{nd,50}$, concentration causing half-maximal fold induction; ITZ and OHITZ, itraconazole and hydroxyl-itraconazole; k_a, first order absorption rate constant; K_i, reversible inhibition constant; $LogP_{o:w}$, logarithm of the octanol-water partition coefficient; MEK, mitogen-activated protein kinases; NA, not applicable; NDA: new drug application; P_{app}, apparent passive permeability; $P_{eff,man}$, effective passive permeability in man; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; q.i.d., four times a day dosing; q.o.d., once every other day; Q_{gut}, a hypothetical flow term for the intestine absorption model; T_{max}: time at maximal concentration in plasma; t.i.d., three times a day; $V_{d,ss}$, volume of distribution at steady state.

6.2. Information Request

6.2.1 Clinical Pharmacology Feb 04, 2015 (02042015IR)

We conducted initial review of the PBPK study report "Assessment of Drug-Drug Interaction Potential between Cobimetinib and CYP3A4 Inhibitors/Inducers using a Physiologically-Based Pharmacokinetic (PBPK) Approach." Please address the following:

1. You used clinical DDI data with itraconazole (Study GP28620) and sensitivity analysis to inform fm,CYP3A of the cobimetinib model.
   a. Besides simulation of exposure ratios, provide simulated Cmax, AUC, and Fg of cobimetinib after oral administration (Study MEK4952g and no-inhibitor arm of Study GP28620) under different fm values and Qgut values used in Table 2.
   b. Provide $f_{m,CYP3A}$ based on in vitro data.
2. Update your simulation of the effect of rifampin on the exposure of cobimetinib using a modified rifampin PBPK model according to SimCYP's recent update with regard to induction potency.
3. Provide the model files used to generate the final PBPK simulations (e.g., drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

Please submit this information by Feb 17, 2014.

6.2.2 Clinical Pharmacology Mar 25, 2015 (03252015IR)

Our PBPK Reviewer has the following request for information. Please provide your response to me via email by April 1, 2015 if possible, and follow that with a formal

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submission to the NDA.

It appears that cobimetinib exposure is generally higher in cancer patients than in healthy subjects based on the data provided in Table 14 in your Summary of Clinical Pharmacology Studies included in the NDA.

a. Submit your justification to support that the PBPK model developed with data from healthy subjects allows the prediction for the magnitude of cobimetinib exposure change by concomitant use of CYP3A modulators in cancer patients.

b. Use cobimetinib and CYP3A modulator models to simulate the following scenarios in patients:

i. Chronic use of a moderate CYP3A inhibitor (e.g., erythromycin 500 mg three times a day [TID] starting on day 1) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.

ii. Short term use of a moderate CYP3A inhibitor (e.g., when cobimetinib exposure has reached steady-state, coadminister erythromycin 500 mg TID for another 14 days) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.

iii. Chronic use of a moderate CYP3A inducer (e.g., efavirenz 600 mg once daily [QD] starting on day 1) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.

iv. Short term use of a moderate CYP3A inducer (e.g., when cobimetinib exposure has reached steady-state, coadminister efavirenz 600 mg QD for another 14 days) on cobimetinib steady-state exposure in cancer patients administered 60 mg daily doses.

Provide the model files used to generate the final PBPK simulations (e.g., drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Submit software specific excel files such as parameter estimation data files and simulation outputs as MS Excel files. Provide study report(s) as PDF files (incorporate screenshots if required).

6.2.3 04032015IR

Based on your assumption of reduced intestinal first-pass metabolism of cobimetinib in cancer patients:

1. Establish an alternative PBPK model that can approximate an increased Fg of Cobimetinib. This can be accomplished by simulating cobimetinib PK using your current drug model in healthy subjects with reduced gut CYP3A content.

2. Use the alternative PBPK model to simulate the following scenarios of the effect of a moderate CYP3A inhibitor (e.g., erythromycin 500 mg three times a day [t.i.d.]) on cobimetinib exposure:

a. Administer cobimetinib (60 mg once daily, q.d.) and inhibitor for 21 days

b. Administer cobimetinib (20 mg q.d.) and inhibitor for 21 days

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c. Administer cobimetinib (60 mg q.d.) for 21 days, initiate inhibitor dosing on day 8 for 14 days

d. Administer cobimetinib (60 mg q.d.) for 7 days, reduce cobimetinib dose to 20 mg q.d. and initiate inhibitor dosing on day 8 for 14 days

e. Administer cobimetinib (60 mg q.d.) for 21 days, initiate inhibitor dosing on day 15 for 7 days

f. Administer cobimetinib (60 mg q.d.) for 14 days, reduce cobimetinib dose to 20 mg q.d. and initiate inhibitor dosing on day 15 for 7 days

g. Administer cobimetinib (60 mg q.d.) for 14 days, interrupt cobimetinib dosing and initiate inhibitor dosing on day 15 for 7 days

For each scenario, include simulated PK profiles of cobimetinib in the absence and in the presence of inhibitor, and summary of simulation results.

6.3. Appendix Tables and Figures

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Appendix Table 48. Physicochemical parameters of cobimetinib PBPK model (Source: Table 4, of ref [1])

Parameters	Value	Methods/References
Mol Weight (g/mol)	531.31	Investigator's_Brochure_RO5185426_GDC-0973
log $P_{o:w}$	3.81	Measured (Investigator's_Brochure_RO5185426_GDC-0973)
pK_a	8.85	Measured (Investigator's_Brochure_RO5185426_GDC-0973)
Compound Type	Monoprotic base	Investigator's_Brochure_RO5185426_GDC-0973
B/P	0.976 [a]	Measured value from in vitro experiments: Choo et al. 2012, Table 2
$f_{u,p}$	0.0583 [b]	Measured value from in vitro experiments: Choo et al. 2012, Table 1
Absorption	First-order absorption model	
$f_{u,gut}$	1	Simcyp default
Q_{gut}	1.45	Simcyp predicted
P_{app} (10^{-6} cm/s)	1.39	Measured value from MDCK cell lines; Choo et al. 2012, page 922
P_{app} scalar	1.07 [c]	Use verapamil P_{app} of 15.2 measured in-house
F_a	1 (20% CV)	Human mass balance study (GP28369)
K_a (hr^{-1})	0.35	Estimated from the cobimetinib alone arm of clinical DDI study
Distribution	Full PBPK model	
V_{ss} (L/kg)	15.3	Simcyp prediction (method 2) with adjusted K_p scalar to match observed V_{ss}
K_p scalar	3.1	Optimized to match observed V_{ss} from phase I PK study
Elimination		
CL_{iv} (L/hr)	14.5	From PK analysis of phase I bioavailability study (MEK4952g)
CL_R (L/hr)	0.35	Back-calculated from results of human mass balance study (CL_R = 3% total CL)
CYP3A4 CL_{int} (µL/min/pmol)	0.445 [d]	Calculated using Simcyp Retrograde Model to achieve fmCYP3A4 of 78% of total CL (14.5L/h)
Additional CL in HLM (µL/min/mg protein)	12.5 [d]	Calculated by Simcyp retrograde model to account for 22% of total CL

[a] Mean B/P at three cobimetinib concentrations (1, 5, and 10 µM)

[b] Mean f_u at three cobimetinib concentrations (1, 5, and 10 µM)

[c] P_{app} reference: Verapamil, scalar 1.07 (based on in-house data for verapamil)

[d] In the retrograde model, the contribution of CYP3A4 to hepatic metabolism was set to be 83% in order to account for 78% of total CL (geometric mean value of the simulated 10 × 15 healthy volunteer population).

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Appendix Table 49. Summary of key input parameters of ITZ and OH-ITZ models (Table 1, [1])

Parameters	ITZ Value	Methods/References	OH-ITZ Value	Methods/References
Mol Weight (g/mol)	705.6	Library [a]	721.7	Library
log $P_{o:w}$	5.66	Library	4.78	Library
pK_a	3.7	Library	2.53/4.91	Library
B/P	0.58	Library	1	Library
$f_{u,p}$	0.016	Library	0.0212	Library
$f_{u,gut}$	0.016	Library	1	Library
P_{app} (10^{-6} cm/s)	57.1	Library	NA	
F_a	1	Library	NA	
K_a (hr^{-1})	1.6	Optimized [b]	NA	
T_{lag} (h)	0.3	Optimized [c]	NA	
K_p scalar	0.032	Optimized [d]	NA	
V_{ss} (L/kg)	15.2	Full-PBPK, predicted [d]	0.5	Minimal-PBPK, user input for best fit [d]
CYP3A4 CL_{int} (µL/min/pmol)	2.44	Optimized [e]	NA	
$V_{max,3A4}$ (pmol/min/pmol)	NA		0.16	Library
$K_{m,u,3A4}$ (µM)	NA		0.027	Library
K_i on CYP3A4 (µM)	0.0013	Library	0.0144	Library
$f_{u,mic}$ CYP3A4	1	Library	1	Library

[a] Refers to Simcyp default compound library (version 13).

[b] Literature value (Waterhouse et al. 2005). K_a = 0.945 hr^{-1} for the oral solution was further optimized to match the observed T_{max} and C_{max}.

[c] Optimized to match simulated result to clinical observed data.

[d] Reported V_{ss} is 10.7 L/kg for ITZ following IV infusion (Heykants et al. 1989), which is much lower than the default value in Simcyp. Kp scalars was adjusted to obtain predicted V_{ss} for ITZ (15.2 L/kg) and user input V_{ss} for OH-ITZ (0.5 L/kg) was used to best fit simulated PK profiles with observed one.

[e] Reported CL_{iv} is 18.7 L/h for ITZ following IV infusion (FDA CDER 1999), which is lower than Simcyp default value. CL_{iv} was adjusted to 15 L/hr to best fit the observed ITZ PK profile obtained from in-house study. CYP3A4 CL_{int} was back-calculated by the Retrograde Model of Simcyp (100% of total clearance contributed by CPY3A4 was assumed).

Appendix Table 50. Modified parameters in midazolam model (Table 2, [1])

Parameters		Simcyp Default File	Modified File	Method
K_a (1/h)		3	4.5	Best fit
V_{max} (pmol/min/pmol of isoform)	Pathway 1-OH	5.23	6.8	Best fit
	Pathway 4-OH	5.2	6.76	Best fit

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Appendix Table 51. Input parameters for efavirenz (Output file submitted to FDA: efavirenz-ddi-output.xlsx)

Parameter (unit)	value
Mol Weight (g/mol)	315.670
log P	4.600
Compound Type	Neutral
B/P	0.740
fu	0.029
Absorption Model	CAT
fu(Gut)	1.000, predicted
Peff,man Type	Regional
Permeability (10^{-6} cm/s)	8.920, Caco-2 cell under passive&Active condition, with Apical:Basolateral pH of 6.5:7.4
Distribution Model	Full PBPK Model according to Poulin and Theil,
Predicted Kp values	Adipose 7.194; Bone 4.491; Brain 4.115; Gut 3.249; Heart 1.013; Kidney 1.561; Liver 1.970; Lung 0.365; Muscle 1.585; Skin 1.931; Spleen 1.590; Pancreas 2.660
Kp Scalar	0.300
Elimination	
fu mic (microsomal free fraction)	0.300
CLint,CYP3A4 (µL/min/pmol of isoform)	0.007
CLint, CYP3A5 (µL/min/pmol of isoform)	0.030
CLint,CYP1A2 (µL/min/pmol of isoform)	0.070
CLint,CYP2B6 (µL/min/pmol of isoform)	0.580
CLint,CYP2A6 (µL/min/pmol of isoform)	0.080
CL R (L/h)	0.000
CYP induction	
Ind max, CYP2B6 (% CV)	5.760 (13.700)
MIA (pmol/mg microsomal protein), CYP2B6	247.164
Ind C50, CYP2B6 (µM) (% CV)	0.820 (71.900)
fu inc	1.000
$\gamma_{,CYP2B6}$ (Hill coefficient)	1.000
Ind max, CYP3A4 (% CV)	6.450 (18.600)
MIA (pmol/mg microsomal protein), CYP3A	1477.693
Ind C50, CYP3A4 (µM) (% CV)	3.930 (52.500)
fu inc	1.000
γ_{CYP3A4}	1.000

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Appendix Table 52. Simulated population representative Cmax ratio, AUC ratio, and Fg of cobimetinib with and without co-administration of ITZ (Source Table 5, [1])

	fmCYP3A4 of Cobimetinib				
	0.25	0.5	0.78	0.9	0.95
AUC ratio [a]	1.79	3.23	6.81	10.42	12.50
C_{max} ratio [b]	1.44	1.92	2.49	2.78	2.89
F_g	0.72	0.57	0.46	0.42	0.41

Note: All simulations were conducted using Population Representative (n = 1 Healthy Volunteer).

[a] AUC ratio: ratio of $AUC_{72.5\text{-}1656(h)}$ of cobimetinib in the presence of ITZ to $AUC_{72.5\text{-}1656(h)}$ in the absence of ITZ. The observed AUC ratio (geometric mean) is 6.72.

[b] C_{max} ratio: ratio of C_{max} of cobimetinib in the presence of ITZ to C_{max} in the absence of ITZ. The observed C_{max} ratio (geometric mean) is 3.17.

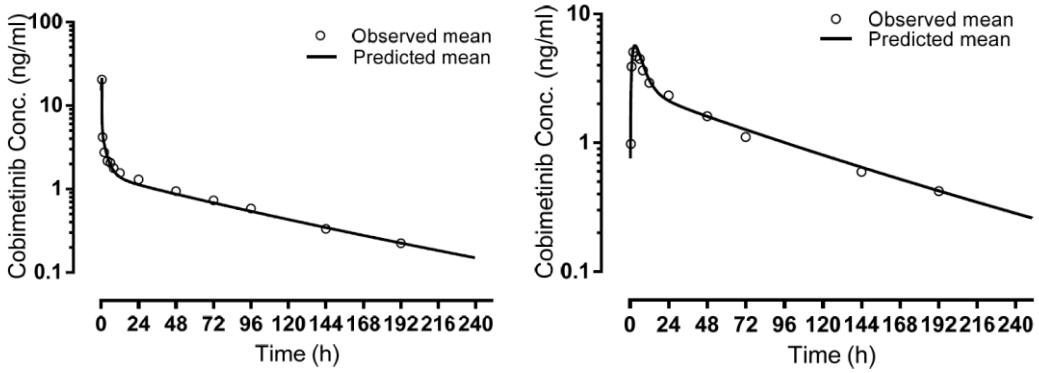
Appendix Table 53. Simulated population representative Cmax, AUC, and Fg of cobimetinib after 10 mg single oral dose (Source Table 1, [2])

$f_{m,CYP3A4}$ (%)	**0.25**	**0.50**	**0.78***	**0.90**	**0.95**
C_{max} (ng/mL)	9.1	7.1	5.7	5.3	5.2
$AUC_{0\text{-}inf}$ (h*ng/mL)	426.0	334.0	266.0	249.0	242.0
F_G (%)	0.72	0.57	0.45*	0.42	0.41

*Simulation output was not archived for 78% $f_{mCYP3A4}$; data was generated from a new simulation, which resulted in a slight change in predicted F_G (0.45).

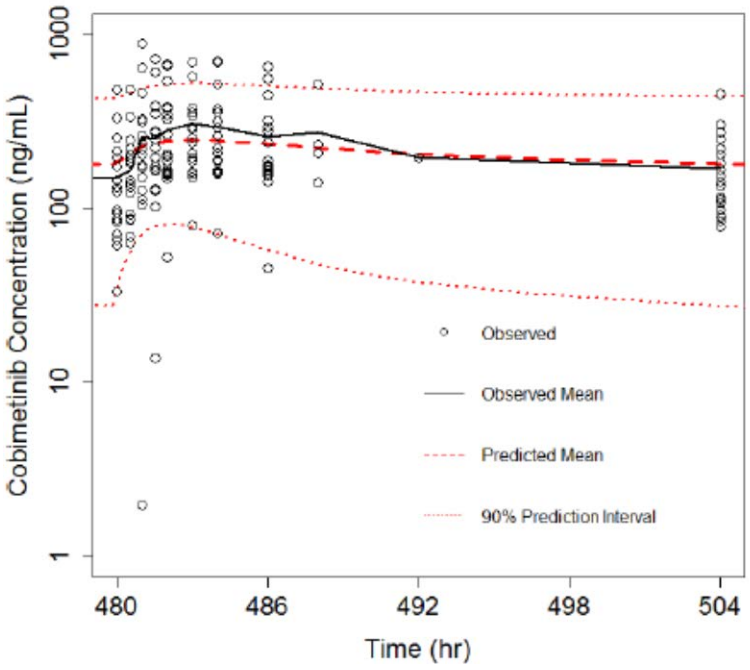
Appendix Figure 54. Observed and simulated plasma concentration-time profiles of cobimetinib using final PBPK model for cobimetinib (left, 2 mg intravenous infusion of 2 mg, and right, 10 mg oral dosing)

Sources: Figures 11 and 12 [1]. A total of 10 trials with 15 subjects per trial in the age range of 18−52 years (proportion of female: 0.34)



Appendix Figure 55. Simulated steady-state (Day 21) mean and 95% prediction interval of cobimetinib using alternative system model with decreased gut CYP3A content [4, 23]

(Source Figure 1, [4])



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Reference ID: 3751393

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/s/

RUBY LEONG
05/10/2015

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05/11/2015

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05/11/2015

PING ZHAO
05/11/2015

VIKRAM P SINHA
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NAM ATIQUR RAHMAN
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HONG ZHAO
05/11/2015
I concur.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206192

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	206192	**Brand Name**	Cotellic
OCP Division (I, II, III, IV, V)	Division V	**Generic Name**	Cobimetinib
Medical Division	DOP2	**Drug Class**	Small molecule; Mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor
OCP Reviewers	Ruby Leong, Pharm.D. (CP) Anshu Marathe, Ph.D. (PM)	**Indication(s)**	In combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations
OCP Team Leaders	Hong Zhao, Ph.D. (CP) Liang Zhao, Ph.D. (PM) Ping Zhao, Ph.D. (PBPK)	**Dosage Form**	20 mg tablet
Date of Submission	Rolling submission: · Part1 - 10/30/2014 · Part 2 - 12/11/2014	**Dosing Regimen**	60 mg once daily for 21 consecutive days followed by a 7-day rest period
Estimated Due Date of OCP Review	04/09/2015	**Route of Administration**	Oral
Medical Division Due Date	To be determined	**Sponsor**	Genentech, Inc.
PDUFA Due Date **Target Action Date**	08/11/2015 To be determined	**Priority Classification**	 Priority

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies to review	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			Module 5.2
HPK Summary	**x**			Module 2.7.2
Labeling	**x**			Module 1.14
Reference Bioanalytical and Analytical Methods	**x**	**36**		
I. Clinical Pharmacology				
Mass balance:	**x**	**1**		Study GP28369
Isozyme characterization:	**x**	**1**		Study 10-0264
Blood/plasma ratio:	**x**	**1**		Study 09-0671
Plasma protein binding:	**x**	**2**		Study 09-0614, 09-2077
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**6**		
multiple dose:				
Patients-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206192

single dose:				
multiple dose:	x	1		Study MEK4592g
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x			Study MEK4592g
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	3		Study (b) (4), Physiologically-Based Pharmacokinetics Report 14-1645
In-vivo effects of primary drug:	x			Study MEK4592g
In-vitro:	x	7		Study 10-0264, 09-0218, 09-0339, 09-0390, 09-1343, 10-1929, 10-3241
Subpopulation studies -				
ethnicity:	x			PopPK
gender:	x			PopPK
pediatrics:				Granted orphan drug designation
geriatrics:	x			PopPK
renal impairment:	x			PopPK
hepatic impairment:	x			PopPK
PD - QT Study:		1		C-QT Analysis Report 14-2571
Phase 2:				
Phase 3:				
PK/PD -		1		Exposure-Response Analysis Report 14-2570
Phase 1 and/or 2, proof of concept:	x			Study MEK4592g, NO25395
Phase 3 clinical trial:	x			Study GO28141
Population Analyses -		1		Population Pharmacokinetics Report 14-2569
Data rich:	x			
Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability	x	1		Study MEK4952g
Relative bioavailability -	x	2		Study MEK4953g, GP28370
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x			Study MEK4953g, MEK4954g
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Granted orphan drug designation
Literature References	x			
Total Number of Studies		64		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206192

	those used in the pivotal clinical trials?				
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			

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	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Exempt from PREA due to orphan drug designation
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Exempt from PREA due to orphan drug designation
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206192

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

The following information request was sent to the Applicant on February 4, 2015:

We conducted initial review of the PBPK study report "Assessment of Drug-Drug Interaction Potential between Cobimetinib and CYP3A4 Inhibitors/Inducers using a Physiologically-Based Pharmacokinetic (PBPK) Approach." Please address the following:

1. You used clinical DDI data with itraconazole (Study GP28620) and sensitivity analysis to inform $f_{m,CYP3A}$ of the cobimetinib model.

    a. Besides simulation of exposure ratios, provide simulated C_{max}, AUC, and F_g of cobimetinib after oral administration (Study MEK4952g and no-inhibitor arm of Study GP28620) under different f_m values and Q_{gut} values used in Table 2.

    b. Provide $f_{m,CYP3A}$ based on in vitro data.

2. Update your simulation of the effect of rifampin on the exposure of cobimetinib using a modified rifampin PBPK model according to SimCYP's recent update with regard to induction potency.

3. Provide the model files used to generate the final PBPK simulations (e.g., drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

Please submit this information by Feb 17, 2014.

Ruby Leong	February 9, 2015
Clinical Pharmacology Reviewer	Date
Hong Zhao	February 9, 2015
Clinical Pharmacology Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUBY LEONG
02/10/2015

HONG ZHAO
02/10/2015
I concur.