CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206192Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Cotellic (cobimetinib)

Date: October 28, 2015
To: File for NDA 206192
From: John K. Leighton, PhD, DABT
Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting and labeling reviews for Cotellic conducted by Drs. Weis and Goheer, and secondary memorandum and labeling provided by Dr. Helms. I concur with Dr. Helms' conclusion that Cotellic may be approved for the proposed indication.

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/s/

JOHN K LEIGHTON
10/28/2015

MEMORANDUM

Date: May 29, 2015
From: Whitney S. Helms, PhD
Pharmacology Team Leader
Division of Hematology Oncology Toxicology for Division of Oncology Products 2
To: File for NDA #206192
Cobimetinib (COTELLIC)
Re: Approvability of Pharmacology and Toxicology

Non-clinical studies examining the pharmacology and toxicology of cobimetinib provided to support NDA 206192 for the use of cobimetinib in combination with vemurafenib for the treatment of patients with BRAFV600E/K mutation positive unresectable or metastatic melanoma were reviewed in detail by Shawna L. Weis, PhD, and M. Anwar Goheer, PhD. The submission included studies of orally administered cobimetinib in mice, rats, and dogs that investigated the drug's pharmacology, pharmacokinetics, safety pharmacology, general toxicology, genetic toxicity (in vivo and in vitro), and reproductive toxicity.

The pharmacology studies submitted to this NDA demonstrate that cobimetinib is an inhibitor of MEK1 and MEK2. MEK1 and MEK2 are ubiquitously expressed proteins that participate in the MAPK/ERK signal transduction cascade. MEK proteins propagate signals between the small GTPase Ras, its downstream immediate effector Raf and the extracellular signal-regulated kinases (ERK1/2). In *in vitro* experiments, cobimetinib demonstrated increased affinity for activated MEK proteins, suggesting that the drug primarily inhibits activation of downstream targets by MEK rather than inhibiting the activation of MEK. Cobimetinib is a kinase inhibitor, consistent with the established pharmaceutical class for other drugs with this type of activity.

Incubation of a V600E positive tumor cell line with cobimetinib resulted in increased apoptosis both alone and, more potently, in combination with the BRAF inhibitor vemurafenib. In a vemurafenib resistant cell line, incubation with the combination of cobimetinib and vemurafenib restored apoptosis to levels similar to those seen with vemurafenib alone in the non-resistant parental line; this increase was accompanied by inhibition of levels of phosphorylated ERK in the resistant cells. In nude mice implanted with BRAF wild type tumors, treatment with vemurafenib resulted in increased tumor growth compared to vehicle. Treatment of these mice with cobimetinib resulted in dose-dependent tumor inhibition. Importantly, the addition of cobimetinib to the vemurafenib treatment regimen in the BRAF wild type tumor-implanted mice prevented the paradoxical vemurafenib-mediated enhancement of tumor growth and resulted in decreased tumor volume. Together these experiments support the rationale for use of the combination of vemurafenib and cobimetinib in patients with BRAFV600 mutated tumors and suggest that the combination may result in longer response durations as well as decreases in the frequency of squamous cell carcinomas reported with the use of BRAF inhibitors as monotherapies.

Sprague Dawley rats and Beagle dogs were the primary models used to investigate the toxicology of cobimetinib. A major target organ for toxicity in rats was the skin. *In vitro* assays

suggest some potential for cobimetinib-mediated phototoxicity which may contribute to skin toxicities seen over time. Skin toxicities and photosensitivity are broadly reported adverse events clinically as well. Gastrointestinal and (b) (4) were noted in both species and are included in the adverse reactions listed in the product label. The adrenal gland, thymus, and lymph nodes were also potential target organs identified in animal studies. In a juvenile study conducted in rats, toxicities appeared to be similar to those seen in adult animals, but were more severe at lower doses. Exposures in juvenile animals were increased compared to adults treated at the same dose level, but decreased over time suggestive of metabolic induction that was either age or compound related. Cobimetinib was negative in assays for genotoxicity. Carcinogenicity was not assessed for cobimetinib and is not required to support the approval of a drug intended to treat patients with advanced cancer.

Ocular toxicity similar to the serous retinopathy and retinal vein occlusion seen clinically has not been well-studied in nonclinical models. Ophthalmologic examinations typically included in general toxicology studies do not appear to predict this toxicity. No clear signs of ocular toxicity were identified in the nonclinical studies submitted to support the cobimetinib NDA.

In an *in vitro* hERG assay, cobimetinib inhibited potassium channel conduction with an IC_{50} of 0.5 μM, suggesting some potential for causing QT prolongation; however, *in vivo* ECG monitoring in dogs showed no effects of cobimetinib on QT prolongation at clinically relevant exposures. In an *in vitro* screening assay cobimetinib also showed some activity against a diltiazem-senstive L-type calcium channel (IC_{50} =0.57 μM). Increased findings of cardiomyopathy compared to findings in control animals were reported in the 4-week rat toxicology study though no other cardiac effects were reported in animal studies. Left ventricular dysfunction, or decreased ejection fraction has been described clinically in studies of cobimetinib in combination with vemurafenib and is included in the label for the drug.

An in vitro screening assay for potential off-target effects of cobimetinib suggested a potential effect of cobimetinib at the human μ opioid receptor agonist site with an IC_{50} of 0.66 μM. This concentration is potentially clinically achievable as a total exposure, though the drug is highly protein bound and concentrations of free drug are much lower than those shown to affect the receptor. In a respiratory safety pharmacology study conducted in rats, administration of a single 300 mg/kg dose of cobimetinib (30 fold higher dose than the high dose used in general toxicology and embryofetal development studies in rats) resulted in a significant decrease in respiratory rate (18%) compared to control animals, suggesting a potential correlative effect on the opioid receptor *in vivo*. While distribution studies of cobimetinib indicate a low potential of the drug to cross the blood brain barrier, some effect of cobimetinib on the opioid receptor cannot be completely dismissed.

The potential off-target effect of cobimetinib identified in the nonclinical data package triggered a consult to the controlled substance staff on the abuse potential for cobimetinib. Given the toxicities associated with use of cobimetinib and the lack of clear signals from clinical trials to suggest patient drug dependency, the division does not believe that the abuse potential for patients is high; however, on a broader scale, the controlled substance staff recommends that, due to the nonclinical findings, an additional nonclinical study to address the abuse potential for cobimetinib be conducted as a postmarketing requirement.

The Applicant did not conduct dedicated studies to assess the effects of cobimetinib on fertility and these studies are not required to support the approval of a drug intended for the treatment of patients with advanced cancer. In the 4-week repeat dose toxicology study in rats, cobimetinib administration resulted in ovarian findings of increased necrosis, decreases in corpora lutea, and cysts at exposures approximately twice those seen at the clinically recommended dose of cobimetinib (60 mg orally, once daily), suggesting a potential for transient effects of the drug on female fertility. In a GLP-compliant embryofetal development study of cobimetinib in Sprague Dawley rats, exposure to the drug during organogenesis resulted in marked increases in post-implantation loss, primarily due to an increased rate of early resorptions including total resorption in 2 dams, at the 10 mg/kg dose level. This dose caused frank maternal toxicity, including 1 early death, and resulted in exposures of between 0.9 and 1.4 times those in humans at the clinically recommended dose. At the same dose, there were findings of decreased fetal weight, malformations of the great vessels, and limited findings of skeletal malformations (fused ribs and small eye sockets). Though this study was conducted in compliance with GLP regulations, based on the number of animals used, it appears to be dose range finding study. Because the resulting resorptions and infrequent malformations of the great vessels occurred at a dose that was approximately equal to the clinical exposure at the recommended dose of cobimetinib and a dose that resulted in maternal toxicology, this study was considered sufficient to provide some basis for informing patients with advanced cancer of the potential reproductive toxicity of cobimetinib in combination with vemurafenib. If the Applicant pursues additional indications, including indications using cobimetinib as a single agent, then additional embryofetal development studies using larger animal numbers are likely warranted. Based on the current study and its mechanism of action, a warning for embryofetal risk is recommended for cobimetinib used in combination with vemurafenib.

Recommendations: I concur with the conclusion of Drs. Weis and Goheer that the pharmacology and toxicology data support the approval of NDA 206192 for COTELLIC. There are no outstanding nonclinical issues that would prevent the approval of COTELLIC for the proposed indication in the $BRAF^{V600E/K}$ positive patient population.

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/s/

WHITNEY S HELMS
05/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206,192
Supporting document/s:	001
Applicant's letter date:	19 December 2014
CDER stamp date:	19 December 2014
Product:	Cotellic®, Cobimetinib
Indication:	Unresectable or metastatic melanoma with BRAFV600 mutation
Applicant:	Genentech Inc 1 DNA Way MS 321B South San Francisco, California 940804990 UNITED STATES
Review Division:	DHOT / DOP2
Reviewer:	Shawna L. Weis, PhD M. Anwar Goheer, PhD
Supervisor/Team Leader:	Whitney S. Helms, PhD
Division Director:	John K. Leighton, PhD, DABT (DHOT) / Patricia Keegan, MD (DOP2)
Project Manager:	Melanie B. Pierce

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Reference ID: 3768701

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1 Executive Summary

1.1 Introduction

Genentech has submitted NDA 206192, seeking approval for the use of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Cobimetinib is a reversible, non-ATP-competitive inhibitor of MEK1 and MEK2. The recommended dose daily oral dose of cobimetinib is 60 mg. In clinical trials, this dose resulted in average exposures of 273 ng/mL (C_{max}) and 4340 ng*hr/mL (AUC).

1.2 Brief Discussion of Nonclinical Findings

Cobimetinib is a kinase inhibitor that inhibits MEK1 and 2 with IC_{50}s of 0.95 and 199 nM, respectively, and the affinity appears to be greater for ATP-bound MEK1, suggesting a measure of selectivity for activated forms of MEK. Cobimetinib also bound the human μ opiod receptor and L-type calcium channels at clinically achievable concentrations of the total drug. Potentially correlated with its activity on the μ-opioid receptor was the observation that in the rat, high-dose (300 mg/kg) cobimetinib administration led to a small (18%) but statistically significant reduction in respiratory rate; however, because cobimetinb exhibited limited CNS penetration, the potential for significant, centrally-mediated opioid pharmacology - such as dependency and withdrawal - is unclear.

The Applicant provided data from murine xenografts demonstrating the anti-tumor activity of cobimetinib in combination with vemurafenib in WT BRAF- and vemurafenib-resistant BRAF V600E-bearing tumors. Consistent with previous observations, administration of vemurafenib in the context of WT BRAF (A431 cells) resulted in paradoxically-enhanced tumor growth whereas cobmetinib, alone or in combination with vemurafenib, suppressed tumor growth relative to vehicle controls. Similarly, in vemurafenib-resistant V600E BRAF-bearing tumors, the combination both increased cellular apoptosis and suppressed tumor growth relative to vemurafenib alone.

Cobimetinib inhibited the hERG potassium channel, with an IC_{50} of 0.5 μM when tested alone, and 0.6 μM when tested combination with vemurafenib; however, there were no treatment-related effects on hemodynamics or ECG parameters (including QTc) in the conscious telemetered beagle dog at peak exposure levels of approximately 2-fold greater than the anticipated human C_{max}. Decreased cardiac function (measured by LVEF) did occurr in patients treated with the combination of cobimetinib and vemurafenib.

The Applicant conducted 4 and 13-week general toxicology studies in rats and dogs. In the dog, the predominant target organ was the GI tract. Other potential histological target organs included the kidney, liver, and thyroid. Exposures at the minimum lethal dose (1 mg/kg/day) during the 13-week toxicity study in the dog were similar to those anticipated in humans (approximately 1X on the basis of Cmax, and about 0.5X on the basis of AUC).

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In the 4-week rat study, the primary target organ was the skin, which may correlate with observations of rash in patients treated with cobimetinib and vemurafenib. Other potential target organs in the rat included the adrenals, thymus, liver, and lymph nodes. Exposures achieved on Day 16 of the 4-week toxicity study in the rat were approximately 3-fold higher than anticipated clinical exposures on the basis of both C_{max} and AUC.

In humans, cobimetinib administration was associated with the formation of serous retinopathy; however, there were no ophthalmic findings in either toxicology species at exposures of ≥ 3-times greater than those expected to occur following a daily dose of 60 mg. While binding to pigmented tissues of the skin and uveal tract was observed and potential phototoxicity was noted in the mouse 3T3 fibroblast assay, no evidence of ocular or dermal phototoxicity was observed in the female LE rat following a single dose of cobimetinib at exposures that were more than 7-fold above (on the basis of C_{max} and AUC) those expected to occur clinically.

In juvenile rats, daily oral doses of 3 mg/kg/day administered between PND 10-38 were associated with mortality. The liver was a target organ in both adult and juvenile rats and hematological variations including lymphocyte depletion were observed in both the 1 month adult and juvenile toxicology studies. Pre-terminal clinical signs included dehydration, ataxia, and cold to touch; however, no clear cause of mortality was defined. TK exposures were higher on Day 1 (PND 10) than on Day 22 (PND 32) in males and females, suggesting metabolic induction (either compound- or age-related). The exposure parameters at the NOAEL of 1 mg/kg/day were 0.02 and 0.015 times the anticipated human Cmax and AUC, respectively.

Cobimetinib was non-mutagenic in the Ames bacterial mutagenicity assay, and negative for induction of structural abnormalities in the in vitro and chromosome aberration assay and in the in vivo micronucleus assay.

The Applicant did not conduct a dedicated study to assess the effects of cobimetinib on fertility; however, reproductive effects were observed in the 4-week toxicology study in the rat, including ovarian findings of increased necrosis, decreases in corpora lutea, and cysts as well as increased vaginal epithelial cell apoptosis in high dose (10 mg/kg) female rats, a dose associated with significant mortality. At the 10 mg/kg dose exposures in the rat were about 3-fold higher on Day 16 (C_{max} and AUC) than those anticipated in humans. No treatment-related findings were reported in recovery animals. These findings may suggest a potential for transient clinical effects on female fertility.

In the embryofetal toxicology study in the rat, exposure to cobimetinib during the period of organogenesis was associated with frank maternal toxicity (body weight loss and lethality) at a dose of 10 mg/kg/day. Embryofetal effects observed at the 10 mg/kg dose level included an increased rate of early resorption, including total litter loss in two dams, and markedly increased post-implantation loss. Decreased fetal body weights

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and an increase in skeletal alterations, including decreased ossification, were observed at the 10 mg/kg dose level. Evidence of teratogenicity was observed at the 10 mg/kg dose level. Findings included malformations of the great vessels (missing and/or misplaced great vessels), and malformations of the eye sockets. Exposures (AUC_{0-24}) at this dose level were 0.9 and 1.4X on Day 1 and Day 11, respectively, of human plasma exposures. These findings support a warning for embryofetal risk in the cobimetinib product label.

Because the number of animals used were low (10 pregnant dams per group) and the exposure levels achieved were low relative to therapeutic plasma levels in humans, it is unclear that the embryofetal risk has been adequately characterized for use in a broader patient population. Therefore, while the data from this dose-ranging study are sufficient to support the co-administration of cobimetinib with vemurafenib in patients with advanced melanoma, the Applicant will likely be required to conduct a definitive embryofetal toxicity study in both the rat and the rabbit if they intend to seek to expand the indication to include other therapeutic areas, particularly in patients whose disease is less advanced.

The binding of cobimetinib to the agonist site of the μ-opioid receptor, in combination with a reduced respiratory rate observed in rats, triggered a consult to the Controlled Substance staff regarding the potential for abuse liability with cobimetinib. Given the toxicities associated with use of cobimetinib and the lack of clear dependency signals in patients, the Division does not believe that the potential for abuse is high; however, if the Controlled Substance staff believes that additional nonclinical studies to address abuse potential are warranted, they will be conducted as postmarketing requirements.

1.3 Recommendations

1.3.1 Approvability

From the nonclinical perspective, cobimetinib is approvable for use in combination with vemurafenib in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

1.3.2 Additional Non Clinical Recommendations

None

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)

Generic Name
Cobimetinib
Code Name

Reference ID: 3768701

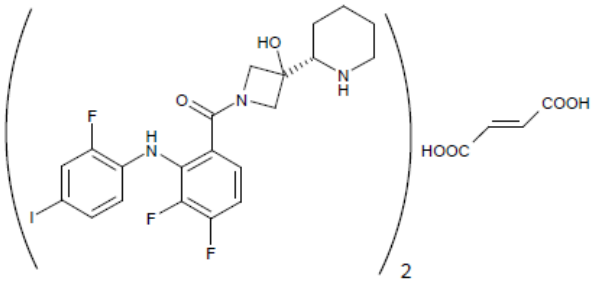
- GDC-0973
- XL518
- EXEL-04285518
- EXEL-5518

Chemical Name
(S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate.

Molecular Formula/Molecular Weight
- Free base: $C_{21}H_{21}F_3IN_3O_2$; 531.32 g/mol
- hemifumarate salt: $C_{46}H_{46}F_6I_2N_6O_8$); 1178.71 g/mol

Structure or Biochemical Description

Figure 1: Structure of cobimetinib hemifumarate



Pharmacologic Class
MEK Kinase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 073,620 (vemurafenib)
- IND [redacted] (b) (4)
- IND 109,307 (cobimetinib +vemurafenib)
- IND [redacted] (b) (4)
- IND [redacted] (b) (4)
- NDA 202,429 (vemurafenib)

2.3 Drug Formulation

Cobimetinib is formulated for oral administration in a 20 mg film-coated tablet. The composition of the cobimetinib formulation is provided in Table 1.

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Table 1: Composition of cobmetinib film-coated tablets, 20 mg

Component	Reference to Standards	Function	Quantity per Unit Dose (mg/tablet)
Tablet Core			
Cobimetinib Hemifumarate	In-house	Active	22. (b) (4)
Microcrystalline Cellulose[b]	NF, Ph. Eur., JP	(b) (4)	
Lactose Monohydrate	NF, Ph. Eur., JP		
Croscarmellose Sodium	NF, Ph. Eur., JP		
Magnesium Stearate	NF, Ph. Eur., JP		
Tablet Core Weight			
Film-Coating Mixture[d]			
Polyvinyl Alcohol	USP, Ph. Eur., JPE		
Titanium Dioxide	USP, Ph. Eur., JP		
(b) (4) PEG 3350	NF, Ph. Eur.		
Talc	USP, Ph. Eur., JP		
(b) (4)	USP, Ph. Eur., JP		
Film-Coating Mixture Weight			
Total Tablet Weight			124.80

NA = not applicable.

(b) (4)

(Excerpted from the Applicant's submission)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The Pharmacology/Toxicology team did not receive any impurity-related questions during the review of this application.

2.6 Proposed Clinical Population and Dosing Regimen

- Indication: Cobimetinib indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations
- Regimen: The recommended dose of cobimetinib is 60 mg orally once daily for the first 21 days of each 28 days in combination with vemurafenib.

2.7 Regulatory Background

IND (b) (4)	20 December 2006
IND 109,307 Filed (cobimetinib + vemurafenib)	31 August 2010
Pre-Phase 3 study design meeting	27 June 2012
End of Phase 2 CMC meeting	27 November 2012
FDA Response to Clinical Pharmacology Plan	22 April 2013

Pre-NDA meeting	29 November 2013
Type B CMC meeting	25 February 2014
Fast-Track Granted	15 August 2014
Proprietary name granted	10 October 2014
NDA Filed	11 December 2014

3 Studies Submitted

3.1 Studies Reviewed

- Evaluation of the Effects of BRAF Inhibitor, Vemurafenib (RG7204/G00044364), and the MEK Inhibitor, Cobimetinib (GDC-0973), on Tumor Growth in the A431 Squamous Epidermoid Xenograft Tumor Model in NCR Nude Mice (Report: 13-1484)
- Kinase Profile and Mechanism of Action Studies of EXEL-5518 (Report: 13-2987)
- Non-clinical combination studies of RO5185426 and MEK inhibitor GDC-0973 in melanoma cell lines and melanoma xenograft models with acquired resistance to RO5185426 (Report 1046219)
- In Vitro Pharmacology Study of EXEL-5518 (Report #859001)
- Effects of GDC-0973 and Vemurafenib on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (Report: 121222.HFO)
- XL518: Effects on General Activity and Behaviour in the Rat Following Oral Administration (Report #2239/016)
- XL518: Measurement Of Respiratory Parameters In The Freely Moving Conscious Rat Using Whole Body Plethysmography (Report #2239/20)
- A 4-Dose Crossover Oral Gavage Cardiovascular Safety Assessment Study of XL518 in Conscious Beagle Dogs
- In Vitro Cross-Species Plasma Protein, Human Serum Albumin, and Alpha-1 Acid Glycoprotein Binding Determination of GDC-0973 (09-0614)
- In Vitro Cross-Species Blood-Plasma Partitioning of [14C]GDC-0973 (Report #09-0671)
- Quantitative Whole Body Autoradiography of Rats Following Oral Administration of 14C-GDC-0973 (Report # 8215690)
- Metabolite Radio-profiling and Identification in Plasma, Urine, Bile, and Feces from Rats Following Oral Administration of [14C]GDC-0973 (Report #09-0833)
- CYP and UGT Reaction Phenotyping of GDC-0973.23 Using Human Liver Microsomes, Recombinant Cytochrome P450 (rCYP), and Recombinant UGT (rUGT) (Report: 10-0264)
- Metabolite radioprofiling and identification in plasma, bile, urine and feces from dogs following oral administration of [^{14}C]GDC-0973 (Report #10619)
- Excretion Mass Balance and Pharmacokinetics of Radioactivity Following a Single Oral Dose of [14C]GDC-0973 to Male and Female Sprague Dawley Rats (Report #274N-0901 Revision 1)
- Determination of Radiolabeled Mass Balance, Routes of Excretion, and Metabolic Profiles of [$_{14}$C]GDC-0973 in Intact and Bile Duct-Cannulated Dogs (Report #8222137)

Reference ID: 3768701

- Single-Dose Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Rats. (b) (4) Study Number 7359-295, Sponsor Reference Number XL518-NC-002.
- Single-Dose Oral Gavage Toxicity and Toxicokinetic Study of XL518 in Dogs. (b) (4) Study Number 7359-296, Sponsor Reference Number XL518-NC-003.
- In Vivo Toxicity and Pharmacokinetic Studies of the Orally Active MEK1 Inhibitor EXEL-04285518 (EXEL-5518) in Rats after 15-Day Repeat-Dosing. Study Report TOX-021406-01-IND
- 4-Week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Rats with a 4-Week Recovery Period. (b) (4) Study Number 7359-29713-Week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Rats with a 4-Week Recovery. (b) (4) Study Number 7359-359
- 4-Week Oral Gavage Toxicity and Toxicokinetic Study of XL518 in Dogs with a 4-Week Recovery. (b) (4) Study Number 7359-298
- 13-Week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Dogs with a 4-Week Recovery. (b) (4) Study Number 7359-360
- XL518: Salmonella-Escherichia coli/Mammalian Microsome Reverse Mutation Assay with a Confirmatory Assay. (b) (4) Study Number 7359-302
- XL518: Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes. (b) (4) Study Number 7359-301
- A 28-Day Oral Gavage Toxicology and Toxicokinetic Study in Juvenile Sprague Dawley Rats with GDC-0973. Testing Facility Study No. 20041064
- A Single-Dose Intravenous Local Tolerance Study with GDC-0973 in Rats with a 13-day Recovery Period. (b) (4) Study Number 8228810
- Neutral Red Uptake Phototoxicity Assay of GDC-0973 in Balb/c 3T3 Mouse Fibroblasts. Testing Facility Study No. 20043661
- Single-Dosage Phototoxicity Study to Determine the Effects of Oral Administration of GDC-0973 on Eyes and Skin in Pigmented Rats. Testing Facility Study No. 20042755

3.2 Studies Not Reviewed

- Method Validation for the Quantitation of GDC-0973 in Rat Plasma by Turbo Ion Spray LC/MS/MS (Report #100408VHDW_GSC.DOC)
- Method Validation of Method BA-M-032.00, Bioanalytical Method for the Determination of XL5 18 and EXEL0382 in Rat Plasma by LC/MS/MS (Report #BA-VP-032.00)
- Method Validation of Method BA-M-033.00, Bioanalytical Method for the Determination of XL5 18 and EXEL0382 in Dog Plasma by LC/MS/MS (Report #BA-VP-033.00)
- Single Dose Pharmacokinetic (PK) Profile of EXEL-04285518 in Male Beagle Dogs (Report #013106-01)
- Single Dose Pharmacokinetic (PK) Profile of EXEL-04285518 in Male Cynomolgus Monkeys (Report #021406-01)
- Single Ascending Dose Pharmacokinetic (PK) Profile of EXEL-04285518 in Female CD Rats (Report #021406-01)
- Single Ascending Dose Pharmacokinetic (PK) Profile of EXEL-04285518 in Female Athymic Nude Mice (Report #030606-01)

Reference ID: 3768701

3.3 Previous Reviews Referenced

The following studies were reviewed by Dr. Timothy Kropp at the time of the original IND submission for IND (b) (4).

- 4-Week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Rats with a 4-Week Recovery Period (7359-297)
- 4-Week Oral Gavage Toxicity and Toxicokinetic Study of XL518 in Dogs with a 4-Week Recovery (7359-298)
- XL518: Salmonella Escherichia coli/Mammalian Microsome Reverse Mutation Assay with a Confirmatory Assay (7359-302)
- XL518: Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes (7359-301)

4 Pharmacology

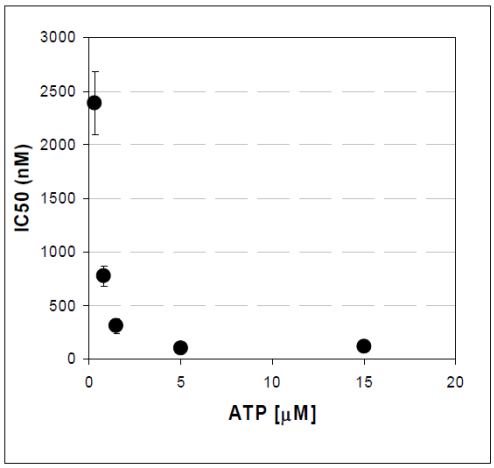
4.1 Primary Pharmacology

4.1.1 Kinase Profile and Mechanism of Action Studies of EXEL-5518 (Report: 13-2987)

The purpose of this study was to characterize the binding affinity and off-target binding profile of EXEL-5518 (cobimetinib), and to determine the mechanism and reversibility of binding to MEK1 and MEK2. Cobimetinib was tested in a panel of 103 recombinant serine-threonine and tyrosine kinases. IC_{50}s of 0.95 and 199 nM were determined for MEK1 and MEK2, respectively; however, inhibition of other kinases was not observed at concentrations of up to 10 µM, suggesting that cobimetinib is selective for MEK1 and MEK2 at physiologically-relevant plasma concentrations.

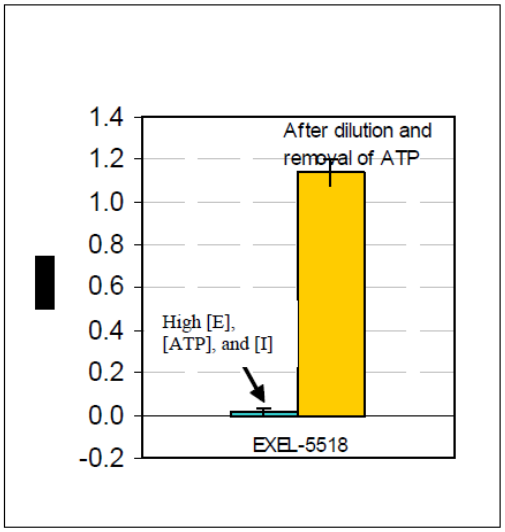
The apparent binding affinity was proportional to ATP concentration over the range tested, suggesting increased affinity for activated MEK. Inhibition was also reversible following washout of the inhibitor and ATP (Figure 3).

Figure 2: Relationship between apparent MEK1 IC50 and ATP concentration



(Excerpted from Applicant's submission)

Figure 3: Recovery of MEK1 activity after inhibition with cobimetinib



(Excerpted from Applicant's submission)

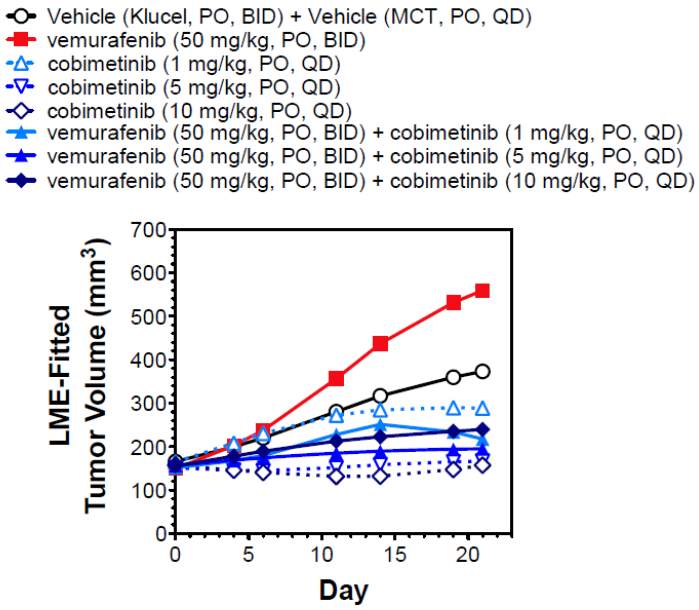
4.1.2 Evaluation of the Effects of BRAF Inhibitor, Vemurafenib (RG7204/G00044364), and the MEK Inhibitor, Cobimetinib (GDC-0973), on Tumor Growth in the A431 Squamous Epidermoid Xenograft Tumor Model in NCR Nude Mice (Report: 13-1484)

The purpose of this study was to evaluate the effect of vemurafenib (a BRAF inhibitor) and cobimetinib (a MEK inhibitor) when administered alone or in combination, in nude mice implanted with xenografts harboring squamous epidermoid tumors (A431 cells, which express WT BRAF). In addition, the study aimed to determine if cobimetinib administration could reverse paradoxical tumor growth observed following vemurafenib treatment of cells expressing wild type BRAF.

Tumors were implanted subcutaneously in the right thorax and permitted to grow to a size of 156 mm^3 prior to initiation of dosing, at which time, animals received daily oral doses of 100 mg/kg vemurafenib per day (administered as a divided dose of 50 mg/kg) alone or in combination with 1, 5, or 10 mg/kg/day cobimetinib, for 21 days. Dose-matched cobimetinib-only groups were also included.

As has been previously reported, administration of vemurafenib stimulated tumor growth in this system. In contrast, administration of cobmetinib alone or in combination with vemurafenib, decreased tumor growth relative to vehicle controls.

Figure 4: Effect of vemurafenib in combination with cobimetinib on A431 xenografts in NCR nude mice



(Excerpted from Applicant's submission)

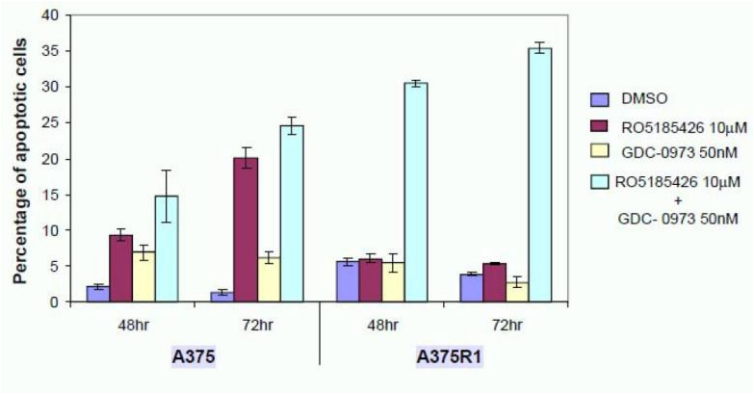
4.1.3 Non-clinical combination studies of RO5185426 and MEK inhibitor GDC-0973 in melanoma cell lines and melanoma xenograft models with acquired resistance to RO5185426 (Report 1046219)

The purpose of this study was to characterize molecular mechanisms of disease progression following initial response to the BRAF inhibitor, RO5185426 (vemurafenib), in $BRAF^{V600E}$ mutant melanoma (A375 cells). The Applicant selected resistant clones following chronic vemurafenib exposure and implanted them into murine SCID-beige hosts. Biochemically, resistant clones exhibit markedly upregulated pERK expression relative to the parental line, suggesting that resistance is mediated in part by compensatory pathways that when induced, overcome the suppression of BRAF-mediated ERK activation.

While cells that were resistant to vemurafenib were also resistant to cobimetinib, the combination of vemurafenib (administered orally twice daily) plus cobimetinib (administered orally once daily) induced apoptosis (Figure 5). This was associated with suppression of pERK (Figure 6) in vitro; however, the effect on pERK formation appears to be largely due to the actions of vemurafenib, since cobimetinib alone did not completely block pERK expression in this assay.

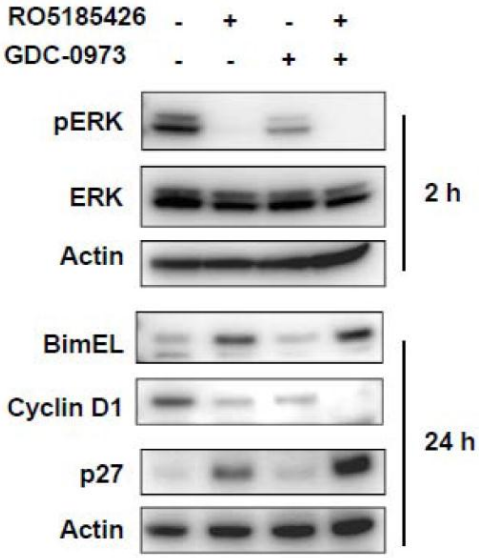
Treatment with the combination also resulted in improved inhibition of tumor growth (Figure 7) and prolonged survival (Figure 8) in vemurafenib-resistant A375 murine xenograft models, suggesting that the combined blockade of RAS/RAF/MEK/ERK is required to suppress the growth of resistant clones.

Figure 5: Induction of apoptosis by vemurafenib (R05185426) and cobimetinib (GDC-0973) in A375 and A375R1 (vemurafenib-resistant) cells



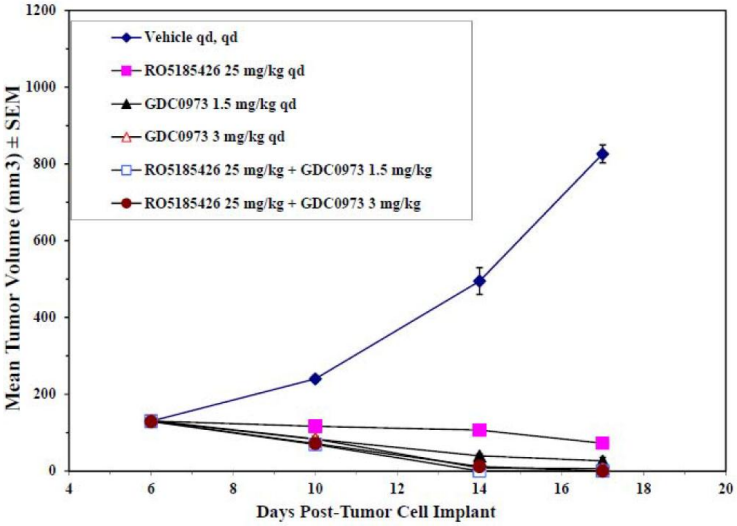
(Excerpted from Applicant's submission)

Figure 6: Effect of vemurafenib + cobimetinib on pERK expression in vemurafenib-resistant cells



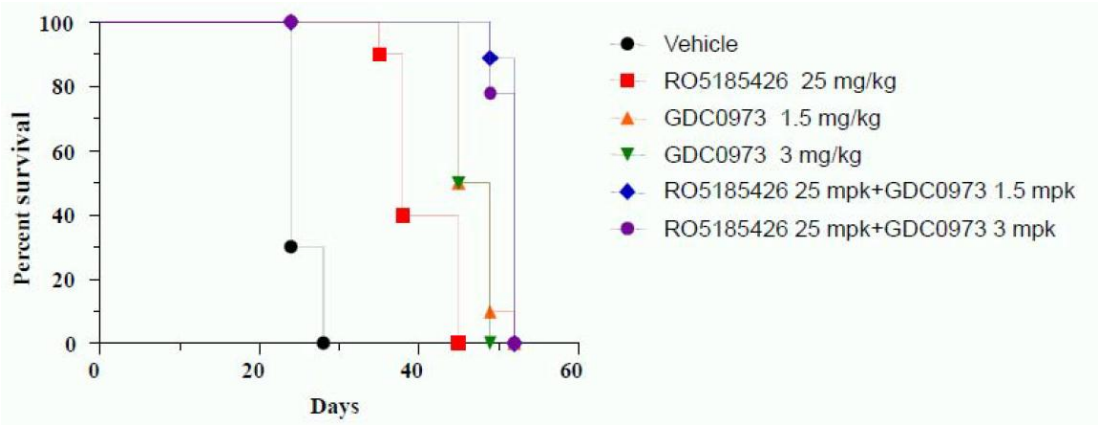
(Excerpted from Applicant's submission)

Figure 7: Effect of cobimetinib + vemurafenib on the growth of vemurafenib-resistant A375 cells in a murine xenograft model



(Excerpted from Applicant's submission)

Figure 8: Survival of single agent-treated vs. control- or combination-treated mice harboring vemurafenib-resistant A375 xenografts



(Excerpted from Applicant's submission)

4.2 Secondary Pharmacology

4.2.1 In Vitro Pharmacology Study of EXEL-5518 (Report #859001)

To evaluate potential off-target pharmacological activities, the Applicant conducted an in vitro pharmacology study of cobimetinib in a panel of recombinant receptors, and enzymes. Cobimetinib exhibited off-target activity in a number of these assays For, compounds that inhibited the binding of reference compounds by ≥50% at 10 µM, the Applicant performed additional concentration-response analyses to obtain an IC_{50}, the results of which are summarized in Table 2.

Table 2: Activity of cobimetinib in a screening panel of recombinant transporters and receptors

Target	IC_{50}
Human β2 Receptor	2 µM
Human M1 Receptor	8.8 µM
Human M2 Receptor	10 µM
Kappa Opioid Receptor	4.8 µM
Human µ Opioid Receptor (agonist site)	0.66 µM
Human 5-HT2B Receptor	2 µM
Nonselective σ Receptor	0.71 µM
Diltiazem-sensitive L-type Ca2+ Channel	0.57 µM
Verapamil-sensitive L-type Ca2+ Channel	6.7 µM
Batrachotoxin-sensitive Na+ Channel	1.9 µM
Human Dopamine Transporter	7.2 µM

4.3 Safety Pharmacology

4.3.1 Effects of GDC-0973 and Vemurafenib on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (Report: 121222.HFO)

The Applicant conducted a GLP-compliant whole cell patch-clamp hERG assay with cobimetinib (GDC-0973) and vemurafenib in stably-transfected HEK293 cells that overexpress the human ether-à-go-go-related gene (hERG), which is a delayed rectifier cardiac potassium ion channel.

Under the conditions of this assay, cobimetinib inhibited hERG channel conductivity, with an IC_{50} of 0.5 µM (Figure 9), suggesting some potential for causing QTc prolongation in vivo. The study met the criteria for a valid test because there was little to no control inhibition (DMSO) over the intervals tested, and the positive control (terfenadine) inhibited the hERG current by 78.5% at 60 nM, as expected, confirming the sensitivity of the system (data not shown).

In this assay, the IC_{50} of vemurafenib in the hERG assay was >10 µM. This contrasts with the previously-reported IC_{50} for vemurafenib (NDA 202429) of 1.24 µM.

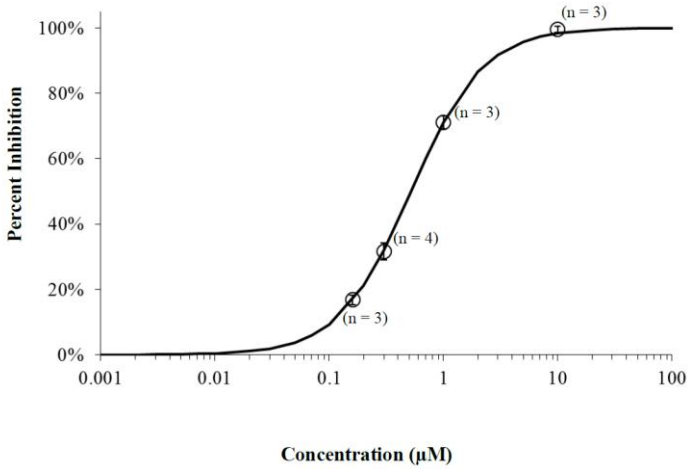
When tested in combination at concentrations of 10 µM vemurafenib + 0.3 µM cobimetinib (the highest concentration that could be tested because of precipitate formation), the combined IC_{50} was 0.6 µM (Figure 10). Because of the limited solubility of the two agents when tested together, it is unclear whether this IC_{50} is accurate. At higher cobimetinib concentrations (i.e. those closer to the half-maximal inhibitory concentration), the apparent IC_{50} of the combination may have been lower.

It should also be noted that this report contained a major GLP deviation, as there were no stability data to confirm that vemurafenib was stable under the conditions of use, as

Reference ID: 3768701

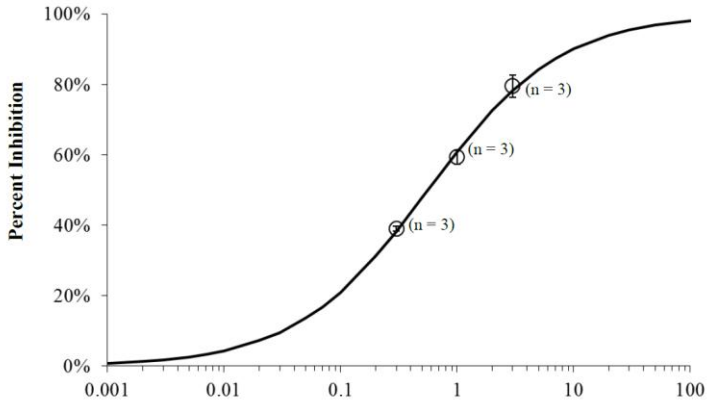
the analytical results did not meet the pre-specified acceptance criteria of (b) (4)% (final concentration of the 0.3 µM solution was 80.4% of nominal). The impact of this deviation is that estimates of the dual cobimetinib + vemurafenib potency in this hERG assay could be underestimated if the concentrations tested are lower (due to degradation, etc.) than the nominal concentrations.The stability of the bulk test article is supported by the Certificate of Analysis, stating that the drug substance met release specifications at the time of analysis (August 2013, with a retest date of (b) (4)).

Figure 9: Concentration-response relationship of cobimetinib in the hERG assay (IC_{50} = 0.5µM)



(Excerpted from Applicant's submission)

Figure 10: Concentration-response-relationship of vemurafenib with 0.3 µM cobimetinib in the hERG assay (IC50 = 0.6 µM)

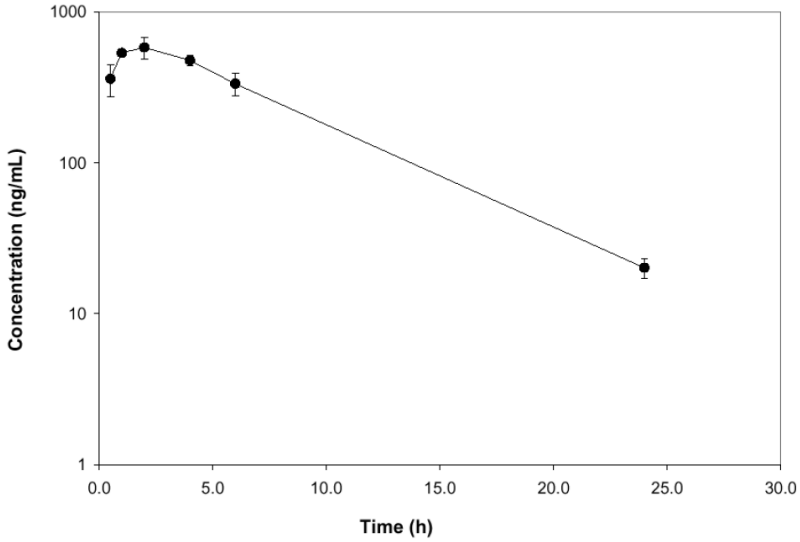


(Excerpted from Applicant's submission)

4.3.2 XL518: Effects on General Activity and Behaviour in the Rat Following Oral Administration (Report #2239/016)

To evaluate the potential CNS effects of cobimetinib, the Applicant performed a functional observational battery (FOB) in the Wistar rat (males only) at doses of between 7.5-30 mg/kg. Animals were fasted overnight prior to administration of test article. Each animal received a single oral dose of cobimetinib or vehicle (distilled water) in a 20 mL/kg dose volume. Rats were examined for general behavior based on the method of Irwin (per (b) (4) SOP). Observations were performed at 30, 60, 120, 240, and 360 minutes post-dose, and animals stayed on-study for a further 7 days for general observations and to monitor for mortality. Blood was sampled from a satellite cohort (high dose only) for toxicokinetic assessment and confirmation of exposure. Dose solutions met pre-specified acceptance criteria ((b) (4)% of nominal) for concentration, and no test article was detected in the vehicle control sample. There were no significant behavioral changes observed in treated groups compared to vehicle controls. Pharmacokinetic parameters are summarized in Table 3, and the concentration time-profile is provided Figure 11.

Figure 11: Concentration-time profile of cobimetinib following a single oral dose of 30 mg/kg in male Wistar rats



(Excerpted from Applicant's submission)

Table 3: Mean pharmacokinetic parameters from male Wistar rats treated with a single oral dose of 30 mg/kg cobimetinib

Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	C_{max}/ Dose (ng/mL)/ (mg/kg)	AUC_{0-t} (h•ng/mL)	AUC_{0-t}/ Dose (h•ng/mL)/ (mg/kg)	AUC_{0-inf} (h•ng/mL)	AUC_{0-inf}/ Dose (h•ng/mL)/ (mg/kg)	$t_{1/2, z}$ (h)
30	2.00	584	19.5	5960	199	6090	203	4.40

AUC_{0-inf}, area under the plasma drug concentration time curve from time zero to time infinity; AUC_{0-t}, area under the plasma drug concentration time curve from time zero to time of the last quantifiable concentration, C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; $t_{1/2, z}$, half-life for the terminal phase; t_{max}, time to reach C_{max}.

Reference ID: 3768701

(Excerpted from Applicant's submission)

4.2.3 XL518: Measurement Of Respiratory Parameters In The Freely Moving Conscious Rat Using Whole Body Plethysmography (Report #2239/20)

To evaluate the potential respiratory effects of cobimetinib, the Applicant performed a study in the Wistar rat. Fasted animals received single oral (gavage) doses of cobimetinib in a 20 mL/kg dose volume at doses of 0, 30, 100 or 300 mg/kg. Respiratory measurements (tidal volume, respiration rate and minute volume) were collected continuously for 4 hours by whole body plethysmography. There were no effects of cobimetinib at doses of up to 100 mg/kg; however, an 18% decrease in respiratory rate was observed at the 300 mg/kg dose level, which was statistically significant when compared with pre-dose values. Although all groups treated exhibited a small decrease in respiratory rate relative to pre-dose rates, the decrease was only statistically significant at the highest dose level (Table 4), and as illustrated in Table 4, the magnitude of the effect increased with dose. This effect may be attributable to the off-target activities of cobimetinib on the μ-opioid receptor.

Table 4: Group mean change from pre-dose

Variable	Group 1	Group 2	Group 3	Group 4	Statistics
TV (mL)	-6.19	-9.76	14.55	26.34	A
RATE (brpm)	114	-951	-2012	-2796*	A
MV (mL)	-925	-2247	-759	-607	A

* P<0.05
** P<0.01
*** P<0.001

A = ANOVA and Dunnett's on area under the change from pre-dose curve

(Excerpted from Applicant's submission)

4.2.4 A 4-Dose Crossover Oral Gavage Cardiovascular Safety Assessment Study of XL518 in Conscious Beagle Dogs

To evaluate the effect of cobimetinib on cardiovascular function, the Applicant conducted a GLP-compliant study in conscious telemetered beagle dogs. Cobimetinib (0.3, 1, and 3 mg/kg) was administered by oral gavage to 4 male beagles in a Latin square crossover study in which all animals received one dose of the vehicle and each dose level of test article in a randomized fashion, according to the design described in Table 5. A washout of at least 6 days was given between each test session. Due to a failure of the implanted telemetry device in one animal (Animal 2M) prior to Session 3, Animal 2M was replaced with Animal 5M, which received all doses of the test article, but did not receive the vehicle. Data from Animal 2M was used as the vehicle control data for Animal 5M in the statistical analysis.

Table 5: Design of the cardiovascular safety pharmacology study in the dog

Dog ID	Test Session 1	Test Session 2	Test Session 3	Test Session 4	XL518 Test Session 5	Test Session 6	Test Session 7	Test Session 8	Test Session 9
5M*	Vehicle (2M)				3 mg/kg		1 mg/kg		0.3 mg/kg
3M	0.3 mg/kg				Vehicle		3 mg/kg		1 mg/kg
7M		1 mg/kg		3 mg/kg		0.3 mg/kg		Vehicle	
11M		3 mg/kg		Vehicle		1 mg/kg		0.3 mg/kg	

*5M only received three doses of test article.

Following each dose of vehicle or test article, readings were taken continuously for 1 minute at 15-minute intervals for the first hour, then hourly for 12 hours post-dose. Blood samples were collected at the end of each 12-hour monitoring interval, for confirmation of exposure. For each variable, the mean of the predose value recorded for each animal at each dose level was taken as the baseline for that animal, and at each timepoint within dose, the change from baseline was calculated. Statistical analyses were performed on the change from the animal's baseline for each parameter at each timepoint. There were no treatment-related effects on any endpoint evaluated (blood pressure, heart rate, or ECG interval durations). All test article formulations met pre-specified acceptance criteria for concentration ([redacted] (b) (4) % of nominal), and test article was not detected in the vehicle control sample. Plasma exposures were approximately proportional with dose over the 10X dose interval, as illustrated in Table 6.

Table 6: Mean plasma exposures (ng/mL) in the cardiovascular safety pharmacology study in the dog

0 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg
BLQ	16.2	60.2	233

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

5.1.1 DISTRIBUTION

5.1.1.1 In Vitro Cross-Species Plasma Protein, Human Serum Albumin, and Alpha-1 Acid Glycoprotein Binding Determination of GDC-0973 (09-0614)

The Applicant assessed plasma protein binding in humans, monkeys, dogs, rabbits, rats and mice, using equilibrium dialysis/HPLC at test article concentrations of 1, 5, or 10 µM. Binding of cobimetinib was high (>90%) across all species tested. Except in dogs, binding was independent of concentration. At physiologically-relevant plasma concentrations (~1 µM) the unbound fraction was ~8X higher in humans relative to dogs and ~2X higher relative to rats (Table 7). Binding to human serum albumin (HSA) and

human alpha-1-acid-glycoprotein (AAG) was approximately 60% and 95%, respectively, at all concentrations tested (Table 8).

Table 7: Mean (±SD) Percent of [14C] cobimetinib bound and unbound fractions in the mouse, rat, rabbit, dog, human and cynomolgus monkey

Species	Total GDC-0973 Concentration [a] (μM)	Percent Bound [^{14}C]GDC-0973	Percent Unbound [^{14}C]GDC-0973
Mouse	1	95.9±0.822	4.10±0.822
	5	96.6±0.0682	3.41±0.0682
	10	96.7±0.199	3.25±0.199
Rat	1	97.2±0.369	2.81±0.369
	5	96.5±0.446	3.55±0.446
	10	96.3±0.274	3.73±0.274
Rabbit	1	94.2±0.319	5.83±0.319
	5	93.0±0.589	7.03±0.589
	10	93.0±0.388	6.99±0.388
Dog	1	99.3±0.0230	0.663±0.0230
	5	98.8±0.236	1.15±0.236
	10	98.6±0.163	1.41±0.163
Cynomolgus Monkey	1	95.5±1.13	4.51±1.13
	5	95.6±0.317	4.40±0.317
	10	95.2±0.270	4.83±0.270
Human	1	94.8±0.351	5.19±0.351
	5	93.5±0.355	6.47±0.355
	10	94.2±0.169	5.83±0.169

[a] Unlabeled+[^{14}C]-labeled GDC-0973 (free-base equivalents).

(Excerpted from Applicant's submission)

Table 8: Mean percent of [14C]Cobimetinib in human AAG and HSA

Protein	Total GDC-0973 Concentration (μM) [a]	Percent Bound [^{14}C]GDC-0973	Percent Unbound [^{14}C]GDC-0973
AAG	1	95.6±0.595	4.35±0.595
	5	95.8±0.187	4.22±0.187
	10	94.7±0.0570	5.27±0.0570
HSA	1	53.1±14.9	46.9±14.9
	5	59.2±0.179	40.8±0.179
	10	59.2±1.24	40.8±1.24

AAG=alpha-1 acid glycoprotein; HSA=human serum albumin.

[a] Unlabeled+[^{14}C]-labeled GDC-0973 (free-base equivalents).

(Excerpted from Applicant's submission)

5.1.1.2 In Vitro Cross-Species Blood-Plasma Partitioning of [14C]GDC-0973 (Report #09-0671)

The partitioning of cobimetinib to blood cells was evaluated in vitro, using anticoagulated male blood (pooled per species from multiple donors) from mouse, rat, rabbit, dog, cynomolgus monkey, and humans. Blood samples were incubated with cobimetinib concentrations of 1, 5, or 10 µM for 60 minutes at 37°C and after centrifugal separation; plasma and cellular components were assessed by liquid scintillation to determine the relative amounts of drug-associated radioactivity in each compartment.

As indicated in Table 9, there was no evidence that cobimetinib accumulated in the cellular constituents of humans or mice, as the radioactivity observed in whole blood was all accounted for by the concentrations measured in the plasma. In the rat, monkey and rabbit, the blood:plasma ratios were >1, suggesting some potential for partitioning to cellular constituents in those species.

Table 9: Blood-Plasma ratio and percent recovery of cobimetinib in whole blood from different species

Species	Total GDC-0973 Concentration (µM) [a]	Blood–Plasma Ratio of [^{14}C]GDC-0973	Recovery of [^{14}C]GDC-0973 (%)
Mouse	1	1.16±0.0246	101±2.73
	5	1.19±0.0273	99.4±0.957
	10	1.27±0.0239	97.0±1.68
Rat	1	1.36±0.0241	99.7±0.412
	5	1.37±0.0191	98.5±1.59
	10	1.51±0.0746	98.6±0.933
Rabbit	1	3.12±0.0812	101±2.68
	5	3.15±0.0783	99.9±0.969
	10	3.22±0.0293	99.3±0.513
Dog	1	0.632±0.0112	93.5±2.10
	5	0.752±0.00870	98.4±0.612
	10	0.936±0.0114	97.2±1.01
Cynomolgus Monkey	1	1.57±0.0349	101± 2.36
	5	1.64±0.0283	100±0.211
	10	1.82±0.0699	101±1.05
Human	1	0.933±0.0141	100±1.18
	5	0.945±0.00659	101±0.414
	10	1.05±0.0129	101±0.678

[a] Unlabeled+[^{14}C]-labeled GDC-0973 (free-base equivalents).

(Excerpted from Applicant's submission)

5.1.1.3 Quantitative Whole Body Autoradiography of Rats Following Oral Administration of 14C-GDC-0973 (Report # 8215690)

To assess tissue distribution of cobimetinib, the Applicant performed a whole-body autoradiography study in the partially-pigmented Long Evans (LE; N = 10) rat and in the Sprague Dawley rat (SD; N = 4). Male animals received a single oral dose of 30 mg/kg [^{14}C]cobimetinib on Day 1, and one carcass per timepoint was evaluated at 0.5, 2, 4, 8, 24, 96, 240, and 672 hours post-dose (LE strain) or at 1, 8, 24, and 120 hours post-dose (SD strain). Blood and plasma were collected at termination, and samples were analyzed by liquid scintillation counting. PK analysis was conducted for blood, plasma and tissues.

Cobimetinib was widely distributed to tissues and organs following oral administration in both strains of rats. The highest levels of exposure were to the GI tract and bile (stomach, intestines, liver), lung, adrenals, urinary bladder, pituitary and eye/uveal tract (LE strain). In the SD rat, high levels of exposure were also observed in the lacrimal glands. There was little exposure to the CNS. The drug distributes to pigmented skin and the uveal tract in LE rats, indicating a potential for phototoxicity.

There was no evidence of partitioning to RBCs in either the Long-Evans or SD rat strains. At all timepoints, the amount of radioactivity in whole blood was comparable to levels observed in plasma. This is consistent with the known plasma protein binding profile of the drug.

Prolonged (up to 240 hours post-dose in LE rats and ≥160h post-dose in SD rats) drug-associated radioactivity was also observed in the liver and kidneys/urinary bladder, suggesting biliary and urinary excretion of the drug and/or its metabolites.

Reference ID: 3768701

Table 10: Timecourse of [14C]cobimetinib exposure as measured by QWBA in blood and tissues of the LE rat

	ng Equivalents ^{14}C-GDC-0973/g									
	Animal Number (Sacrifice Time)									
Matrix	B19627 (0.5 Hours)	B19628 (2 Hours)	B19629 (4 Hours)	B19630 (8 Hours)	B19631 (24 Hours)	B19632 (72 Hours)	B19633 (96 Hours)	B19634 (240 Hours)	B19635 (480 Hours)	B19636 (672 Hours)
Adrenal gland	19100	53700	57600	39300	3330	BLQ	BLQ	BLQ	ND	ND
Bile	127000	167000	153000	56600	14500	ND	ND	ND	ND	ND
Blood	878	1730	1350	592	BLQ	ND	ND	ND	ND	ND
Bone	387	702	965	466	ND	ND	ND	ND	ND	ND
Bone marrow	3500	17900	15400	13800	723	ND	ND	ND	ND	ND
Brain cerebellum	BLQ	299	364	BLQ	BLQ	ND	ND	ND	ND	ND
Brain cerebrum	BLQ	374	345	BLQ	BLQ	ND	ND	ND	ND	ND
Brain choroid plexus	3140	9560	11600	11600	1020	ND	ND	ND	ND	ND
Brain medulla	BLQ	393	380	BLQ	BLQ	ND	ND	ND	ND	ND
Brain olfactory lobe	BLQ	303	275	BLQ	BLQ	ND	ND	ND	ND	ND
Bulbo-urethral gland	NR	16800	17100	10700	1050	ND	ND	ND	ND	ND
Cecum	3510	10000	11300	9310	2010	BLQ	BLQ	ND	ND	ND
Contents, cecum	BLQ	4030	8080	515000	27400	520	3510	BLQ	ND	ND
Contents, esophageal	172000	6810	32100	1200	726	ND	ND	ND	ND	ND
Contents, large intestine	BLQ	BLQ	5380	755000	60400	1170	3470	BLQ	ND	ND
Contents, small intestine	1500000	1160000	2900000[a]	122000	3520	565	17700	BLQ	ND	ND
Contents, stomach	1470000	407000	138000	4500	451	BLQ	742	ND	ND	ND
Diaphragm	6670	16600	13800	6240	506	ND	ND	ND	ND	ND
Epididymis	297	1200	1920	1040	965	BLQ	BLQ	ND	ND	ND
Esophagus	21300	27200	35400	4720	341	ND	ND	ND	ND	ND
Exorbital lacrimal gland	1880	14800	15400	24900	2510	BLQ	BLQ	ND	ND	ND
Eye	418	2570	3120	5540	4520	1890	1460	1070	607	613
Eye Lens	ND	ND	ND	ND	ND	ND	ND	ND	ND	BLQ
Eye uveal tract	3030	17300	22400	39500	25800	13700	8750	7300	4790	4460
Fat (abdominal)	865	1160	763	552	BLQ	ND	ND	ND	ND	ND
Fat (brown)	6360	25200	12600	5630	267	ND	ND	ND	ND	ND
Harderian gland	1380	11500	13700	18400	9960	365	BLQ	BLQ	ND	ND
Intra-orbital lacrimal gland	1800	12400	15400	26700	2430	BLQ	ND	ND	ND	ND
Kidney	14700	29500	27900	12900	1630	692	659	348	BLQ	ND
Kidney cortex	15900	28800	27900	12800	1890	707	733	281	ND	ND
Kidney medulla	12600	32500	28700	13600	1060	BLQ	BLQ	BLQ	ND	ND
Large intestine	2380	10500	13400	15800	60000	BLQ	BLQ	ND	ND	ND
Liver	93200	89200	78200	35800	15100	5450	4940	1070	BLQ	ND
Lung	11800	46800	59700	51500	2490	ND	ND	ND	ND	ND
Lymph nodes	1730	9780	11300	16800	2290	ND	ND	ND	ND	ND
Meninges	ND	2390	2190	961	ND	ND	ND	ND	ND	ND
Muscle	1700	7110	6420	4690	289	ND	ND	ND	ND	ND
Myocardium	8650	18000	13700	7630	505	ND	ND	ND	ND	ND
Nasal turbinates	399	1290	3180	2550	847	ND	ND	ND	ND	ND
Pancreas	5280	26300	20400	11000	589	ND	ND	ND	ND	ND
Pituitary gland	5900	37100	33500	44600	14600	1300	542	ND	ND	ND
Preputial gland	982	5650	14100	10400	5060	1720	1010	695	BLQ	ND
Prostate gland	1400	8530	8410	11300	1110	BLQ	BLQ	ND	ND	ND
Salivary gland	5240	25500	26800	16400	6450	ND	BLQ	ND	ND	ND
Seminal vesicle	BLQ	1040	1020	4110	1290	ND	ND	ND	ND	ND
Skin (nonpigmented)	806	4170	4440	3220	825	ND	ND	ND	ND	ND
Skin (pigmented)	1230	4660	5200	3480	4760	1700	2740	899	536	501
Small intestine	2980	9810	15300	17300	1210	BLQ	BLQ	ND	ND	ND
Spinal cord	BLQ	490	350	427	BLQ	ND	ND	ND	ND	ND
Spleen	11300	34400	28900	24900	3040	BLQ	BLQ	BLQ	ND	ND
Stomach	3850	9700	10500	5540	396	ND	ND	ND	ND	ND
Stomach mucosa	9390	22500	22800	4620	1360	ND	ND	ND	ND	ND
Stomach wall	1660	5070	6500	4540	499	ND	ND	ND	ND	ND
Testis	BLQ	556	838	960	871	506	BLQ	BLQ	ND	ND
Thymus	1300	7920	8100	11400	2010	ND	ND	ND	ND	ND
Thyroid	9350	30400	16800	14500	982	BLQ	ND	ND	ND	ND
Urinary bladder	6030	45900	12700	5370	358	ND	ND	ND	ND	ND
Urine	1750	57900	53400	6760	BLQ	BLQ	288	BLQ	ND	ND
von Ebner's gland	ND	22000	21100	25300	ND	ND	ND	ND	ND	ND

BLQ Below the limit of quantitation (<264 ng equivalents ^{14}C-GDC-0973/g).
ND Not detectable (sample shape not discernible from background or surrounding tissue).

(Excerpted from Applicant's submission)

Table 11: Timecourse of [14C]cobimetinib exposure as measured by QWBA in blood and tissues of the SD rat

	ng Equivalents ^{14}C-GDC-0973/g			
	Animal Number (Sacrifice Time)			
Matrix	B19637 (1 Hour)	B19638 (8 Hours)	B19639 (24 Hours)	B19640 (120 Hours)
Adrenal gland	23900	35000	3420	BLQ
Bile	140000	41200	ND	ND
Blood	1100	594	BLQ	ND
Bone	306	388	BLQ	ND
Bone marrow	7040	12500	1240	ND
Brain cerebellum	BLQ	BLQ	BLQ	ND
Brain cerebrum	BLQ	BLQ	BLQ	ND
Brain choroid plexus	3050	5530	1720	ND
Brain medulla	BLQ	311	BLQ	ND
Brain olfactory lobe	BLQ	BLQ	BLQ	ND
Bulbo-urethral gland	5870	9960	878	ND
Cecum	3950	15600	1190	ND
Contents, cecum	880	321000	59100	BLQ
Contents, esophageal	56900	936	2180	BLQ
Contents, large intestine	1670	496000	119000	486
Contents, small intestine	1330000	51700	12700	ND
Contents, stomach	421000	7190	7030	ND
Diaphragm	10000	4900	1080	ND
Epididymis	484	2230	1740	ND
Esophagus	4070	3400	554	ND
Exorbital lacrimal gland	6010	30000	10400	BLQ
Eye	555	431	BLQ	ND
Eye lens	ND	ND	ND	ND
Eye uveal tract	3250	3350	544	ND
Fat (abdominal)	1210	1360	BLQ	BLQ
Fat (brown)	10600	6610	1120	ND
Harderian gland	2670	18000	12000	ND
Intra-orbital lacrimal gland	4150	27400	10600	ND
Kidney	21200	11800	3430	496
Kidney cortex	21000	11700	3750	683
Kidney medulla	18900	12400	3040	BLQ
Large intestine	3820	6720	1440	ND
Liver	67400	27300	14800	3760
Lung	20900	31300	3870	ND
Lymph nodes	2950	14400	3490	ND
Meninges	1070	1500	ND	ND
Muscle	2570	3800	551	ND
Myocardium	12400	6270	1060	ND
Nasal turbinates	545	1840	343	ND
Pancreas	12100	8760	1900	ND
Pituitary gland	9090	29600	5920	ND
Preputial gland	2710	10100	3420	2600
Prostate gland	2120	2930	754	ND
Salivary gland	10300	12600	2380	ND
Seminal vesicle	598	1020	1230	ND
Skin (nonpigmented)	1680	3250	657	BLQ
Small intestine	10900	8320	7390	ND
Spinal cord	BLQ	BLQ	BLQ	ND
Spleen	17700	23500	4080	BLQ
Stomach	6120	4280	1000	ND
Stomach mucosa	11600	3510	1600	ND
Stomach wall	1650	4510	888	ND
Testis	BLQ	621	792	288
Thymus	2210	9860	2740	ND
Thyroid	15100	15700	1050	ND
Urinary bladder	5100	4840	4560	286
Urine	13300	12200	1230	BLQ
von Ebner's gland	ND	16200	2080	ND

BLQ Below the limit of quantitation (<264 ng equivalents ^{14}C-GDC-0973/g).
ND Not detectable (sample shape not discernible from background or surrounding tissue).

(Excerpted from Applicant's submission)

5.1.2 METABOLISM

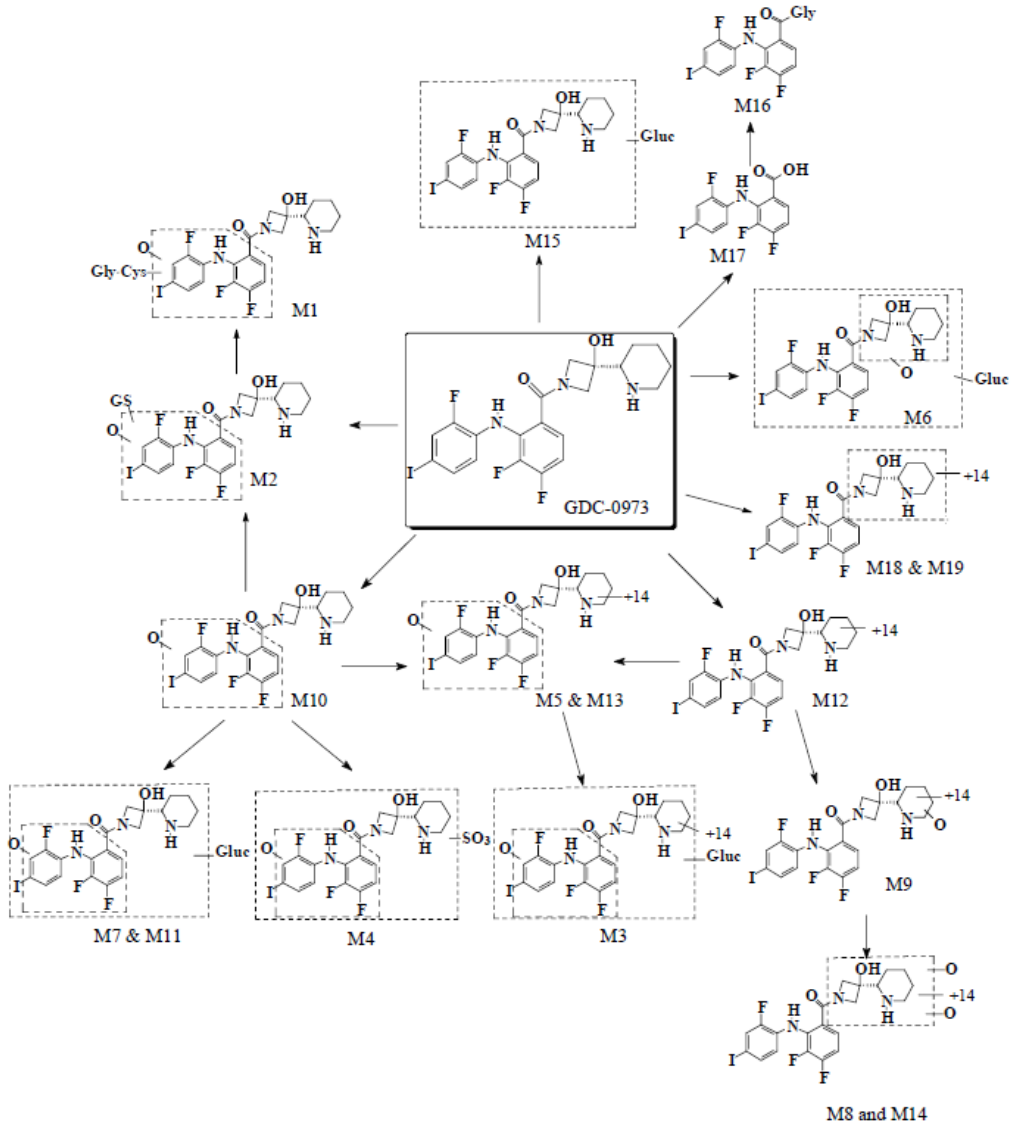
5.1.2.1 Metabolite Radio-profiling and Identification in Plasma, Urine, Bile, and Feces from Rats Following Oral Administration of [14C]GDC-0973 (Report #09-0833)

To characterize the metabolism of cobimetinib, the Applicant performed a single-dose study in the SD rat, and evaluated concentrations of radioactivity in the blood, bile, urine

and feces following administration of a single oral dose of 30 mg/kg (400 µCi/kg) of [^{14}C]cobimetinib. Samples were collected over a 192 hour period post-dose during which the total recovery of radioactive dose from all collected matrices was 88.7% and 90.0% of the administered dose from intact male and female rats, respectively.

The major circulating species was parent. Unchanged parent accounted for approximately 63 and 74% (by AUC) of the circulating dose in males and females, respectively. There were eleven circulating metabolites, of which, only M16, accounted for more than 4% of the administered dose.

Figure 12: Proposed metabolic pathway of cobinetinib in the rat



Gly = glycine; Gluc = glucuronide, Gly-Cys = glycinylcysteine; GS = glutathione

(Excerpted from Applicant's submission)

The major route of elimination was via the feces. In the first 48 hours of sample collection, 83.5 and 79.7% of the recovered dose was accounted for in feces from males and females, respectively. Of the recovered dose, 56.8% and 67.1% of the drug-related material was structurally identified, of which, only a small fraction (5.6% and 9.1% in males and females respectively) was recovered as unchanged parent. The majority of the fecally-eliminated material (40.8% and 51.2% of the administered dose in males and females, respectively), consisted of M10 metabolite (an hydroxylated metabolite; Figure 12). None of the other fecal metabolites accounted for more than 4.5% of the total administered dose.

In bile duct-cannulated males and females, respectively, 80.6 and 74.2% of the eliminated dose was recovered in the first 48 hours. Of that amount, only ~ 1% of the dose was unchanged parent. The bulk of the drug-related material detected in bile (40.2 and 50.6% in males and females, respectively) was M7 metabolite, which was structurally characterized as a glucuronide conjugate of the M10 metabolite.

Urinary excretion was considered a minor route of elimination, and accounted for < 5% of the delivered dose in males and females.

Table 12: Estimated plasma AUC0-48 and PK parameters for cobimetinib and its metabolites in the rat

Metabolite Code	$[M+H]^+$ or $[M-H]^-$ *m/z*	HPLC R_t (min)	Male					Female				
			AUC_{0-48} (ng-Eq*hr/mL)	%[b]	C_{max} (ng-Eq/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC_{0-48} (ng-Eq*hr/mL)	%[b]	C_{max} (ng-Eq/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
TRA[a]			22738	100	1553	4	9.37	30183	100	1958	4	9.61
GDC-0973	532[c]	46.4	14403	63.3	910	4	10.1	22351	74.1	1145	8	9.75
M7	724[c]	32.6	D	D	D	D	D	1109	3.7	204	1	NA[e]
M10	548[c]	40.6	D	D	D	D	D	136	0.5	6.59	24	NA[e]
M13	562[c]	48.5	268	1.2	9.46	24	NA[e]	D	D	D	D	D
M5	562[c]	49.6	146	0.6	22.8	4	NA[e]	D	D	D	D	D
M9	562[c]	53.6	270	1.2	33.4	1	18.9	349	1.2	65.4	4	NA[e]
M12	546[c]	55.0	789	3.5	47.4	24	NA[e]	792	2.6	118	4	NA[e]
M14	578[c]	56.0	262	1.2	65.2	1	1.95	D	D	D	D	D
M16	449[d]	60.0	1526	6.7	120	4	18.2	882	2.9	72.1	4	7.53
M17	392[d]	65.0	221	1.0	38.0	1	13.9	285	0.9	18.0	8	NA[e]

D: detected by radioprofiling and/or LC-MS; however, not enough data points for the calculation of AUC values.

[a] TRA = Concentration of total radioactivity in plasma samples from rats (Table C-1)

[b] $\%AUC_{0-t} = AUC_{0-t}$ (individual metabolite region)/AUC_{0-t} (plasma TRA) x 100%. Only those peaks which were detected at least at three time-points were integrated.

[c] $[M-H]^+$ in positive ion mode

[d] $[M-H]^-$ in negative ion mode

[e] Not applicable; insufficient data points (less than two data points past t_{max}) for reliable $t_{1/2}$ determination.

Note: M18 and M19 were detected only by LC-MS. All the PK values were calculated using WinNonlin™ version 4.1.

(Excerpted from Applicant's submission)

Table 13: Percent distribution (%dose) of GDC-0973 and selected metabolites in 0-72 hour urine and 0-48 hour feces from intact rats and the 0-48 hour bile samples from bile duct cannulated rats

Metabolites	$[M+H]^+$ or $[M-H]^-$ m/z	HPLC R_t (min)	Dose (%)							
			Urine (Group 1) (0-72 hr)[a]		Feces (Group 1) (0-48 hr)[b]		Sum of Urine and Feces (Group 1)		Bile (Group 2) (0-48 hr)[c]	
			Male	Female	Male	Female	Male	Female	Male	Female
GDC-0973	532[f]	46.4	0.3	0.7	5.6	9.1	5.9	9.8	0.9	1.2
M1	724[f]	24.0	ND	ND	ND	ND	ND	ND	3.0	2.4
M2	853[f]	25.8	ND	ND	ND	ND	ND	ND	3.8	1.1
M7	724[f]	32.6	0.1	0.1	ND	ND	0.1	0.1	40.2	50.6
M3	738[f]	34.0	<0.1	<0.1	ND	ND	<0.1	<0.1	1.0	0.8
M11	724[f]	36.6	<0.1	<0.1	ND	ND	<0.1	<0.1	3.2	2.7
M10	548[f]	40.6	0.2	<0.1	40.8	51.2	41.0	51.2	5.0	4.7
M15	708[f]	42.0	0.1	<0.1	ND	ND	<0.1	<0.1	1.3	1.2
M4	628[f]	45.0	<0.1	<0.1	ND	ND	ND	ND	1.3	0.2
M13	562[f]	48.5	<0.1	<0.1	0.4	<0.1	0.4	<0.1	0.2	0.1
M5	562[f]	49.6	<0.1	<0.1	4.5	2.4	4.5	2.4	0.9	0.3
M6	724[f]	50.0	0.1	0.1	ND	ND	0.1	0.1	ND	0.2
M8	578[f]	51.0	<0.1	0.1	ND	ND	ND	0.1	1.6	0.8
M9	562[f]	53.6	<0.1	0.2	1.6	1.4	1.6	1.6	0.8	0.7
M12	546[f]	55.0	<0.1	<0.1	1.0	0.9	1.0	0.9	0.2	0.7
M14	578[f]	56.0	<0.1	0.6	2.3	1.4	2.3	2.0	1.4	0.6
M16	449[g]	60.0	ND	<0.1	ND	ND	ND	<0.1	ND	<0.1
M17	392[g]	65.0	<0.1	<0.1	0.6	0.7	0.6	0.7	0.1	<0.1
Subtotal[d]			0.8	1.8	56.8	67.1	57.6	68.9	65.0	68.2
Total percentage of excretion[e]			2.06	3.27	83.5	79.7	85.6	83.0	80.6	74.5

ND: Non-detectable; $[M+H]^+$ = protonated molecular ion; $[M-H]^-$ = deprotonated molecular ion; m/z = mass to charge ratio; RT = retention time

[a] %Dose of each metabolite in the pooled 0-72-hour male or female rat urine. Relative percent distribution in the urine samples from HPLC radio-profiles can be founded in Table L-7 and Table L-8.

[b] %Dose of each metabolite in the pooled 0-48-hour male or female rat feces. Relative percent distribution in the fecal samples from HPLC radio-profiles can be founded in Table L-9 and Table L-10.

[c] %Dose of each metabolite in the pooled 0-48-hour male or female rat bile. Relative percent distribution in the bile samples from HPLC radio-profiles can be founded in Table L-5 and Table L-6.

[d] These values represent the total percentage of the dose for the listed metabolites; the remainder of the radioactivity was distributed in various peaks (each represents <5% of the dose) throughout the radio-chromatogram. These peaks were not characterized.

[e] These data represent total percentage of the excretion from each route in the time period of sample pooled (Table D-1).

[f] $[M+H]^+$ in positive ion mode.

[g] $[M-H]^-$ in negative ion mode

Note: M18 and M19 were detected only by LC-MS.

(Excerpted from Applicant's submission)

5.1.2.2 CYP and UGT Reaction Phenotyping of GDC-0973.23 Using Human Liver Microsomes, Recombinant Cytochrome P450 (rCYP), and Recombinant UGT (rUGT) (Report: 10-0264)

The Applicant performed a study of cobimetinib in human liver microsomes using selective inhibitors of CYPs (cytochrome P450 enzymes) and UGTs (uridine 5'-diphospho-glucuronosyltransferases) to identify the enzymes responsible for its metabolism. The results of this study demonstrated that cobimetinib undergoes NADPH-dependent oxidative metabolism in human liver microsomes that can be inhibited by the pan-CYP inhibitor, ABT. To identify which CYP enzyme was responsible for the metabolism of cobimetinib, the Applicant performed a series of inhibition studies using selective inhibitors of specific CYP isoenzymes. The results,

which are summarized in Table 14, indicate that cobimetinib is metabolized primarily by CYPs 3A4 and 3A5.

Data in patients demonstrated the presence of a glucuronide metabolite in human plasma (denoted human metabolite M15). To determine the potential for DDI resulting from inhibition of this metabolite, the Applicant incubated cobimetinib with recombinant UGTs. As illustrated in Table 15, the formation of M15 appears to be mediated at least in part by rhUGT2B7. This was confirmed in HLMs using the UGF2B7 inhibitor, fluconazole. In the presence of the inhibitor, there was a ~33-44% decrease in the percent of M15 at the end of the incubation (Table 16).

Table 14: Relative proportion of cobimetinib remaining after 60-minute incubation with HLM in the presence of selective 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.

(Excerpted from Applicant's submission)

Table 15: Relative percentage of M15 present after incubation with rUGT enzymes

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%.

(Excerpted from Applicant's submission)

Table 16: Relative percentage of M15 present after incubation with HLMs or rUGT in the presence of UGT2B7 inhibitor fluconazole

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%.

(Excerpted from Applicant's submission)

5.1.2.3 Metabolite radioprofiling and identification in plasma, bile, urine and feces from dogs following oral administration of [^{14}C]GDC-0973 (Report #10619)

The purpose of this study was to identify the metabolites of cobimetinib in intact and bile duct-cannulated dogs following administration of a single oral 5 mg/kg (20 µCi/kg) dose. Plasma samples were collected predose, and at 1, 2, 4, 6, 24 and 48 hours post-dose. Samples from each individual (N = 6) each timepoint were subsequently pooled by timepoint. Pooled urine samples were collected for the following intervals: 0-6, 6-12, and 12-24 hours post-dose, and pooled fecal samples were collected at 24 hour intervals through the end of the study. Extracted samples were fractionated by HPLC and analyzed for radiation content by scintillation counting. Metabolite characterization

was accomplished by LC-MS/MS in conjunction with a radioactivity monitor to identify metabolite peaks.

The mean recovery from all matrices was between 91.4-91.7% from intact male and female beagle dogs. The major circulating species in dog plasma was the parent. Ten minor metabolites were identified in the plasma (M9, M12, M15, M17, M26, M28, M30, M32, M40 and M42). None accounted for more than 9% of the total circulating radioactivity. Among the identified metabolites, M9+M40 (combined) and M12 accounted for 8.8 and 6.9%, respectively, of the circulating radioactivity (Table 16). Other, lower-abundance minor species identified by LC/MS included M8, M10, M14, M18, M19, M20, M31, M33, M34, M37, M38, M39, and M41.

Eleven metabolites were identified in urine (Table 17). In the dog, urine was a minor route of clearance; only ~7% of the total dose was cleared in the urine in male and female dogs over the 240 hour post-dose period, and of that, the majority was eliminated during the first 96 hours (Table 17). Each of the metabolites eliminated in urine represented <1% of the total dose. Unchanged parent represented between 0.2-0.3% of the eliminated dose in urine. The following metabolites were identified in urine: M9, M17, M20, M21, M26, M28, M32, M36, M39 M40 and M42.

Fecal elimination was the major route of clearance in the dog. Between 81.8-83.3% of the total dose was identified in feces of male and female dogs, respectively, over the 240 hour post-dose period, and the majority of that was eliminated during the first 96 hours. The following metabolites were identified in feces: M9, M10, M12, M17, M21, M28, M29, M32, M33, M34, M35, M36, M39, M40, M42, and M43. The most prominent of these (each accounting for 2.8-8.0% of the administered dose) were M9, M10, M21, M28, M34, M35, M40, and M42. In addition, other low-abundant metabolites identified by LC/MS included M26, M30, M31, and M41.

Approximately 65% of the dose was recovered in bile during the 168 hour sampling period in male BDC dogs, the majority of which was eliminated during the first 72 hours (Table 17). Unchanged parent accounted for only 3% of the total dose. The predominant metabolites were M7, M9, M17, M20, M22, M24+M25, M28, and M40, each of which accounted for between 2.2-4.9% of the administered dose. Eleven other metabolites were identified, which individually accounted for < 2% of the administered dose. Other, lower-abundance species included M8, M14, M18, M27, M31, M37, M38, M39, and 2F-4I-aniline. These were identified by LC/MS.

Reference ID: 3768701

Table 17: Excretion (% dose) of cobimetinib and its major metabolites in urine and feces from intact dogs (Group 1) and in bile from BDC dogs (Group 2)

Metabolites	$[M+H]^{+f}$ or $[M-H]^{-g}$ *m/z*	HPLC R_t (min)	Dose excreted (%)						
			Urine (Group 1) (0-96 hr)[a]		Feces (Group 1) (0-72 hr)[b]		Sum of Urine and Feces (Group 1)		Bile (Group 2) (0-72 hr)[c]
			Male	Female	Male	Female	Male	Female	Male
GDC-0973	532	56.6[i]	0.28	0.21	3.24	2.36	3.52	2.57	3.13[i]
M1	724	27.4	ND	ND	ND	ND	ND	ND	1.68
M7	724	36.4	ND	ND	ND	ND	ND	ND	4.88
M9	562	71.6	0.77	0.78[j]	2.97	7.09[k]	3.74	7.87[j,k]	3.72
M10	548	44.4	ND	ND	4.08	4.49	4.08	4.49	ND
M12	546	76.4	ND	ND	1.93	2.13	1.93	2.13	1.75
M15	708	46.1	ND	ND	ND	ND	ND	ND	1.35
M17 (Exel-0382)	392[g]	86.1	0.14	0.14	2.20	2.25	2.34	2.39	3.43
M20	598	18.9	0.40	0.41	ND	ND	0.4	0.41	4.72
M21	422	24.4	0.56	0.52	6.91	7.96	7.47	8.48	ND
M22	736	25.6	ND	ND	ND	ND	ND	ND	3.04
M23	720	26.6	ND	ND	ND	ND	ND	ND	1.42
M24+M25	754, 724	34.9	ND	ND	ND	ND	ND	ND	2.23
M28	564	47.1[i]	0.21	0.18	4.31	4.49	4.52	4.67	3.44[i]
M29	578	58.4	ND	ND	1.04	1.22	1.04	1.22	ND
M30	548	46.9	ND	ND	ND	ND	ND	ND	0.85
M32	563	80.1	1.04	0.81	0.96	0.92	2.00	1.73	0.63
M33	564	52.4	ND	ND	ND	ND	ND	ND	0.93
M34	578	57.7	ND	ND	4.77	5.47	4.77	5.47	ND
M35	562	61.1[i]	ND	ND	3.37	2.83	3.37	2.83	0.83[h]
M36	579	68.4	0.29	0.29	2.70	2.67	2.99	2.96	0.70
M39	564	64.4	0.14	0.16	1.80	1.90	1.94	2.06	ND
Unknown	NA	69.9	ND	ND	ND	ND	ND	ND	0.98
M40	565	71.6	0.15	0.78[j]	4.90	7.09[k]	9.87	7.87[j,k]	3.44
M42	521	79.4	0.99	0.82	3.33	3.44	4.32	4.26	0.86
M43	562	60.4[i]	ND	ND	1.55	1.99	1.55	1.99	0.62[h]
Subtotal[d]			4.97	4.32	51.1	51.2	56.1	55.5	44.6
Total percentage of excretion[e]			6.79	6.17	79.2	81.1	86.0	87.3	63.4

ND: Non-detectable; $[M+H]^+$ = protonated molecular ion; $[M-H]^-$ = deprotonated molecular ion; *m/z* = mass to charge ratio; R_t = retention time

[a] % Dose of each metabolite in the pooled 0-96-hr male or female dog urine. Relative percent distribution in the urine samples from HPLC radioprofiles can be founded in Table N-7 and Appendix L.

[b] % Dose of each metabolite in the pooled 0-72-hr male or female dog feces. Relative percent distribution in the fecal samples from HPLC radioprofiles can be founded in Table N-8 and Appendix M.

[c] % Dose of each metabolite in the pooled 0-72-hr male dog bile. Relative percent distribution in the bile samples from HPLC radioprofiles can be founded in Table N-4 and Appendix K.

[d] These values represent the total percentage of the dose for the listed metabolites; the remainder of the radioactivity was distributed in various peaks (each represents <5% of the dose) throughout the radio-chromatogram. These peaks were not characterized.

[e] These data represent total percentage of the excretion from each route in the time period of sample pooled (Table C-1, Table C-2, and Table C-3).

[f] $[M+H]^+$ in positive ion mode.

[g] $[M-H]^-$ in negative ion mode; only Excel-0382 was analyzed in negative ion mode.

[h] The two compounds coeluted in bile. %distribution of each compound in the coeluted fraction was calculated based on the data obtained by Dynamic flow (Figure K-3); M35 (0.83%dose), M43 (0.62% dose). However, they were separated in feces radioprofiling.

[i] The retention time of GDC-0973 and metabolite M28, M35, and M43 was shifted later in bile sample.

[h] The two compounds, M35 and M43, coeluted in bile. %distribution of each compound in the coeluted fraction was calculated based on the data obtained by Dynamic flow (Figure K-3); M43 (0.62% dose), M35 (0.83%dose). They were separated in feces radioprofiling.

[i] The retention time of GDC-0973 and M28 was slightly later in dog bile sample due to matrix effects.

[j,k] The two compounds coeluted in female bile and urine.

(Excerpted from Applicant's submission)

Table 18: Estimated plasma AUC_{0-24} and PK parameters for cobimetinib and its metabolites following oral administration to intact male and female dogs (Group 1)

Metabolite Code	$[M+H]^+$ *m/z*	HPLC R_t (min)	Male and Female				
			AUC_{0-24} hr*ng-Eq./mL	%[b]	C_{max} (ng-Eq./mL)	T_{max} (hr)	$T_{1/2}$ (hr)
TRA[a]			21608	100	1470	3	9.00
GDC-0973	532[c]	~55	13075	60.5	794	3	9.81
M9 + M40	562/565[c]	71.6	1893	8.76	116	3	10.9
M12	546[c]	76.6	1499	6.94	124	3	9.86

[a] TRA = Concentration of total radioactivity in the extractable plasma samples from dogs (Table N-5). Note that the unextractable residues (in pellets) were excluded.

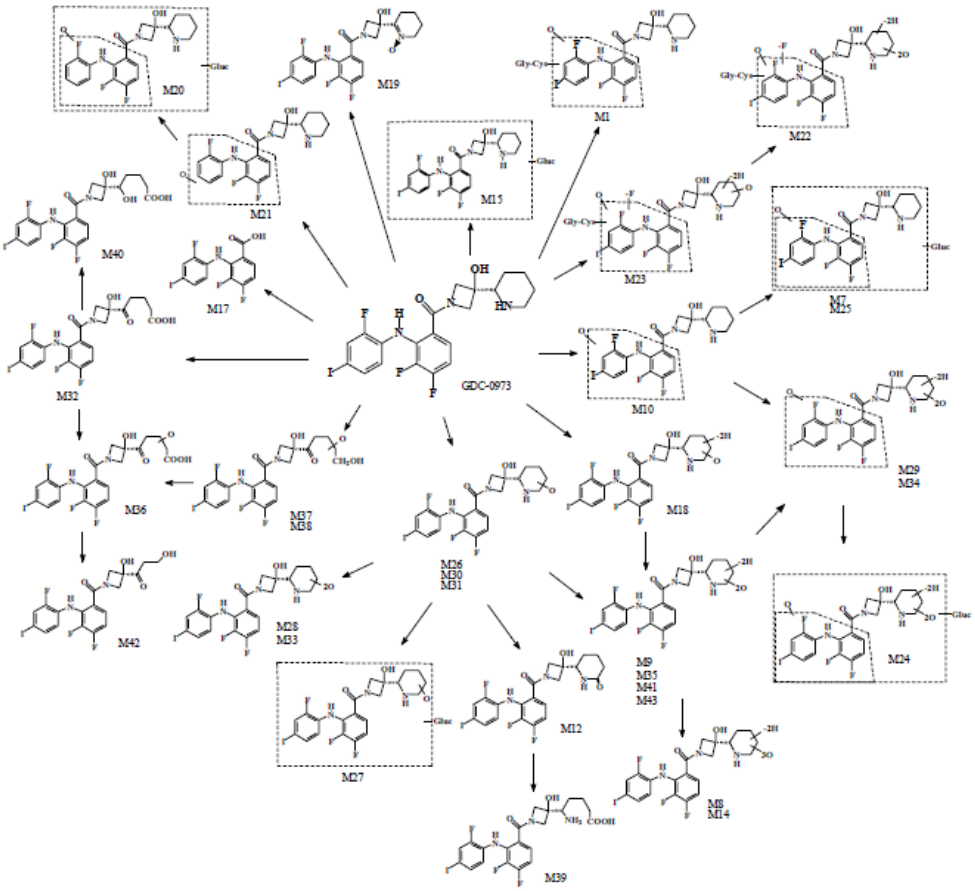
[b] $\%AUC_{0-t} = AUC_{0-t}$ (individual metabolite region)/AUC_{0-t} (plasma TRA) x 100%. Only those peaks which were detected at least at three time-points were integrated.

[c] $[M+H]^+$ in positive ion mode.

Note that the AUC value was calculated using WinNonlin software. The concentration of plasma samples at 0.5-, 3-, 6-, 12-, and 24-hr were used for the calculation of PK parameters.

(Excerpted from Applicant's submission)

Figure 13: Proposed metabolic pathway for cobimetinib in the dog



Gluc = glucuronic acid, Gly-Cys = glycinylcysteine

Note that the position of F, I, may have been changed upon oxidation and/or conjugation on 2F-4I-phenyl moiety.

The bold arrows indicated the major metabolic pathways.

(Excerpted from Applicant's submission)

5.1.3 EXCRETION

5.1.3.1 Excretion Mass Balance and Pharmacokinetics of Radioactivity Following a Single Oral Dose of [14C]GDC-0973 to Male and Female Sprague Dawley Rats (Report #274N-0901 Revision 1)

The purpose of this study was to determine the extent and rate of total radioactivity excreted by male and female SD rats in the urine, feces and bile, and to evaluate the PK in male and female rats. All animals received a single oral dose of [^{14}C] cobimetinib in 0.5% methylcellulose and 0.2% Tween 80 in water. Group 1 consisted of 3M and 3F SD rats for evaluation of mass balance. The radiolabeled material was mixed with unlabeled material to achieve a specific activity of 400 µCi/kg. A separate group (Group 2) of 3M and 3F bile duct-cannulated rats was used to characterize excretion of radioactivity in bile, urine and feces. Group 3 consisted of 3M and 3F rats used for PK of total plasma radioactivity. As illustrated in Table 19 and Figure 14 and Figure 15, the study achieved mass balance. As indicated in Table 19, excretion in bile accounted for a large proportion of the elimination in BDC rats, which suggests that approximately 75-80% of the fecally-eliminated material was excreted in the bile – likely subsequent to Phase 1 and/or Phase 2 metabolic processes – rather than as unabsorbed parent drug. Urinary excretion represents a minor route of elimination in both intact and BDC rats.

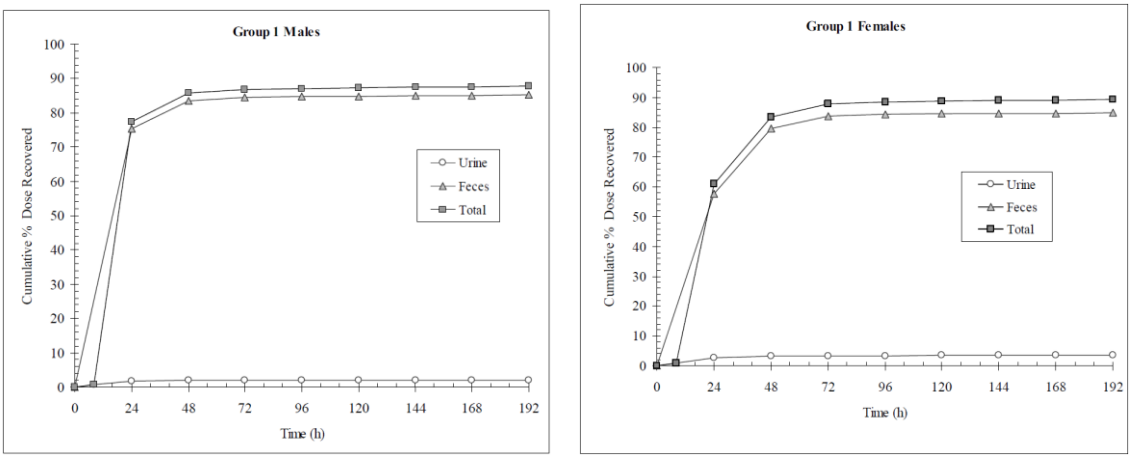
Table 19: Summary of radioactivity collected following oral administration of [^{14}C] Cobimetinib to Group 1 and Group 2 male and female rats

	% of Dose Recovered			
	Group 1 Intact Males (0-192 h)	Group 1 Intact Females (0-192 h)	Group 2 BDC Males (0-48 h)	Group 2 BDC Females (0-48 h)
Urine	2.2 ± 0.3	3.5 ± 0.5	2.6 ± 0.3	4.4 ± 0.4
Feces	85.2 ± 1.6	84.8 ± 2.8	8.0 ± 1.3	8.4 ± 0.8
Bile	NS	NS	80.6 ± 2.3	74.4 ± 1.9
Cage Residue	0.5 ± 0.4	1.2 ± 0.6	0.4 ± 0.1	0.9 ± 0.1
Carcass	0.9 ± 0.3	0.6 ± 0.1	ND	5.1±1.4
Total	88.7 ± 2.0	90.0 ± 1.6	91.6 ± 0.9	93.1 ± 1.3

NS: No sample
ND: Not determined since total recovery for Group 2 was >90% without including carcasses.

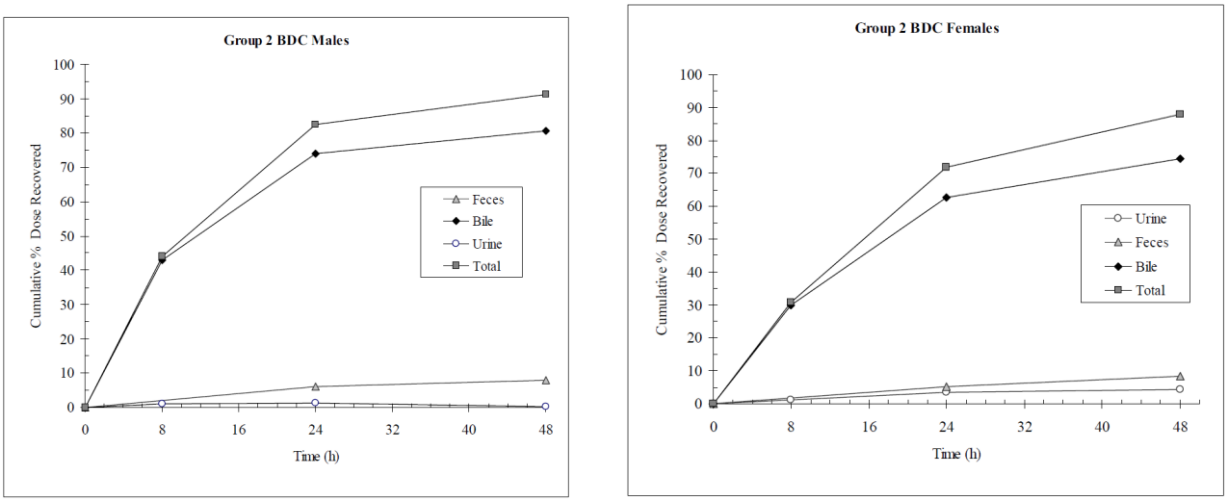
(Excerpted from Applicant's submission)

Figure 14: Mean cumulative recovery of radioactivity for Group 1 (intact) male (top) and female (bottom) rats following oral administration of [^{14}C] cobimetinib



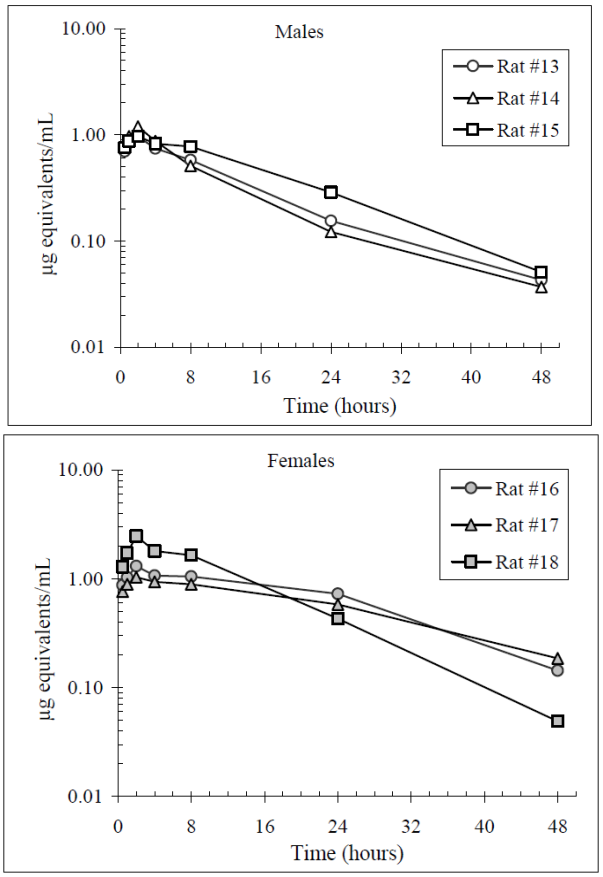
(Excerpted from Applicant's submission)

Figure 15: Mean cumulative recovery of radioactivity for Group 2 (BDC) male (top) and female (bottom) rats following oral administration of [14C] cobimetinib



(Excerpted from Applicant's submission)

Figure 16: Individual plasma concentration-time profiles of total radioactivity for Group 2 (PK) male (top) and female (bottom) rats following oral administration of [14C] cobimetinib



(Excerpted from Applicant's submission)

5.1.3.2 Determination of Radiolabeled Mass Balance, Routes of Excretion, and Metabolic Profiles of [^{14}C]GDC-0973 in Intact and Bile Duct-Cannulated Dogs (Report #8222137)

The purpose of this study was to assess the PK and excretion of [^{14}C] cobimetinib in intact male and female beagle dogs and to BDC male beagle dogs following a single oral dose of 5 mg/kg (20 µCi/kg). Average pharmacokinetic parameters in blood and plasma are summarized in Table 20 for intact and BDC dogs. Peak exposures were observed in intact dogs at 3 hours post dose, and there was no evidence of a gender effect on exposure. Consistent with the known protein-binding profile of cobimetinib, there was no evidence of differential partitioning to the cellular compartment, as plasma radioactivity levels were comparable to those of whole blood.

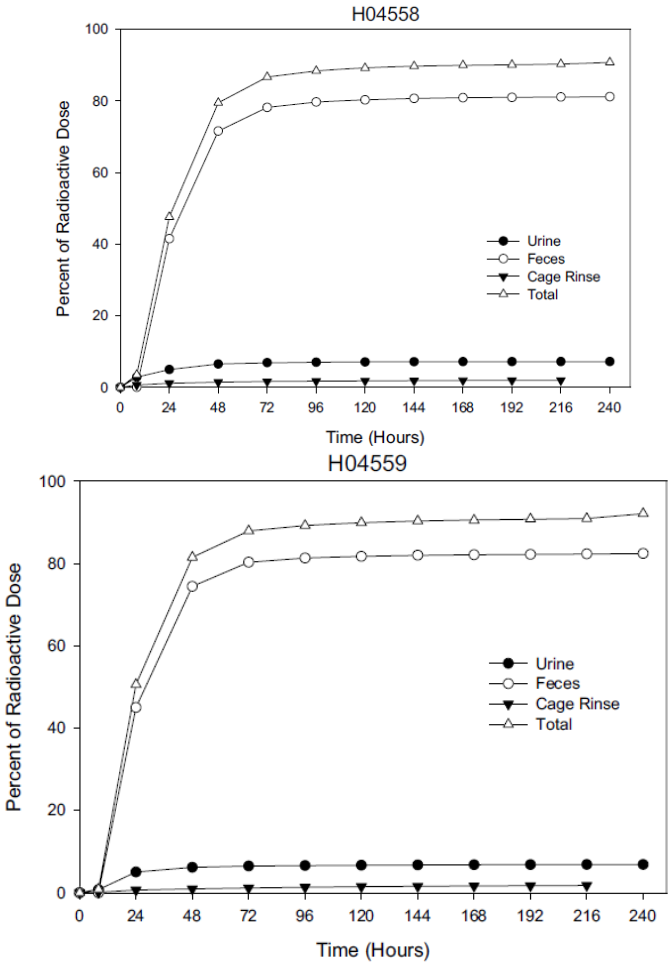
As indicated in Figure 17 and Figure 18, fecal elimination accounted for the majority of the radioactivity in both males and females and elimination was essentially complete within 72 hours. As illustrated in Figure 19, of the fecally-eliminated dose, a significant proportion was accounted for by biliary excretion. Approximately 60% of the dose

measured was present in bile. As in the rat, urinary excretion in the dog accounts for a small proportion of the eliminated dose.

Table 20: Average pharmacokinetic parameters for [^{14}C] cobimetinib in male and female dogs

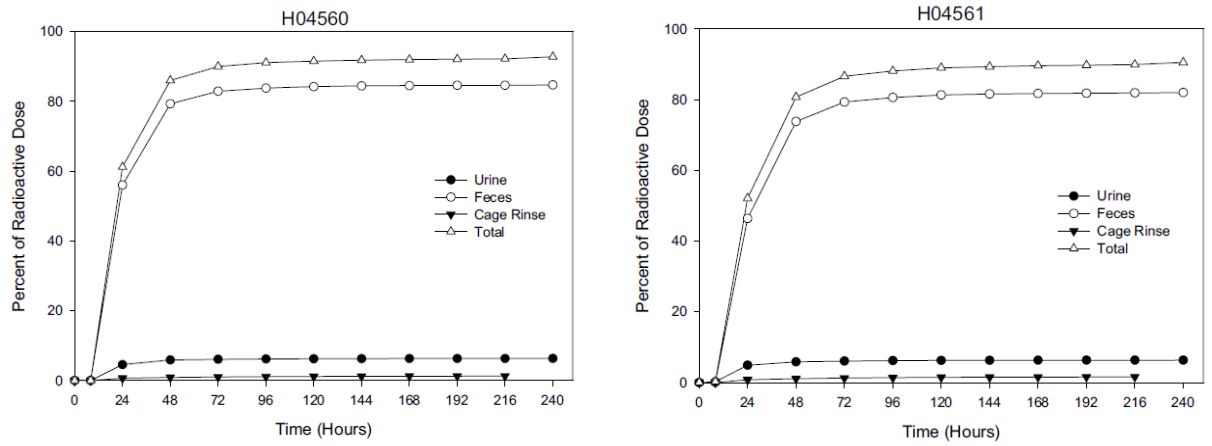
Treatment	Tmax (hr)	Cmax (ng eq/g)	T1/2 (hr)	AUCT (ng eq*hr/g)	AUC∞ (ng eq*hr/g)
Blood Intact M	3.00	1000	150	21400	26200
Plasma Intact M	3.00	1550	141	31600	37000
Blood Intact F	3.00	869	153	17900	22800
Plasma Intact F	3.00	1400	170	28400	35000
Blood BDC M	1.00	1250	113	23400	27000
Plasma BDC M	1.00	1960	111	37400	41200

Figure 17: Cumulative percent of radioactive dose in urine, feces, and cage rinse at specified intervals post-dose in individual intact male dogs



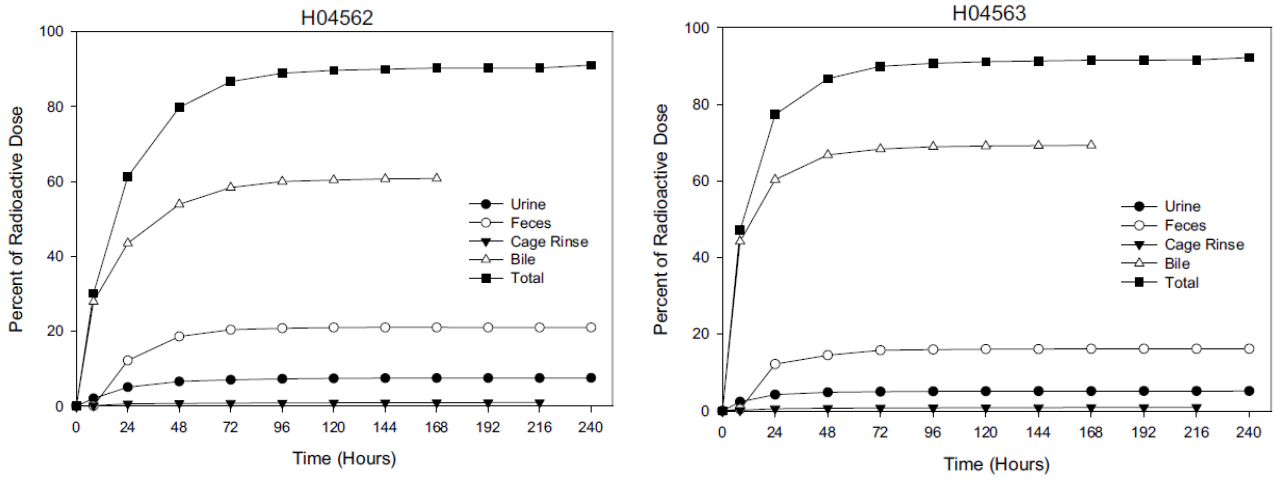
(Excerpted from Applicant's submission)

Figure 18: Cumulative percent of radioactive dose in urine, feces, and cage rinse at specified intervals post-dose in individual intact female dogs



(Excerpted from Applicant's submission)

Figure 19: Cumulative percent of radioactive dose in urine, feces, cage rinse and bile at specified intervals post-dose in individual BDC male dogs



(Excerpted from Applicant's submission)

6 General Toxicology

The Applicant conducted toxicology studies of up to 13-weeks duration in the dog and the rat. Findings were similar across all studies; however, some of the reproductive effects observed in the 4-week studies were not observed in the 13-week studies, which were conducted at lower doses. In the 4-week toxicology studies in the rat and dogs, increased apoptosis/necrosis was observed in the corpora lutea and follicular cysts were observed in the ovaries of female rats. An increase in vaginal epithelial cell apoptosis was also observed in high dose (10 mg/kg) rats. Exposures at this dose level

were about 3-fold higher (C_{max} and AUC) than those observed in humans. No histopathological changes were noted in the reproductive organs of dogs at any dose level; however, it is unclear if the dogs were sexually mature. Exposures at the high dose (1 mg/kg) in this study were less than those observed in humans; C_{max} was approximately 0.8 times the human peak levels, and AUCs were 0.5-0.25 times those observed in humans.

6.2.1 Repeat-Dose Toxicity

Study title: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Rats with a 4-Week Recovery

Study no.:	7359-359
Study report location:	4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	09 July 2007 (first dose)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug: XL518 Lot: 3725-C-R0-01-12-1 Purity: 99.4%

Key Study Findings

- There were no treatment-related effects on any endpoint measured. Occasional clinical signs of skin sores and alopecia were noted in some treated animals; however, there was no apparent relationship to dose.
- There was one preterm death (a high dose male) that occurred on Study Day 30. There were no gross or microscopic findings and no changes in organ weights or preterminal clinical signs that correlated with this outcome; thus, the cause of death was not determined.
- The NOAEL for XL518 in the rat after 13-weeks of daily oral administration was 1 mg/kg/day on the basis of the one preterm death in the high dose group.

Reference ID: 3768701

Methods

Doses:	0, 0.3, 1, and 3* mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	Distilled water
Species/Strain:	Rattus norvegicus, Sprague Dawley (Crl:CD(SD))
Number/Sex/Group:	10/sex (main) 5/sex (recovery in control and high dose groups)
Age:	~ 7 weeks at initiation of treatment
Weight:	Male: 222 to 271 g Female: 170 to 217 g
Satellite groups:	Toxicokinetics: 12/sex/group
Unique study design:	Toxicokinetic assessment of putative metabolite EXEL0382
Deviation from study protocol:	Reported deviations appear to be unlikely to affect overall study interpretation

*The selected high dose of 3 mg/kg/day was based on the observation of significant mortality at the 10 mg/kg dose level in the 1-month study.

Observations and Results

Mortality

There was one preterm death on Study Day 30 in the high dose group. The animal was found dead in its cage following clinical pathology collection. The Applicant considered the cause of death to be procedure-related; however, as the death occurred in a high dose animal, contribution by the test article to the animal's demise cannot be excluded. There were no histopathological changes adequate to assign a cause of death.

All other animals survived to scheduled termination on Study Day 93 or post-dose (Recovery) Day 29.

Clinical Signs

The incidences of the following clinical signs in treated cohorts exceeded those of concurrent controls with no clear relationship to dose: Malocclusion, reactivity/sensitivity to touch, swollen front digits, red discharge from eye(s), alopecia, rough haircoat, and skin scabs.

Body Weights

Unremarkable

Reference ID: 3768701

Table 21: Male Group Mean Body Weights

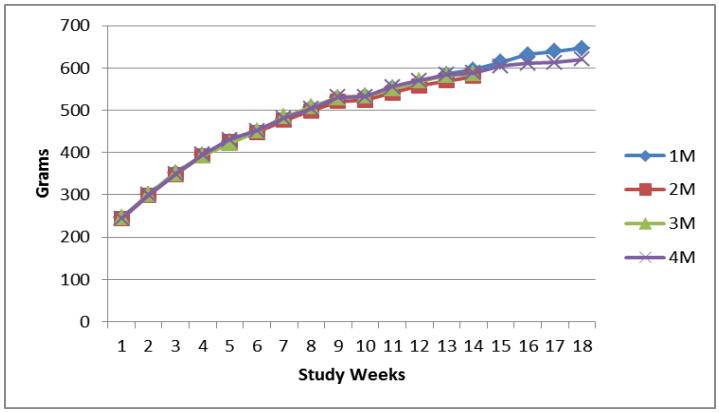
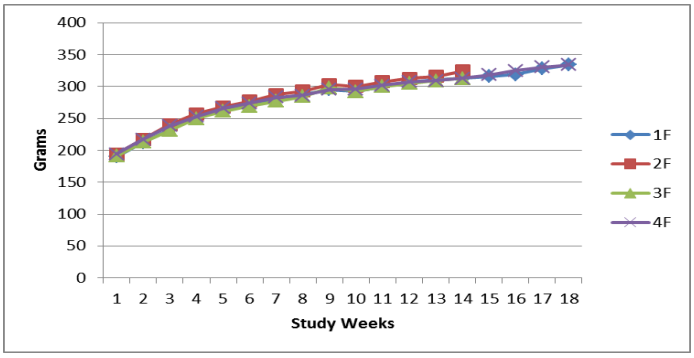


Table 22: Female Group Mean Body Weights



Feed Consumption

Generally unremarkable. A slight decrease in feed consumption was noted in treated animals vs. concurrent controls, particularly late in the study; however, there was no demonstrable effect on body weights.

Ophthalmoscopy

Pale linear streaks were observed in the right and left retinas of 1 mid-dose female. It is unclear whether this effect was treatment-related; however, because it was not noted at the predose examination, an effect of treatment cannot be excluded.

Hematology

Unremarkable.

Clinical Chemistry

There were minor effects on a number of clinical chemistry parameters (decreased cholesterol, increased AST, decreased total protein, decreased albumin and A:G ratio) in females that were neither dose-related in magnitude nor consistently observed over the dose interval (i.e. were transient), and were therefore considered toxicologically insignificant.

Urinalysis

Unremarkable

Gross Pathology

Table 23 summarizes the gross observations. Aside from the finding in the low-dose male lung, there were no correlating histological findings for the observations recorded.

Table 23: Summary of Gross observations

Observation	1M	2M	3M	4M	1F	2F	3F	4F
Lung, discolored		1						
Stomach, glandular, discolored		1						1R
LN, mandibular, discolored		1		1				1
LN, mandibular, large	1	2	3	3			1	

Organ Weights

Unremarkable

Histopathology

Adequate Battery

Yes

Peer Review

No

Histological Findings

The type and severity of histopathological findings observed in treated rats is consistent with the range of findings commonly observed in this age and strain of animals and is therefore of uncertain toxicological significance.

Table 24: Summary of histological findings in the rat

Group (mg/kg/Day)	0	0.3	1	3	0	0.3	1	3
Organ, Histopathological Description **Sex**	Male				Female			
Heart, cardiomyopathy, degenerative	4+2R			6+1R	2			
Kidney, chronic progressive nephropathy	6			5+2R	2R			2+1R
--mineralized tubules								2+1R
Liver, lipidosis, focal				1				
--microvesicular lipidosis, periportal	2R			1+3R				
Lungs, pneumonia, subacute				1				
--hemorrhage, hemoglobin crystals		1						
--pigmented macrophages		1						
Pituitary, hyperplasia, focal, anterior lobe				1				
Prostate, inflammation, subacute				2+2R	--	--	--	--
Rectum, parasitism (nematode)	1				3			1R
Testes, tubular degeneration, unilateral	1R			3				

R = recovery cohort

Reference ID: 3768701

Toxicokinetics

Exposures (peak and overall) to XL518 and its putative metabolite were generally proportional over the dose range evaluated on Day 1 (Table 25 and Table 26). There was evidence of accumulation over the dosing interval in males and females. For both the parent and the metabolite, total accumulation for all dose groups was generally less than 2X over the 90-day dosing period.

Table 25: Summary of mean toxicokinetic parameters for XL518 on Days 1, 45 and 90 after daily oral administration of 0.3, 1 or 3 mg/kg for 13 weeks

Dose (mg/kg)	Day	Sex	$t_{1/2,z}$ (hr)	t_{max} (hr)	C_{max} (ng/mL)	Cmax/D (ng/mL/mg/kg)	AUC_{0-24} (hr*ng/mL)	AUC_{0-24}/D (hr*ng/mL/mg/kg)	AR_{Cmax}	$AR_{AUC0-24}$
0.3	1	F	10.1	6	1.33	4.43	19.0	63.3	NA	NA
		M	NR	8	1.04	3.47	14.0	46.7	NA	NA
	45	F	7.63	4	4.93	16.4	50.0	167	3.71	2.63
		M	6.08	8	1.65	5.50	26.9	89.7	1.59	1.92
	90	F	6.94	4	4.48	14.9	47.4	158	3.37	2.49
		M	7.25	2	2.19	7.30	28.1	93.7	2.11	2.01
1	1	F	4.86	8	6.07	6.07	67.2	67.2	NA	NA
		M	5.85	4	4.74	4.74	50.4	50.4	NA	NA
	45	F	4.34	8	18.3	18.3	185	185	3.01	2.75
		M	9.48	4	8.21	8.21	101	101	1.73	2.00
	90	F	9.41	4	17.8	17.8	176	176	2.93	2.62
		M	5.90	4	9.57	9.57	114	114	2.02	2.26
3	1	F	6.09	6	24.4	8.13	318	106	NA	NA
		M	3.75	8	17.3	5.77	176	58.7	NA	NA
	45	F	6.45	4	57.6	19.2	749	250	2.36	2.36
		M	4.01	8	35.5	11.8	389	130	2.05	2.21
	90	F	5.91	2	77.4	25.8	772	257	3.17	2.43
		M	7.64	4	41.4	13.8	460	153	2.39	2.61

$AR_{AUC0-24}$, accumulation ratio on Days 45 and 90 based on AUC_{0-24}; ARC_{max}, accumulation ratio on Days 45 and 90 based on C_{max}; AUC_{0-24}, area under the plasma concentration-time curve from time 0 to dosing interval of 24 hours; AUC_{0-24}/D, dose-normalized AUC_{0-24}; C_{max}, observed maximum plasma concentration; C_{max}/D, dose-normalized C_{max}; F, female; M, male; $t_{1/2,z}$, terminal phase half-life; t_{max}, time to reach the maximum plasma concentration; NA, not applicable; NR, not reported due to insufficient data at the terminal phase

(Excerpted from Applicant's submission)

Table 26: Summary of mean toxicokinetic parameters of putative metabolite, EXEL0382, on Days 1, 45, and 90 after daily oral administration of 0.3, 1, or 3 mg/kg for 13 weeks

Dose (mg/kg)	Day	Sex	t_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (ng/mL/mg/kg)	AUC_{0-24} (hr*ng/mL)	AUC_{0-24}/D (hr*ng/mL/mg/kg)	%$AUC_{EXEL0382}/AUC_{XL518}$
1	1	F	12	0.237	0.237	1.90	1.90	2.83
		M	NR	NR	NR	NR	NR	NR
	45	F	12	0.356	0.356	3.80	3.80	2.05
		M	NR	NR	NR	NR	NR	NR
	90	F	12	0.346	0.346	4.02	4.02	2.28
		M	NR	NR	NR	NR	NR	NR
3	1	F	12	0.577	0	5.61	1.87	1.76
		M	12	0.427	0	4.53	1.51	2.57
	45	F	12	0.974	0.325	14.1	4.70	1.88
		M	8	0.555	0	6.15	2.05	1.58
	90	F	2	1.50	0.500	21.4	7.13	2.77
		M	8	0.893	0.298	12.2	4.07	2.65

AUC_{0-24}, area under the plasma concentration-time curve from time 0 to dosing interval of 24 hours; AUC_{0-24}/D, dose-normalized AUC_{0-24}; %($AUC_{EXEL0382}/AUC_{XL518}$), %(ratio AUC_{0-24} of EXEL0382 to AUC_{0-24} of XL518)*100; C_{max}, observed maximum plasma concentration; C_{max}/D, dose-normalized C_{max}; F, female; M, male; t_{max}, time to reach the maximum plasma concentration; NA, not applicable; NR, not reported or calculated due to composite mean data concentration below the LLOQ

(Excerpted from Applicant's submission)

Dosing Solution Analysis

Concentration verification was performed on Weeks 1, 4, 9 and 13. All results met pre-specified acceptance criteria.

Homogeneity was performed during Week 1 and all samples met pre-specified acceptance criteria for homogeneity; thus, homogeneity was not conducted again.

6.2.2 Repeat-Dose Toxicity

Study title: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Dogs with a 4-Week Recovery

Study no.:	7359-360
Study report location:	4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	20 June 2007 (1st dose)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug: XL518 Hemifumarate Lot: 3725-C-R0-01-12-01 Purity: 99.4% (HPLC % area)

Key Study Findings

- Mortality was observed at doses of 1 and 3 mg/kg.
- The dose-limiting toxicity in the dog appears to be GI toxicity.
- Other potential histological target organs include kidney, liver, and thyroid.

Methods

Doses:	0, 0.3, 1.0, 3.0/1.0 mg/kg/Day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Distilled water
Species/Strain:	Caninis familaris (Beagle dog; Source: (b) (4))
Number/Sex/Group:	7/Sex in Control and high dose groups 5/Sex in mid- and low-dose groups
Age:	4 months 3 weeks to 5 months 2 weeks of age
Weight:	Males: 7.8 to 10.9 kg Females: 5.8 to 8.3 kg
Satellite groups:	None
Unique study design:	Dose-Reduction: Following dose administration

	on Study Day 10, high dose animals received a dose-holiday and resumed dosing on Day 22 at a dose of 1 mg/kg/Day Replacement: 1 Group 3 male (H46714) that died on Day 1 was replaced on Day 3.
Deviation from study protocol:	Reported deviations appear to be unlikely to have affected overall study interpretation.

Observations and Results

Mortality

Five dogs died at unscheduled intervals (2/sex at the 3 mg/kg dose level and 1 female at the 1 mg/kg dose level).

Preterm Decedent	Observations
H46714 (M) 1 mg/kg	This animal reportedly died on Day 1 of dosing and was replaced; the replacement animal received the same number. There is no cause of death for the Day 1 decedent assigned to this number. All data for the decedent were replaced with those of the replacement.
H46719 (M) 3 mg/kg	Hypoactivity; hypersalivation; bloody liquid/nonformed feces; weight loss; decreased body condition and feed consumption; reddish-brown dried porphyrin crusts on eyelids; dark brown to black liquid diarrhea stained on perianal hair. Animal euthanized on Day 10. Macroscopic Observations: glandular stomach (discolored, mucosa, fundic, red); jejunum (discolored, mucosa, entire, red) Microscopic targets: esophagus, duodenum, jejunum, ileum, cecum, colon, rectum; pancreas; thymus. Cause of death: GI toxicity (esophagus, inflammation / gastro enteropathy)
H46720 (M) 3 mg/kg	Hypoactivity, body weight loss, diarrhea, hypersalivation, red/brown ocular discharge, decreased feed consumption; sunken eyes; injected sclera with yellow/green ocular mucoid discharge. No feed consumption; liquid feces; Animal euthanized on Day 8. Macroscopic Observations: Duodenum, cecum (discolored mucosa, entire, red) Microscopic Targets: kidney, esophagus, duodenum, colon, pancreas, lymph node, thymus, tongue, testis, epididymis Cause of Death: GI toxicity (esophagus, inflammation / gastro enteropathy)

Reference ID: 3768701

H46737 (F) 1 mg/kg	Liquid feces; body weight loss; reduced feed consumption; liquid yellow/brown/black feces with frank blood. Decreased body condition. Animal was euthanized on Day 58. Macroscopic Observations: stomach (discolored pyloric mucosa) Microscopic Targets: marrow, liver, kidney, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, spleen, lymph nodes, thymus, ovary. Cause of Death: GI toxicity (esophagus, inflammation / gastro enteropathy)
H46744 (F) 3 mg/kg	Hypoactivity, excessive salivation, red-tinged/mucoid/liquid feces; recumbency. Euthanized in extremis Day 7. Macroscopic Observations: colon and rectum (discolored, mucosa, entire, red) Microscopic Targets: liver, kidney, esophagus, stomach, duodenum, colon, cecum, rectum, thymus, ovary Cause of Death: GI toxicity (esophagus, inflammation / gastro enteropathy)
H46748 (F) 3 mg/kg	Excessive salivation, hypoactivity, mucous membranes dark pink/purple; bloody/mucoid/black tarry feces. Animal euthanized in extremis on Day 7. Death listed as accidental; however, clinical signs were consistent with those of other preterm deaths. Macroscopic Observations: None Microscopic Targets: Liver, kidney, urinary bladder, esophagus, duodenum, colon, ileum, cecum, thymus, ovary Cause of Death: Gavage-related death

Clinical Signs

The following clinical signs were considered treatment-related: dehydration, thin appearance, hypoactivity, recumbency, excess salivation, emesis, discolored/liquid feces, alopecia, clear/cloudy discharge from eyes.

Reference ID: 3768701

Body Weights

Figure 20: Mean Body Weights in Males

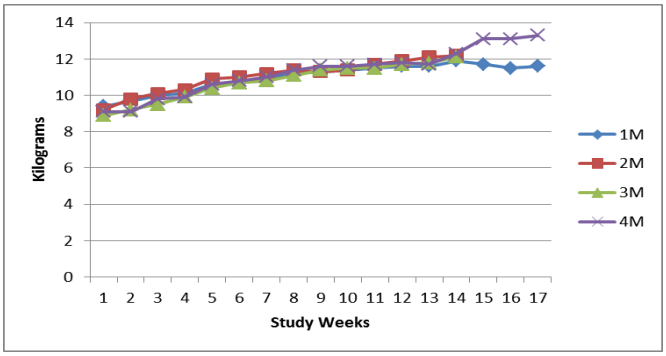
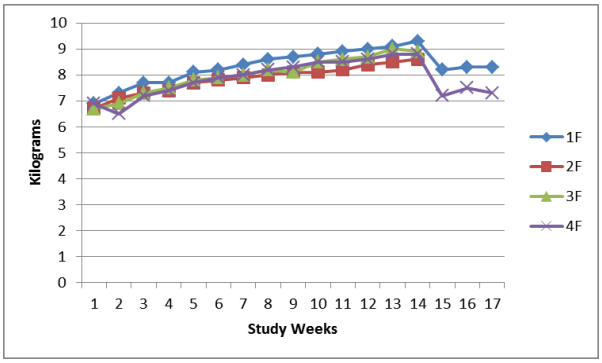


Figure 21: Mean Body Weights in Females



Feed Consumption

Generally unremarkable. All treated females exhibited a statistically-significant reduction in feed consumption during Study Week 13, but this was likely unrelated to treatment, as no treatment-related effect on feed consumption was noted at other times during the study.

Ophthalmoscopy

Unremarkable

ECG

Unremarkable

Hematology

Unremarkable. Sporadic, statistically-significant changes in mean hematology appeared to have lack relationship with dose, were inconsistently observed (i.e. transient), or were within the range of normal values.

All preterm decedents except for Female H46737 in Group 3 died prior to the first dosing-phase blood collection timepoint on Day 30. Consistent with the signs of GI bleeding observed in preterm decedents, this female exhibited low red cell indices (RBCs, Hgb, Hct) but did not exhibit increased reticulocytes (i.e. non-regenerative). Other hematology parameters appeared to be within normal ranges.

Several surviving high-dose animals also exhibited low red cell indices during the dosing phase; however, there were no statistically significant effects on mean parameter values.

Clinical Chemistry

Unremarkable

Urinalysis

Unremarkable

Gross Pathology

See “mortality” for gross findings observed in preterm decedents.

Organ Weights

Unremarkable

Histopathology

Adequate Battery
Yes
Peer Review
No

Histological Findings

The dose-limiting effect associated with XL518 administration in the dog is GI toxicity, particularly to the esophagus. A summary of histological findings is provided in Table 27.

Table 27: Histopathological changes of likely or equivocal relationship to XL518 administration

Group (mg/kg/Day)	**0**	**0.3**	**1**	**3/1**	0	0.3	1	3/1
Organ, Histopathological Description **Sex**	**Male**				**Female**			
Adrenal, cortex, vacuolation			1		1R	2		
Brain, perivascular lymphocytic cuffing					1			
--hemorrhage						1		
Cecum, necrosis/chronic active inflammation				1†			1†	2†
--mucosal gland dilatation w/necrotic cell debris								1†
--congestion			1	1†				1†

Group (mg/kg/Day)	**0**	**0.3**	**1**	**3/1**	0	0.3	1	3/1
Organ, Histopathological Description **Sex**	**Male**				**Female**			
Colon, necrosis/chronic active inflammation				1†			1†	2†
--mucosal gland dilatation w/necrotic cell debris				1†		1	1†	1†
--congestion/hemorrhage				1†			1	1†
Duodenum, necrosis/chronic active inflammation				2†				2†
--hyperplasia, epithelium				2†			1†	
--crypt gland dilatation w/necrotic debris	3	1	2	2†+2+1R	1+1R	1	1†+3	2†+1R
Epididymis, immature				2†				
Esophagus, necrosis/chronic active inflammation, mucosa/submucosa			2†	2†			1†	2†
--erosion/ulceration				2†			1†	2†
--chronic inflammation, mucosal gland		1	4		2	1	1	1R
--dilatation, mucosal gland			1					
--edema				1†				1†
Heart, mineralization, aortic wall		1						
--mineralization, myocardium	1R							
Ileum, necrosis/chronic active inflammation							1†	1†
--erosion/ulceration							1†	
--congestion				1†			1†	
Jejunum, crypt gland dilatation w/necrotic cell debris				1†	1		1†	
Kidney, mineralization, tubule	5+2R	5	1†+5	3+2R	4+2R	4	1†+3	2†+3+2R
--chronic inflammation, cortex, focal	1	1			1			
--dilatation, pelvis		2			1	1		
--angiectasis		1						
--regeneration, tubule cell			1					
--chronic inflammation, pelvis, focal			1					
--dilatation, tubule(s)					1			
Lacrimal gland, inflammation, chronic				1R	1R			1R
Liver, foci of chronic inflammation	2+2R	3	5	1+2R	5+2R	3	3	1†+1+2R
--congestion								1†
--hyperplasia, bile duct								1†
--neutrophils, sinusoidal space								
LN, Iliac,								
LN, Mandibular, pigment		1						
--congestion/hemorrhage						1		
LN, Mesenteric, congestion/hemorrhage	3	2	4	1†+2	3+1R	2	3	
--pigment			1					
--inflammation, chronic-active							1†	
Lungs, foci of chronic inflammation	4+2R	4	4	2+1R	4+2R	4	2	1+1R
--infiltrate, lymphocyte, perivasuclar	4	5	3	2+2R	4	4	4	2+2R
--edema								1†
--inflammation, chronic-active								1†
--congestion								1†
Marrow, Femur, hyperplasia, myeloid							1†	

Group (mg/kg/Day)	**0**	**0.3**	**1**	**3/1**	0	0.3	1	3/1
Organ, Histopathological Description **Sex**	**Male**				**Female**			
Marrow, Sternum, hyperplasia, myeloid							1†	
Ovary, corpora lutea, not present	--	--	--	--	4+1R	3	4	2†+3+1R
--cyst, follicle	--	--	--	--				1R
Pancreas, apoptosis, acinar, increased		1						
--depletion, zymogen granules				2†				
Parathyroid, cyst	1	1						
Pituitary, cyst	1	1	1		1+1R	1		
Prostate, inflammation, chronic	1	1	1					
Rectum, necrosis/chronic active inflammation				1†			1†	1†
--congestion				1†				
Salivary Gland, mandibular, infiltrate, lymphocytes	1	1	1	1	2			1
Skin, inflammation, chronic				1R				
Spleen, congestion	2		1		1+1R		1†+1	1
Stomach, Glandular, inflammation, chronic-active, esophagus-cardiac junction		1						1†
--ulceration, esophagus-cardiac junction								1†
--inflammation, chronic-active, pyloric mucosa							1†	1†
--congestion/hemorrhage, pyloric mucosa								1†
Testes, degeneration		1	1		--	--	--	--
--immature				2†	--	--	--	--
Thymus, depletion/necrosis, lymphocytes	1R		2†					
Thyroid, inflammation, chronic			1					
--cyst, follicle							1	
Tongue, inflammation, chronic-active				1†				1
--ulceration, esophagus-cardiac junction				1†				
--inflammation, chronic					1			
Urinary bladder, chronic active inflammation, serosal wall								1†

† = Preterm decedent; R = recovery cohort

Toxicokinetics

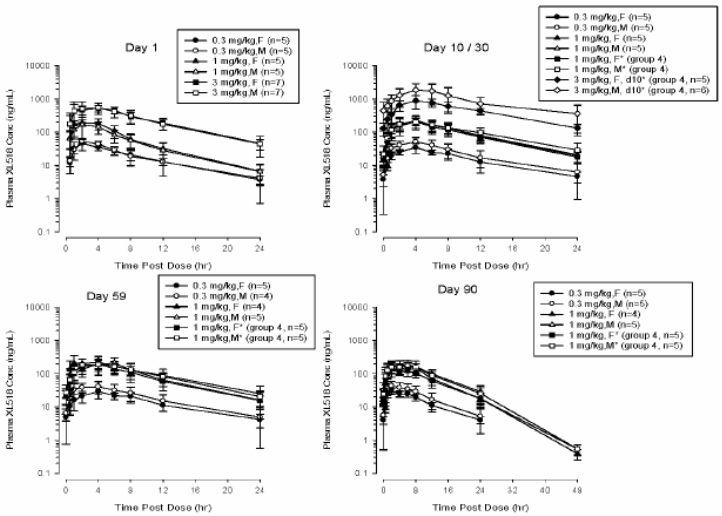
Test article was detectable but low in control animals (2-4X of the LLOQ of 0.2 ng/mL); thus, the cause remains unclear (i.e. bioanalytical control sample contamination, misdosing, inadvertent exposure of control animals via physical contact with dosed animals, etc.).

Exposure (peak and AUC) in dogs was approximately dose-proportional over the range between 0.3-3 mg/kg in males and females on Day 1. Beyond Day 10, exposure (Cmax and AUC) appeared to increase greater than dose-proportionally over the dose range tested. There was no consistent effect of sex on exposure.

Table 28: Summary of toxicokinetic exposure parameters for cobimetinib in dogs on Days 1, 10/30, 59, and 90

Dose (mg/kg)	Sex	Day	T1/2	Cmax	AUC_T
0.3	F	1	6.48	47.9	396
		30	7.33	34.3	362
		59	7.06	29.9	320
		90	7.32	30.5	330
0.3	M	1	7.00	53.6	423
		30	6.96	52.6	525
		59	6.43	43.5	452
		90	6.44	46.4	480
1	F	1	4.96	221	1460
		30	6.21	213	2160
		59	5.24	253	2220
		90	5.31	204	2110
1	M	1	4.97	194	1210
		30	5.87	230	2160
		59	6.86	229	2130
		90	6.45	195	2460
3	F	1	5.87	585	5480
		10	7.49	892	10400
3	M	1	5.98	602	5470
		10	10.8	2310	19300

Figure 22: Mean plasma concentration-time profiles on Days 1, 10/30, 59 and 90 in the dog



* Due to the unscheduled deaths in the 3 mg/kg dose group (2/sex in Group 4), the surviving Group 4 animals (5/sex) were given a dosing holiday after dosing on Day 10 with dosing reinitiated at 1 mg/kg dose on Day 22 (designated 3.0/1.0 mg/kg Group 4 animals)

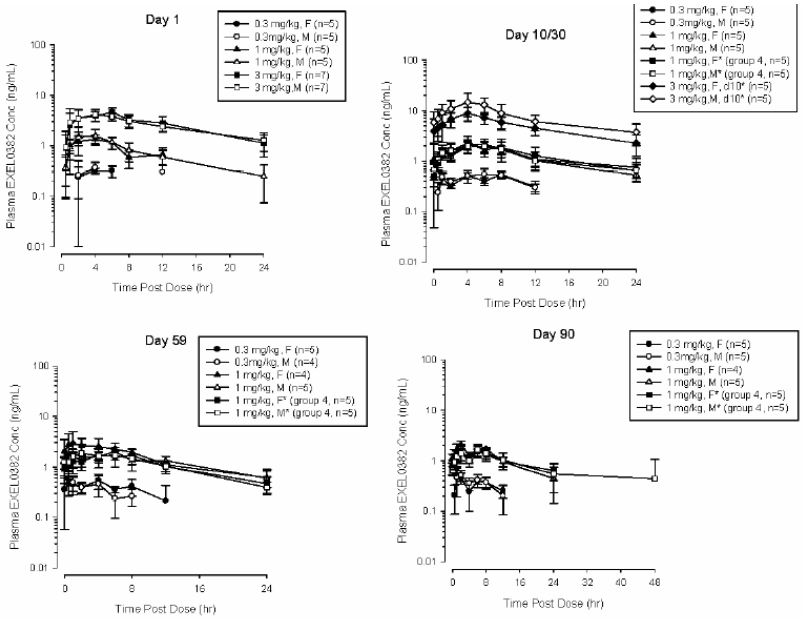
(excerpted from the Applicant's submission)

The putative metabolite, EXEL0382, was measurable in all animals; however exposure appeared to be low (~ 100X lower) relative to that of cobimetinib. There was no apparent effect of sex on the exposure to EXEL0382.

Table 29: Summary of toxicokinetic exposure parameters for cobimetinib metabolite EXEL0382 in dogs on Days 1, 10/30, 59, and 90

Dose (mg/kg)	Sex	Day	T1/2	Cmax	AUC_T
0.3	F	1	4	0.374	3.12
		30	5	0.562	7.85
		59	3.6	0.586	6.40
		90	1.4	0.538	6.25
0.3	M	1	5.2	0.596	4.11
		30	2.5	0.598	7.26
		59	2	0.536	3.98
		90	1.6	0.570	5.68
1	F	1	3.4	1.47	15.7
		30	4.8	2.27	30.7
		59	2.88	3.37	35.1
		90	3.5	2.12	27.8
1	M	1	2.6	1.74	16.7
		30	5.6	2.16	27.7
		59	6.8	2.05	28.7
		90	4.4	1.68	23.4
3	F	1	5.4	4.77	61.8
		10	3.6	9.11	114
3	M	1	4.4	4.60	58.5
		10	4.7	16.9	168

Figure 23:Mean plasma concentration-time profiles for cobimetinib putative metabolite EXEL0382 on Days 1, 10/30, 59 and 90 in the dog



* Due to the unscheduled deaths in the 3 mg/kg dose group (2/sex in Group 4), the surviving Group 4 animals (5/sex) were given a dosing holiday after dosing on Day 10 with dosing reinitiated at 1 mg/kg dose on Day 22 (designated 3.0/1.0 mg/kg Group 4 animals.

Excerpted from the Applicant's submission

Dosing Solution Analysis

Met pre-specified acceptance criteria for concentration.

7 Genetic Toxicology

The following is summary is adapted from the review of Dr. Timothy Kropp for IND (b) (4).

- XL518 was negative for induction of reverse mutations in the Ames assay using *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and *E. coli* strain WP2uvrA, at concentrations of up to 1000 µg/plate with and without metabolic activation by Aroclor-induced rat liver microsomes.
- XL518 was also found to be negative for the induction of structural chromosome aberrations in the in vitro chromosome aberration assay in primary cultured human peripheral blood lymphocytes when tested at concentrations of up to 120 µg/mL in the presence of metabolic activation by rat liver S9 fractions, and at concentrations of up 40 µg/mL in the absence of metabolic activation.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: In Vivo Rat Bone Marrow Micronucleus Assay with GDC-0973

Study no:	8286760
Study report location:	4.2.3.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	18 June 2013 (Treatment start)
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Drug: GDC-0973 Lot: BS1112SA01 Purity: 99.2%

Key Study Findings

- Cobimetinib was negative for micronucleus formation under the conditions of this assay
- There were no preterm deaths and no abnormal clinical signs noted at the dose levels evaluated.

Methods

Doses in definitive study:	0, 3, 10, 30, 60 mg/kg
Frequency of dosing:	2 doses, 24-hours apart
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5% (w/v) methycellulose solution with 0.2%

	(v/v) polysorbate 80 (Tween 80)
Species/Strain:	*Rattus norvegicus*, Sprague Dawley (Crl:CD(SD))
Number/Sex/Group:	10 Males/Group
Satellite groups:	None
Basis of dose selection:	Toxicity
Negative control:	Vehicle
Positive control:	Deionized water

Study Validity

Sample analysis for concentration and homogeneity met pre-specified acceptance criteria, the results in test groups were within the range previously observed for animals of this age and strain (laboratory range for vehicle control males: 0.00-0.48 % micronucleated PCEs), and the positive control results were within the range of historical control data (Laboratory range: 0.10-6.45 % micronucleated PCEs for cyclophosphamide-treated males); thus, the study met the criteria for a valid test.

Results

There was no increase in micronucleated erythrocytes in treated animals; thus, under the conditions of this study, GDC-0973 was considered to be negative for induction of micronuclei when administered twice to male Sprague Dawley rats (Table 30).

Table 30: Summary of results from the 2-dose rat micronucleus assay

Treatment	Dose	Harvest Time (hours)	% Micronucleated PCEs Mean ± SD Male	Ratio PCE:NCE Mean ± SD Male
Vehicle	10 mL/kg/day	24	0.03 ± 0.03	0.92 ± 0.06
Positive[a]	60 mg/kg	24	1.95 ± 1.02*	0.78 ± 0.09*
Test Article	3 mg/kg/day	24	0.06 ± 0.05	0.90 ± 0.14
	10 mg/kg/day	24	0.07 ± 0.03	0.86 ± 0.09
	30 mg/kg/day	24	0.09 ± 0.02	0.79 ± 0.11
	60 mg/kg/day	24	0.06 ± 0.07	0.87 ± 0.11

* Significantly greater than the corresponding vehicle control, $p \leq 0.01$.
Vehicle = 0.5% (w/v) methylcellulose solution with 0.2% (v/v) polysorbate 80 (Tween 80)
Positive = Cyclophosphamide
PCE = Polychromatic erythrocyte
NCE = Normochromatic erythrocyte
[a] Positive control animals dosed once approximately 24 hours prior to harvest timepoint.

(Excerpted from Applicant's submission)

8 Carcinogencity

Carcinogenicity studies were not conducted and are not required to support the approval of a drug intended to treat patients with advanced cancer.

9 Reproductive and Developmental Toxicology

9.2 Embryonic Fetal Development

Study title: An Embryo-Fetal Developmental Toxicity Study of GDC-0973 Administered by Oral Gavage in Rats.

Study no.:	Testing Facility Study No. 20036990 Genentech, Inc. Reference No. 13-0026
Study report location:	4.2.3.5.2
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	March 13, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GDC-0973, batch # BS1112SA01, 99% purity

Key Study Findings

- Oral administration of GDC-0973 at 10 mg/kg/day caused mortality (1/10) and embryo/fetal toxicity.
- Soft tissue (great vessel) malformations were noted in 1 pup per litter from 3 different dams, and skeletal abnormalities in the eye sockets were observed in high dose pups.
- Maternal plasma exposures to drug increased with dose levels and were similar on study Days 1 (GD 7) and 11 (GD 17).
- NOAEL was 3mg/kg with Cmax of 75 ng/mL and AUC of 662 ng/mL*hr on GD 17.

Methods

Doses:	0.3, 1, 3, or 10 mg/kg
Frequency of dosing:	Daily from DG 7 through 17
Dose volume:	5 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.5% (w/v) methylcellulose solution with 0.2% (v/v) polysorbate 80 (Tween 80)
Species/Strain:	Crl:CD(SD) Sprague Dawley rats
Number/Sex/Group:	10
Age:	66 days

Reference ID: 3768701

Weight: 184 g to 231 g
Satellite groups: Yes (TK)
Study design:
- Five dose groups were used (Vehicle, 0.3, 1, 3 and 10 mg/kg)
- Pregnant dams were dosed with vehicle or test article by daily oral gavage from Gestation Days 7 through 17
- Caesarean sections were performed on Gestation Day 21

Deviation from study protocol: Reported deviations are considered unlikely to have affected overall study interpretation.

Group (main/TK)	Test material	Dose level (mg/kg)	Concentration (mg/mL)	Number of animals	
				Main study	Toxicokinetics
1/6	Vehicle*	0	0	10	3
2/7	GDC-0973	0.3	0.06	10	9
3/8	GDC-0973	1.0	0.2	10	9
4/9	GDC-0973	3	0.6	10	9
5/10	GDC-0973	10	2	10	9

*-MCT (0.5% (w/v) methylcellulose solution with 0.2% (v/v) polysorbate 80 (Tween® 80)

Dose justification: The doses were selected based on the 4 week toxicity study in rats where 3 mg/kg was the highest tolerated dose and 10 mg/kg/day resulted in 3 female deaths on Days 13-15.

Observations and Results

Mortality: (twice daily)

10 mg/kg – One rat euthanized on GD 20 due to moribund condition. All tissues appeared normal at necropsy. The litter consisted of 18 early resorptions in utero.

Clinical Signs: (daily)

Scab on one or more locations on the body (head, mouth, neck, back, chest, and/or inguinal area (3 and 10 mg/kg), mild to moderate dehydration (10 mg/kg), sparse hair coat (0.3, 1 and 10 mg/kg) ungroomed coat (10 mg/kg), hunched posture (10 mg/kg), red and/or brown fur at one or more locations on the body (10 mg/kg), slight or moderate excess salivation (10 mg/kg), chromodacryorrhea (10 mg/kg), excessive grooming at one or more

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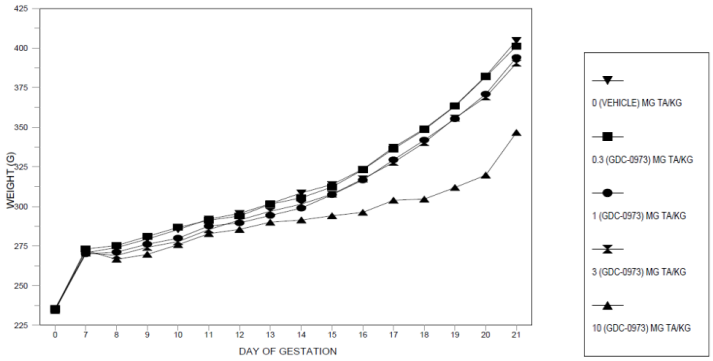
locations on the body (10 mg/kg), and red perivaginal substance (10 mg/kg).

Body Weight: (daily)

Dose-related decreases in body weight gain, significant at the high dose level were reported.

Maternal Body Weights (g)



Feed Consumption: (DGs 0, 7, 10, 13, 15, 18, and 21)

Dose-related non-significant decreases in food consumption were recorded.

Maternal Relative Food Consumption Values (g/kg/day)

Group	1	2	3	4	5
Dose (mg/kg/day)	0	0.3	1.0	3.0	10
Days 7-10	77	78	72	68	63
Days 10-13	78	78	75	76	74
Days 13-15					
Days 15-18	73	80	74	70	64
Days 18-21	63	66	67	63	71
Days 7-21	73	75	72	69	71

Days – Days of gestation

Toxicokinetics: Maternal Samples at 1, 2, 4, 8, and 24 hr. postdose on GDs 7 (Day 1) and 17 (Day 11).

Dose level (mg/kg/day)	T_{max} (hr)		C_{max} (ng/mL)		AUC (ng*h/mL)	
	GD 7	GD 17	GD 7	GD 17	GD 7	GD 17
0.3	4.0	8.0	3.6	4.3	57.6	69.3
1	8.0	8.0	17.9	19.8	247	299
3	4.0	2.0	69.5	57.4	659	662
10	8.0	8.0	258	388	3770	6020

Dosing Solution Analysis: Precision and accuracy criteria were met.

Necropsy: (scheduled euthanasia on GD 21 for main study animals & on GD18 for TK rats)

10 mg/kg – Decreased total litter size, live litter size, and fetal weights (combined, male and female) compared to control animals.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Caesarean Section Observations (mean)

Group	1	2	3	4	5
Dose (mg/kg/day)	0	0.3	1.0	3.0	10
Rats examined (N)	10	10	10	10	9
Corpora lutea	15.3	15.7	15.2	15.8	15.2
implantations	14.7	14.9	14.7	14.9	14.4
Preimplantation loss (%)*	3.6	5.3	3.3	5.0	4.9
Litter sizes	14.4	14.2	13.8	14.5	10.4
Live fetuses	14.4	14.1	13.7	14.5	10.4
Dead fetuses	0.0	0.1	0.1	0.0	0.0
Early resorptions	0.3	0.7	0.2	0.4	4.0
Late resorptions	0.0	0.0	0.7	0.0	0.0
Post-implantation loss (%)	2.0	5.5	6.8	2.7	26.8
Dams with any resorptions (%)	20	50	30	40	77.8
Dams with all conceptuses dead or resorbed (%)	0	0	0	0	22.2
Dams with viable fetuses (%)	100	100	100	100	77.8

** = number of corpora lutea – number of implantations / number of corpora lutea * 100*

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Litter Observations (Caesarean-Delivered Fetuses)

Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Litters with one or more live fetuses	N	10	10	10	10	7
Implantations	Mean	14.7	14.9	14.7	14.9	14.3
Live fetuses	N	144	141	137	145	94
	Mean	14.4	14.1	13.7	14.5	13.4
Live male fetuses	N	63	69	74	76	57
Live male fetuses/litter (%)	Mean	43.6	48.7	53.5	52.3	60.7
Live fetal body weights (grams)/litter	Mean	5.7	5.9	5.5	5.6	4.3
Male fetuses	Mean	5.9	5.9	5.6	5.8	4.4
Female fetuses	Mean	5.5	5.6	5.3	5.4	4.1
Dead or resorbed conceptuses/litter (%)*	Mean	2.0	5.5	6.8	2.7	5.9

* =percent dead or resorbed conceptuses per litter

Fetal Alterations – Caesarean-Delivered Live Fetuses – Day 21 of Gestation

Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Litters evaluated	N	10	10	10	10	7
Fetuses evaluated	N	144	142	130	145	94
Live	N	144	141	137	145	94
Dead	N	0	1	1	0	0
Litters with fetuses with any alteration observed	N	4	3	2	1	4
	%	40	30	20	10	57
Fetuses with any alteration observed	N	4	3	2	1	5
	%	2.8	2.1	1.5	0.7	5.3
Fetuses with any alteration/litter (%)	Mean	2.9	2.4	1.8	0.6	5.3

Fetal Gross External Alterations - Caesarean-Delivered Live Fetuses
Day 21 of Gestation

Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Litter evaluated	N	10	10	10	10	7
Litters with live fetuses	N	10	10	10	10	7
Fetuses evaluated	N	144	142	138	145	94
Live	N	144	141	137	145	94
Dead	N	0	1	1	0	0
Hindlimb, rotated,	N	0	1	0	0	0
Litter incidence	%	0	10	0	0	0
Fetal incidence	N	0	1	0	0	0
	%	0	0.7	0	0	0

Fetal Soft Tissue Alterations - Caesarean-Delivered Live Fetuses – Day 21 of Gestation

Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Litters evaluated	N	10	10	10	10	7
Litters with live fetuses	N	10	10	10	10	7
Fetuses evaluated	N	69	69	66	70	46
Live	N	69	69	65	70	46
Dead	N	0	0	1	0	0
Eyes, microphthalmia						
litter incidence	N	1	0	0	0	1
	%	10	0	0	0	14
Fetal incidence	N	1	0	0	0	1
	%	1.4	0	0	0	2.2
Eyes, retina folded						
Litter incidence	N	1	0	1	0	0
	%	10	0	10	0	0
Fetal incidence	N	1	0	1	0	0
	%	1.4	0	1.5	0	0

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Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Brain, ventricle, moderate dilation						
Litter incidence	N	1	0	0	0	0
	%	10	0	0	0	0
Fetal incidence	N	1	0	0	0	0
	%	1.4	0	0	0	0
Vessels, innominate artery absent (1 /7 pups from Dam 2145)						
Litter incidence	N	0	0	0	0	2
	%	0	0	0	0	29
Fetal incidence	N	0	0	0	0	2
	%	0	0	0	0	4
Vessels interrupted aortic arch,						
Litter incidence	N	0	0	0	0	1
	%	0	0	0	0	14
Fetal incidence	N	0	0	0	0	1
	%	0	0	0	0	2.2
Vessels, left subclavian arises from pulmonary (1 /6 pups from Dam 2147)						
Litter incidence	N	0	0	0	0	1
	%	0	0	0	0	14.3
Fetal incidence	N	0	0	0	0	1
	%	0	0	0	0	2.2
Vessels, right subclavian arises to the left of the left subclavian (1 /6 pups from Dam 2146)						
Litter incidence	N	0	0	0	0	1
	%	0	0	0	0	14
Fetal incidence	N	0	0	0	0	1
	%	0	0	0	0	2.2

Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Vessels, right subclavian passes dorsal to the trachea and esophagus (1 /6 pups from Dam 2146)						
Litter incidence	N	0	0	0	0	1
	%	0	0	0	0	14.3
Fetal incidence	N	0	0	0	0	1
	%	0	0	0	0	2.2

Fetal Skeletal Tissue Alterations - Caesarean-Delivered Live Fetuses
Day 21 of Gestation

Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Litters evaluated	N	10	10	10	10	7
Litters with live fetuses	N	10	10	10	10	7
Fetuses evaluated	N	75	73	72	75	48
Live	N	75	72	72	75	48
Dead	N	0	1	0	0	0
Skull, eye socket, small						
Litter incidence	N	0	0	0	0	1
	%	0	0	0	0	14
Fetal incidence	N	0	0	0	0	1
	%	0	0	0	0	2
Cervical vertebrae, cervical rib at 7th cervical vertebra						
Litter incidence	N	2	0	0	0	0
	%	20	0	0	0	0
Fetal incidence	N	2	0	0	0	0
	%	2.7	0	0	0	0

Group		1	2	3	4	5
Dose (mg/kg/day)		0	0.3	1.0	3.0	10
Thoracic vertebrae, centrum, bifid						
Litter incidence	N	0	1	1	1	0
	%	0	10	10	10	0
Fetal incidence	N	0	1	1	1	0
	%	0	1.4	1.4	1.3	0
Ribs, fused						
Litter incidence	N	0	0	0	0	1
	%	0	0	0	0	14.3
Fetal incidence	N	0	0	0	0	1
	%	0	0	0	0	2.1
Pelvis, pubis, incompletely ossified						
Litter incidence	N	0	1	0	0	0
	%	0	10	0	0	0
Fetal incidence	N	0	1	0	0	0
	%	0	1.4	0	0	0

Fetal Ossification Sites - Caesarean-Delivered Live Fetuses – Day 21 of Gestation

Group		1	2	3	4	5
Dose level (mg/kg/day		0	0.3	1.0	3.0	10.0
Litter examined	N	10	10	10	10	7
Fetuses examined	N	75	72	72	75	48
Ossification sites per fetus per litter						
Hyoid	Mean	1.0	1.0	1.0	1.0	1.0
Vertebrae						
Cervical	Mean	7	7	7	7	7
Thoracic	Mean	13.10	13.05	13.04	13.14	13.15
Lumbar	Mean	5.90	5.95	5.95	5.85	5.86
Sacral	Mean	3.00	3.00	3.00	3.00	3.00
Caudal	Mean	7.67	7.95	7.60	7.55	6.71
Ribs, (pairs)	Mean	13.06	13.03	13.03	13.10	13.11

Group		1	2	3	4	5
Dose level (mg/kg/day		0	0.3	1.0	3.0	10.0
Sternum						
Manubrium	Mean	1.00	1.00	1.00	1.00	1.00
Sternal centers	Mean	4.00	4.00	3.99	4.00	3.94
Xiphoid	Mean	1.00	1.00	0.99	1.00	0.96
Forelimb						
Carpals	Mean	0.00	0.00	0.00	0.00	0.00
Metacarpals	Mean	4.00	4.00	3.99	4.00	3.97
Digits	Mean	5.00	5.00	5.00	5.00	5.00
Phalanges	Mean	8.57	8.36	8.43	8.62	7.46
Hindlimb						
Tarsals	Mean	0.03	0.10	0.03	0.02	0.00
Metatarsals	Mean	4.94	4.94	4.91	4.82	4.26
Digits	Mean	5.00	5.00	5.00	5.00	5.00
Phalanges	Mean	7.10	7.30	6.37	6.41	5.14

9.4 Juvenile Studies:

Study title: A 28-Day Oral Gavage Toxicology and Toxicokinetic Study in Juvenile Sprague Dawley Rats with GDC-0973

Study no.: Testing Facility Study No. 20041064

Study report location: 4.3.2.5.4

Conducting laboratory and location: (b) (4)

Date of study initiation: April 23, 2013

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Drug: GDC-0973
Lot # BS1112SA01
Purity: 99.2% HPLC (% w/w)

Key Study Findings

- GDC-0973 administration at 3 mg/kg/day resulted in 2 deaths (10%)
- TK exposures were higher in females than males
- TK exposures were higher on Day 1 (PND 10) than on Day 22 (PND 32) in males and females, suggestive of metabolic induction (either compound-related or age-related).
- Histopathological target organs included the kidney, liver, spleen, and thymus.

Reference ID: 3768701

Methods

Doses:	Toxicokinetics -0.3, 1.0, 3, or 10 mg/kg/day Main – 0.3, 1.0, or 3.0 mg/kg/day
Frequency of dosing	Daily for 28 days from PNDs 10 through 38
Route of administration:	Oral gavage
Dose volume:	1 mL/kg
Formulation/Vehicle:	MCT (0.5% methylcellulose solution with 0.2% polysorbate 80)
Species/Strain:	Crl:CD(SD) Sprague Dawley rats
Number/Sex/Group:	Toxicokinetics – 30 Main - 10
Age:	Pregnant dams were received by the testing facility and litters were delivered naturally. Treatment began on Postnatal Day 10 (PND 10) Animals were weaned on PND 21.
Weight:	11.5 to 26.8 g for male pups 9.0 to 25.2 g for female pups
Satellite groups:	Yes
Unique study design:	30/sex for TK
Deviation from study protocol:	

Group No a, b.	Test Material	Dose Level (mg/kg)	Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Main Study Animals (M/F)	No. of TK Study Animals (M/F)
1	Vehicle	0	0	1	10/10	-
2	GDC-0973	0.3	0.3	1	10/10	-
3	GDC-0973	1	1	1	10/10	-
4	GDC-0973	3	3	1	10/10	-
6	Vehicle	0	0	1	-	6/6
7	GDC-0973	0.3	0.3	1	-	30/30
8	GDC-0973	1	1	1	-	30/30
9	GDC-0973	3	3	1	-	30/30
10	GDC-0973	10	10	1	-	30/30

-: Not applicable

[a] Groups 1 to 4 are Main Study Rats designated for toxicity assessment. Groups 6 to 10 are satellite groups designated for TK assessment. Initiation of dosing was staggered, with Day 1 for TK rats on 23 to 26 April 2013 and for Main Study rats on 12 to15 May 2013).

[b] Group 5 was removed from the study due to toxicity observed in Group 10.

Animals were dosed from Postnatal Day 10 (PND 10 or Study Day 1) for 28 days.

Reference ID: 3768701

Observations and Results

Mortality:

The high dose of 10 mg/kg exceeded the MTD and led to the death of 10 males and 7 females. The Applicant states that there were no gross or microscopic changes in animals that explained of the cause of morbidity/mortality. Remaining animals in that dose group were euthanized on Study Day 4. Preterminal clinical signs are summarized in Table 31 and Table 32. In addition, two animals in the 3 mg/kg dose group (1 male and 1 female) did not survive to scheduled termination. Preclinical signs for animals in the 3 mg/kg dose level are summarized in Table 33.

Table 31: Preterminal clinical signs in male juvenile rats at the 10 mg/kg dose level

Rat Number	2205	2302	2303	2304	2401	2404	2405	2502	2504	2505
Doses Administered	1	3	2	3	2	2	2	1	3	3
Mode of Death	FD	FD	FD	FD	FD	FD	FD	FD	FD	FD
Day of Death	PND 11	PND 13	PND 12	PND 12	PND 12	PND 12	PND 12	PND 11	PND 13	PND 13
Clinical Observations:										
Appeared Normal	X	-	X	-	X	X	X	X	-	-
Mild dehydration	-	PND 12	-	-	-	-	-	-	-	-
Decreased motor activity	-	-	-	PND 12	-	-	-	-	-	-
Cold to touch	-	-	-	PND 12	-	-	-	-	-	-
Moderate dehydration	-	-	-		-	-	-	-	PND 12	PND 12
Pale extremities	-	-	-	PND 12	-	-	-	-		
All tissues appear normal	X	X	X	X	X	X	X	X	X	X
Body weight change (grams)	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR

- = Finding not present; PND = Postnatal Day; UR = Unremarkable
FD = Found Dead

(excerpted from the Applicant's submission)

Table 32: Preterminal clinical signs in female juvenile rats at the 10 mg/kg dose level

Rat Number	2406	2407	2408	2410	2508	2509	2510
Doses Administered	3	3	3	3	2	3	3
Mode of Death	FD	FD	FD	FD	FD	FD	FD
Day of Death	PND 13	PND 13	PND 13	PND 13	PND 12	PND 13	PND 13
Clinical Observations:							
Appeared Normal	X	X	-	-	X	-	-
Mild dehydration	-	-	-	-	-	-	-
Whole body pale	-	-	-	-	-	-	PND 12
Cold to touch	-	-	-	PND 12	-	-	PND 12
Moderate dehydration	-	-	PND 13	PND 12	-	PND 12	PND 12
All tissues appear normal	X	X	X	X	X	X	X
Body weight change (grams)	UR	UR	UR	UR	UR	UR	UR

- = Finding not present; PND = Postnatal Day; UR = Unremarkable
FD = Found Dead

(excerpted from Applicant's submission)

Table 33: Preterminal clinical signs at the 3 mg/kg dose level

Rat Number	3204	3206
Doses Administered	7	8
Mode of Death	Found Dead	Found Dead
Day of Death	PND 17	PND 17
Appeared Normal	-	-
Mild dehydration	PND 15	PND 14
Decreased motor activity	PND 16	PND 15-17
Pale extremities	PND 15-16	-
Cold to touch	PND 16	PND 15-17
Ataxia	PND 16	PND 16-17
Ptosis	PND 16	PND 16-17
Impaired righting reflex	PND 16	PND 17
Thin body condition	PND 16	PND 16-17
Moderate dehydration	-	PND 15
Hyperpnea	PND 16	PND 17
Severe dehydration	PND 16	PND 16-17
Discoloration (whole body pale)	PND 16	PND 15-17
Body weight change (grams)	UR	-3.9 (PND 10 to 17)
Cumulative food consumption (grams)	-	-
All tissues appear normal	X	X
Histopathology	a	a

- = Finding not present; PND = Postnatal Day; UR = Unremarkable

[a] Tissues showed varying degrees of post-mortem change, which compromised interpretation, but no gross or histologic lesions were identified in these animals and the cause of death could not be determined.

(excerpted from Applicant's submission)

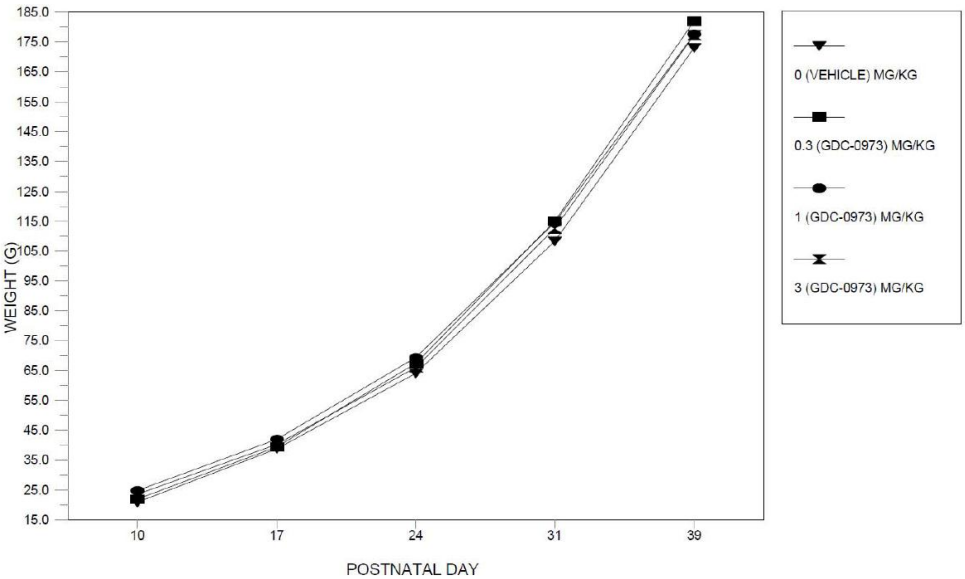
Clinical Signs: (twice daily)

Aside from the observations noted in Table 33, there were no treatment-related clinical signs.

Body Weights: (daily)

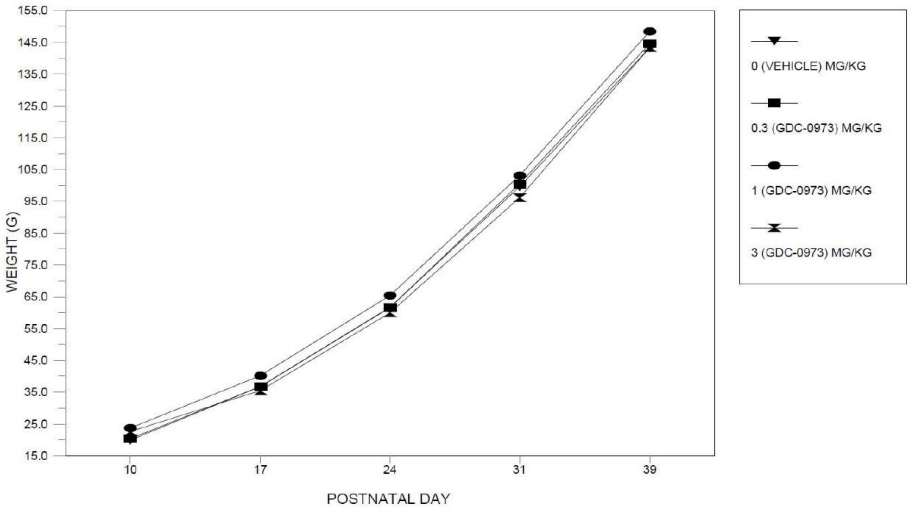
Unremarkable

Table 34: Juvenile male body weights



(excerpted from Applicant's submission)

Table 35: Juvenile female body weights



(excerpted from Applicant's submission)

Feed Consumption:

Performed twice weekly during the postweaning period. Generally unremarkable – animals that received the test article had slightly higher feed consumption than control rats.

Ophthalmoscopy:

Not conducted

Hematology: (PND 39)

Treatment with cobimetinib increased red cell parameters (RBCs, HGB, and HCT) in an dose-related fashion in males and females. There were other statistically significant changes from control mean values that were observed; however, the magnitude of the changes were generally not dose-related they were not observed in both sexes; therefore, the changes are of uncertain relationship to treatment.

Table 36: Changes (%) in mean hematology parameters vs. concurrent control

	2M	3M	4M	2F	3F	4F
RBC (10^6/mL)	**4.6**	**12.1**	**12.3**	2.3	**6.1**	**5.7**
Hgb (g/dL)	2.7	**6.2**	**8.0**	0.9	**2.6**	**3.4**
HCT (%)	3.1	**6.3**	**7.8**	1.3	2.6	**3.4**
MCH (PG)	-0.9	**-4.7**	**-3.3**	-1.0	-2.4	-1.0
MCHC (G/dL)	0.3	0.3	0.7	0.0	1.0	0.7
MCV (fL)	-1.2	**-5.2**	**-4.1**	-1.0	-3.3	-2.3
RET (10^9/L)	1.3	4.3	11.2	0.2	3.8	8.5
PLT (10^3/mL)	**11.7**	3.8	7.8	10.2	5.4	6.7
RDW (%)	-0.6	1.3	1.3	0.7	2.7	2.7
LEU (10^3/mL)	0.7	7.8	-15.1	-16.4	-13.8	**-25.1**
LYM (10^3/mL)	7.3	-4.3	-20.7	-15.9	-20.4	**-28.9**
MONO (10^3/mL)	-27.3	24.2	-6.1	-21.2	0.0	3.0
SEG NEUT (10^3/mL)	-23.1	**63.8**	11.3	-19.2	**36.7**	-4.2
EOS (10^3/mL)	-37.5	0.0	**-50.0**	-30.0	-30.0	-30.0
BASO (10^3/mL)	0.0	50.0	-50.0	0.0	0.0	-50.0
LUC (10^3/mL)	-6.9	-20.8	-5.6	-13.5	-51.0	-20.8

Clinical Chemistry: (PND 39)

There was an dose-related decrease in mean serum triglyceride levels in males and in mid- and high-dose females. Increased bilirubin was noted in mid- and high-dose females, and in mid- and high-dose males; however, the levels in males did not achieve statistical significance vs. concurrent controls. There were no histopathological correlates to these findings.

Other sporadic changes in other clinical chemistry parameters were observed; however, they either lacked a dose-relationship or were present in only one sex and are therefore of uncertain relevance to the test article.

Table 37: Changes (%) in mean clinical chemistry parameters vs. concurrent control

	2M	3M	4M	2F	3F	4F
AST (IU/L)	-1.3	10.0	16.3	1.4	**21.7**	13.0
ALT (IU/L)	-5.6	-7.4	1.9	-11.1	-2.2	6.7
ALP (IU/L)	-17.7	-4.9	-14.0	-5.5	-5.1	8.4
GGT (IU/L)	-38.5	-30.8	-46.2	-63.0	-77.8	**-85.2**
TBIL (mg/dL)	0.0	7.7	23.1	20.0	**40.0**	**30.0**
CHOL (mg/dL)	-7.7	-12.8	-1.3	**-17.1**	-8.5	2.4
TRIG (mg/dL)	-5.3	**-43.6**	**-53.2**	**31.3**	**-40.6**	**-29.7**
TP (g/dL)	**9.1**	**3.5**	**3.5**	4.1	1.5	1.3
ALB (g/dL)	**8.0**	1.1	**3.4**	**5.0**	1.1	2.8
GLOB (g/dL)	**10.8**	**7.2**	3.6	2.8	2.3	-0.6
A/G (ratio)	-3.1	**-6.3**	-0.6	2.5	-1.3	4.4
GLUC (mg/dL)	2.7	1.4	-13.1	-3.2	**-18.5**	-8.8
UN (mg/dL)	-13.3	**-20.0**	**-20.0**	-6.7	-6.7	-6.7
CREA (mg/dL)	5.6	**16.7**	0.0	0.0	5.3	-10.5
Ca (mg/dL)	0.5	0.4	-1.7	-0.6	-1.9	-1.0
PHOS (mg/dL)	**10.2**	**10.9**	**17.3**	0.6	3.6	5.4
Na (mM)	0.0	**1.4**	0.7	0.0	0.0	0.0
K (mM)	-2.4	-3.6	4.0	2.4	0.8	1.4
Cl (mM)	-1.0	0.0	0.0	-1.0	-1.0	-1.0
CK (IU/L	-0.5	27.0	77.3	-3.9	71.1	31.9
Bicarb (mM)	4.5	**9.1**	4.5	-4.3	4.3	4.3

Urinalysis:

Not performed

Gross Pathology:

Gross findings are summarized in the table below.

	0	0.3	1	3	0	0.3	1	3
Kidney, cyst, clear		1	1			4	1	
--cyst			1				1	
Spleen, abnormal appearance; raised, white		1						
Uterus, cyst; horn	--	--	--	--			1	

Organ Weights:

Statistically significant changes in mean absolute or relative (body weight-adjusted or brain weight-adjusted) organ weights were noted for a number of tissues. Of the tissues listed in Table 38, there were histopathological correlates only in the kidney, spleen and

thymus. The decreased thymus weights were correlated with histopathological changes (single cell necrosis).

Decreased serum triglyceride and increased total serum bilirubin levels suggests that the reduction in liver weights may have biological significance despite a lack of histopathological changes.

Table 38: Absolute and relative organ weights of selected tissues

	1M	2M	3M	4M	1F	2F	3F	4F
Brain (ABS)	1.9	2.0	1.9	1.9	1.7	**1.8**	**1.8**	**1.8**
--rel. to body wt.	1.1	1.1	1.1	1.1	1.2	1.3	1.2	1.3
--rel. to brain wt.	--	--	--	--	--	--	--	--
Liver (ABS)	7.9	8.1	7.2	**6.9**	6.6	6.5	**6.0**	**5.8**
--rel. to body wt.	4.5	4.5	**4.0**	**3.9**	4.7	4.5	**4.0**	**4.0**
--rel. to brain wt.	420.8	416.6	**370.3**	**362.2**	375.0	356.2	**323.7**	**319.2**
kidneys (ABS)	1.7	1.8	1.6	1.7	1.4	1.5	1.4	1.5
--rel. to body wt.	1.0	1.0	**0.9**	1.0	1.0	1.0	0.9	1.1
--rel. to brain wt.	92.5	92.1	84.8	91.5	82.2	82.0	76.2	83.0
spleen (ABS)	0.6	0.7	0.6	**0.5**	0.5	0.5	0.5	**0.4**
--rel. to body wt.	0.4	0.4	0.4	**0.3**	0.3	0.3	0.3	0.3
--rel. to brain wt.	33.5	33.2	32.3	28.4	28.1	**24.7**	25.0	**22.3**
Thymus (ABS)	0.7	0.7	**0.6**	0.6	0.6	0.6	**0.4**	0.5
--rel. to body wt.	0.4	0.4	0.3	0.3	0.4	0.4	**0.3**	**0.4**
--rel. to brain wt.	34.8	34.3	**28.6**	32.2	35.4	32.3	**24.2**	**29.5**
Thyroid/Parathyroid (ABS)	0.0	0.0	**0.0**	**0.0**	0.0	**0.0**	**0.0**	**0.0**
--rel. to body wt.	10.4	**9.0**	**8.6**	**8.5**	12.9	**10.2**	**8.7**	**10.0**
--rel. to brain wt.	1.0	0.8	**0.8**	**0.8**	1.0	**0.8**	**0.7**	**0.8**

Red = $p < 0.05$

Histopathology:

Adequate Battery: **Yes**

Peer Review: **Yes**

Histological Findings

Histopathological examination of high-dose (10 mg/kg) males and females was not conducted. In other preterm decedents (1M and 1F at 3 mg/kg/day), autolysis reportedly precluded evaluation of most tissues.

Group (mg/kg/Day)	**0**	**0.3**	**1**	**3**	**0**	**0.3**	**1**	**3**
Organ, Histopathological Description **Sex**	**Male**				**Female**			
Eyes, Rosette, Retina**	2	4		4	1		1	1
Heart, metaplasia, osseous; artery								1

Group (mg/kg/Day)	0	0.3	1	3	0	0.3	1	3
Organ, Histopathological Description **Sex**	**Male**				**Female**			
Kidney, fibrosis; cortical	1					2		1
--fibrosis; medullary	1							
--basophilia; cortical, tubular	2	1	1		2	4	3	1
--dilatation; pelvis	1	1		2				
--infiltration, mixed cell; pelvis								1
--cyst; cortical						2		
Lungs; thrombosis			1†					
--congestion**	1				1			2
Liver; vacuolation, fatty			1†				1†	
--vacuolation, glycogen**	10	10	10		10	10	10	4
--infiltration, mononuclear cell		1			1	1	1	
Muscle, skeletal; infiltration, mixed cell						1		
Prostate; infiltration, mononuclear**	1	2		3	--	--	--	--
Spleen; fibroplasia, capsular		1						
--infiltration, neutrophilic; capsular		1						
Stomach; cyst; glandular							1	
Thymus; single cell necrosis	1	5	8	7	1		5	6

† = preterm decedent; ** = increasing severity with dose

Toxicokinetics: Plasma levels were higher on Study Day 1 than Day 28 in both sexes.
Exposure to cobimetinib was greater than dose-proportional on Day 1, as a 30X increase in dose produced a 43- to 170-fold increase in overall (AUC) exposure in females and males, respectively. There was evidence of increased clearance, as exposures were markedly lower on Day 28 relative to Day 1 (Table 39).

Table 39: Summary of mean toxicokinetic parameters on Days 1 and 22 in juvenile rats

Dose level (mg/kg/day)	Sex	Cmax (ng/mL)		AUC (ng*h/mL)	
		Day 1	Day 22	Day 1	Day 22
0.3	F	20.5	1.45	89.2	16.1
	M	1.92	1.44	34.3	10
1.0	F	27	4.95	438	63.7
	M	26.1	4.32	371	60.6
3	F	142	26.3	2240	213
	M	29.3	39.9	585	244
10	F	284	-	3900	-
	M	329	-	5830	-

Dosing Solution Analysis:
Met pre-specified acceptance criteria for concentration (b) (4)% of nominal) and homogeneity (b) (4)% of nominal).

10 Special Toxicology Studies

Study title: Neutral Red Uptake Phototoxicity Assay of GDC-0973 in Balb/c 3T3 Mouse Fibroblasts

Study no.:	20043661
Study report location:	4.2.3.7.7
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19 August 2013
GLP compliance:	Yes, with exceptions
QA statement:	Yes
Drug, lot #, and % purity:	Drug: GDC-0973 Lot: BS1112SA01 Purity: 99.2% (Assay – HPLC - %W/W)

The objective of this study was to evaluate the phototoxicity of cobimetinib (GDC-0973) in murine (Balb/c 3T3) fibroblasts when cultured in the presence or absence of $5J/cm^2$ ultraviolet (UVB) irradiation from a xenon arc solar simulator equipped with a Shott WG filter. The positive control agent was promethazine.

Cobmetinib demonstrated probable phototoxicity, based on a photoirritancy factor (PIF) of 2.168, and cytotoxic potential. The PIF for promethazine, in comparison, was 67.931.

The assay met the criteria for a valid test (OD_{540} in solvent-treated cells was ≥ 0.4; the radiation sensitivity of solvent-treated cells was > 80%, and all survival and sensitivity parameters of promethazine-treated cells were within the range of historical control data.

Study title: Single-Dosage Phototoxicity Study to Determine the Effects of Oral Administration of GDC-0973 on Eyes and Skin in Pigmented Rats

Study no.:	20042755
Study report location:	4.2.3.7.7
Conducting laboratory and location:	(b) (4)
Date of study initiation:	14 October 2013
GLP compliance:	Yes, with exceptions

Reference ID: 3768701

QA statement: Yes
Drug, lot #, and % purity: Drug: GDC-0973
Lot: BS1112SA01
Purity: 99.2% (Assay – HPLC - %W/W)

The purpose of this study was to evaluate the effects of cobimetinib on the skin and eyes of female Crl:LE (Long-Evans) rats, a standard animal model of phototoxicity. Animals received a single oral dose of cobimetinib followed by 4 hours of irradiation using a xenon lamp (simulated sunlight) and were subsequently evaluated for clinical signs of enhanced dermal phototoxicity, including erythema, edema, flaking, ulceration and scab formation; and histopathological analysis of skin and eyes. Animals were euthanized on Day 4 and histopathological assessments of the eyes and associated structures were performed.

There were no skin reactions in either the lightly or darkly pigmented sites of female Crl:LE rats at any dose level tested. There was no dose-related ocular toxicity as assessed by clinical ophthalmic examination or histopathological evaluation. Therefore, under the conditions of this assay, cobimetinib was negative for induction of dermal or ocular phototoxicity in female Crl:LE rats. Concurrent TK assessments demonstrated robust test article exposure, as indicated in Table 40.

Table 40:Mean GDC-0973 PK Parameters in Female Rat Plasma Following oral administration of 5, 15, or 60 mg/kg of cobimetinib on Day 1

Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-t)}$ (ng•hr/mL)
5	4	74.9	1180
15	4	388	5970
60	4	1990	31,200

(excerpted from Applicant's submission)

11 Integrated Summary and Safety Evaluation

Cobimetinib is a reversible, non-ATP-competitive inhibitor of MEK1 and MEK2. The Applicant is seeking approval for the use of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E or V600K mutations.

The MEK 1/2 proteins are members of the mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is a pivotal regulator of cell growth and survival, and participates in a number of other functions such as angiogenesis and cell migration, that support the growth and spread of tumors. Under normal circumstances, activation of the MAPK pathway is tightly regulated. In many cases, MAPK signaling is initiated by binding of growth factors to their cognate receptors. Receptor activation then triggers activation of signaling transducers such as the small GTPase RAS, which propagates downstream signals via members of the RAF and MEK family members.

Reference ID: 3768701

Figure 24: Schematic of the Ras/Raf/MEK Signaling Pathway

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c.f. Openi (http://openi.nlm.nih.gov/detailedresult.php?img=3260807_oncotarget-02-135-g001&query=null&req=4&npos=-1)

A number of mutations in key MAPK family members are associated with the development and progression of cancer. Specific missense mutations, such as the BRAF V600E mutation (in which glutamic acid is substituted for valine) or the V600K mutation (in which lysine is substituted for valine) are strongly associated with the formation of such cancers as melanoma. Due to the vital role of the MAPK pathway and the potential for improved tolerability, identification of inhibitors specific for mutant BRAF (particularly those that spare wild-type isoforms) has been a high priority in the treatment BRAF-driven cancers. Drugs like vemurafenib that inhibit oncogenic BRAF act by suppressing downstream signaling, often measured by phosphorylation of downstream targets like ERK (pERK); however, in tumors that are driven by other MAPK mutations (such as oncogenic RAS or upregulated RTKs), vemurafenib can increase pERK activity (termed 'paradoxical' MAPK activation). This paradoxical activation of ERK may occur through compensatory upregulation of other RAF family members and subsequent RAF dimer formation leading to activation of the pathway. Paradoxical MAPK activation stimulates tumor growth; thus, vemurafenib is restricted to patients who test positive for the BRAF V600E or V600K mutations. Even in patients positive for oncogenic BRAF mutations, however, drugs such as vemurafenib impose a strong selection bias in favor of clones that carry other growth-promoting mutations

(Hatzivassiliou, et al., 2010); thus, initial responders often develop rapid vemurafenib resistance.

Pharmacology
Cobimetinib inhibits MEK1 and 2 with IC_{50}s of 0.95 and 199 nM, respectively and the affinity appears to be greater for ATP-bound MEK1, suggesting a degree of selectivity for activated forms of MEK. The Applicant provided data from murine xenografts demonstrating the activity of cobimetinib in combination with vemurafenib in the treatment of both WT BRAF- and vemurafenib-resistant V600E BRAF-bearing tumors. Consistent with previous observations, administration of vemurafenib in the context of WT BRAF (A431 cells), resulted in enhanced tumor growth, whereas administration of cobmetinib alone or in combination with vemurafenib, suppressed tumor growth relative to vehicle controls. Similarly, in vemurafenib-resistant V600E BRAF-bearing tumors, the combination both synergistically increased cellular apoptosis and suppressed tumor growth relative to vemurafenib alone (the activity of which was comparable to vehicle in the resistant line).

Pharmaokinetics
Cobimetinib plasma protein binding was high (>90%) across all species tested, and except in dogs, binding was independent of concentration. Wide tissue distribution was observed in the rat following oral administration. The highest levels of exposure were to the GI tract and bile (stomach, intestines, liver), lung, adrenals, urinary bladder, pituitary and eye/uveal tract (LE strain). In the SD rat, high levels of exposure were also observed in the lacrimal glands. There was little exposure to the CNS. The drug distributes to pigmented skin and the uveal tract in LE rats, and data from an in vitro murine phototoxicity assays demonstrated a potential for phototoxicity; however, data from an in vivo assay in the partially pigmented LE rat, failed to demonstrate potentiation of phototoxicity following single dose exposure to cobimetinib.

Cobimetinib is extensively metabolized in humans and animals. The predominant clearance pathways include CYP3A-mediated oxidation and subsequent glucuronidation by UGT2B7. Cobimetinib is primarily eliminated via the feces.

Safety Pharmacology
Cobimetinib is a potent hERG inhibitor, with an IC_{50} of 0.5 µM. In combination with vemurafenib, the combination IC_{50} was 0.6 µM; however, there were no treatment-related effects on hemodynamics or ECG parameters (including QTc) when cobimetinib was evaluated in the conscious telemetered beagle dog at plasma concentrations that were comparable to the human Cmax following administration of the recommended 60 mg daily oral dose. ECG-effects resulting from hERG channel inhibition may have been masked by the drug's observed activity other ion channels (e.g. L-type calcium channels).

The Applicant also evaluated effects of cobimetinib on CNS and respiratory function. There were no effects observed in the functional observational battery in the rat when cobimetinib was administered at oral doses of between 7.5-30 mg/kg. Peak exposures

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achieved in the CNS safety pharmacology study were approximately two-times higher than those observed in humans following administration of the 60 mg oral dose.

In the whole-body plethysmography study, doses of 300 mg/kg led to a small (18%) reduction in respiratory rate in the rat. This may have been related to the observed off-target activity of cobimetinib on μ-opioid receptors.

Toxicology

Cobimetinib was tested in 4- and 13-week GLP-compliant toxicology studies in the dog and the rat. In the 4-week rat study, oral doses of 10 mg/kg were associated with hematological effects (decreased lymphocytes, RBC indices, and WBCs). The major target organs were adrenal gland, liver, thymus, and lymph nodes, and skin. In females treated at the high dose level there were also ovarian findings of necrosis, decreased corpora lutea, and cysts. Exposures observed at this dose level in males and females were 2.9 and 0.67X, respectively, the human exposure level at the 60 mg dose level on Day 1, though exposures in females at Day 16 (when terminal sacrifice occurred for the gender) were approximately twice those observed at the recommended human dose.

In the 13-week rat study, there were no treatment-related effects on any endpoint measured after daily oral administration of cobimetinib. The NOAEL in the 13-week rat study was 3 mg/kg/day, which was the highest dose tested. Exposures (AUC_{0-24}) achieved in this study were less than 20% of those anticipated to occur in humans at the 60 mg dose level.

In juvenile rats, daily oral doses of 3 mg/kg/day administered between PND 10-38 were associated with mortality. While the cause of death was not defined, preterminal clinical signs included dehydration, ataxia, cold to touch and thin body condition. Other findings in surviving animals included mild changes in clinical pathology, including decreased triglycerides and increased total bilirubin, minimally increased mature red cell mass (erythrocytes, hemoglobin and hematocrit) and mildly decreased lymphocyte counts at 3 mg/kg/Day. The decreased lymphocytes counts were associated with organ weight and microscopic changes in the thymus. There were no histologic correlates to clinical chemistry changes sufficient to explain the mortality. TK exposures were higher on Day 1 (PND 10) than on Day 22 (PND 32) in males and females, suggestive of metabolic induction (either compound- or age-related). The exposure parameters at the NOAEL of 1 mg/kg/day were 0.02 and 0.015 times the anticipated human Cmax and AUC, respectively on Day 28 due to the increased metabolic clearance. Day 1 exposures parameters at the NOAEL dose level were approximately 0.1X of the anticipated AUC and Cmax in humans.

The dog was the most sensitive toxicological species for this compound. In the 4-week dog study, doses (0.1-1.0 mg/kg) were insufficient to assess toxicity; however, in the 13-week dog study, mortality was observed in the dog at doses of 1 and 3 mg/kg (20 and 60 mg/m^2). The dose-limiting toxicity in the dog appears to be GI toxicity. Other potential histological target organs include the kidney, liver, and thyroid. Exposures

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(AUC_{0-24}) at this dose level were between 2.4 and 4.4-fold higher in females and males, respectively, than those anticipated clinically.

No treatment-related histopathological changes were noted in the reproductive organs of dogs at any dose level or in either study; however, it is unclear if the dogs were sexually mature. A finding of testis degeneration was observed in one low dose male and one mid-dose male in the 13-week study; however, the young age and apparent lack of a dose response suggests that these effects are of equivocal relationship to treatment. Exposures at the high dose (1 mg/kg) in the 4-week toxicology study were less than those observed in humans; C_{max} was approximately 0.8 times the human peak levels, and AUCs were between 0.5-1X times those anticipated clinically in males and females, respectively.

In the embryofetal toxicology study in the rat, exposure to cobimetinib during the period of organogenesis was associated with frank maternal toxicity (body weight loss and lethality) at a dose of 10 mg/kg/day. Embryofetal effects observed at the 10 mg/kg dose level included markedly increased post-implantation loss, primarily due to an increased rate of early resorption, including total litter loss in two dams. Decreased fetal body weights and an increase in skeletal alterations were observed at the 10 mg/kg dose level. Evidence of teratogenicity was also observed at the 10 mg/kg dose level. Findings included malformations of the great vessels (missing and/or misplaced great vessels), and malformations of the eye sockets. Exposures (AUC0-24) at this dose level were 0.9 and 1.4X of the human plasma exposure at the 60 mg dose level on Day 1 and Day 11, respectively.

At the 3 mg/kg dose level, minor decrements in maternal body weight were observed. These were not considered adverse, and there were no fetal or maternal toxicities attributable to treatment at this dose level; thus, the NOAEL for maternal and developmental toxicity in this study was considered to be 3 mg/kg/Day. Exposures at this dose level were approximately 15% of those observed at the 60 mg dose level in humans. Because the number of animals used were low (10 pregnant dams per group) and the exposure levels achieved were low relative to therapeutic plasma levels in humans, it is unclear that the embryofetal risk has been adequately characterized for use in a broader patient population. Therefore, while the data from this dose-ranging study are sufficient to support the co-administration of cobimetinib with vemurafenib in patients with advanced melanoma, the Applicant will likely be required to conduct a definitive embryofetal toxicity study in both the rat and the rabbit if they intend to seek to expand the indication to include other therapeutic areas, particularly in patients whose disease is less advanced.

Cobimetinib was non-mutagenic in the Ames bacterial mutagenicity assay, and negative for induction of structural abnormalities in the in vitro and chromosome aberration assay and in the in vivo micronucleus assay.

The binding of cobimetinib to the agonist site of the μ-opioid receptor, in combination with a reduced respiratory rate observed in rats, triggered a consult to the Controlled

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Substance staff regarding the potential for abuse liability with cobimetinib. Given the toxicities associated with use of cobimetinib and the lack of clear dependency signals in patients, the Division does not believe that the potential for abuse is high; however, if the Controlled Substance staff believes that additional nonclinical studies to address abuse potential are warranted, they will be conducted as postmarketing requirements.

Based on the review of the supporting nonclinical studies, there are no outstanding nonclinical issues that must be addressed to support the use of this drug in patients with advanced cancer, thus, the pharmacology/toxicology review team recommends the approval of this marketing application. Additional studies to evaluate abuse potential may be required by the Controlled Substances Division. If deemed necessary, such studies will be conducted as postmarketing requirements.

References

Hativassilliou, G. et al., 2010. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature*. 464: 431-436.

12 Appendix

Review of 4-week rat study excerpted from the review of IND (b) (4) by Dr. Timothy Kropp.

Reference ID: 3768701

Study title: 4-week Oral Gavage Toxicity and Toxicokinetic Study with XL518 in Rats with a 4-week Recovery Period (Audited Draft Report).

Key study findings:

Mortality was seen in 10 mg/kg ♂ and ♀. Hematological effects at 10 mg/kg included decreased lymphocytes, RBC, HGB, HCT and increased leucocytes. The major organs effected were the adrenals, thymus, and lymph nodes with patterns of necrosis, apoptosis, and hyperplasia. Significant skin ulcerization and acanthosis was also seen at high doses.

Study no.: XL518-NC-004
Volume #, and page #: Vol 6, pg 170
Conducting laboratory and location: (b) (4)

Date of study initiation: 2 Aug 2006
GLP compliance: draft report
QA report: yes ( ) no (X) Not signed
Drug, lot #, and % purity: XL518, Lot 2422-013-1, 99.4% purity

Methods

Doses: 0, 1, 3, 10 mg/kg daily for 28 days
Species/strain: rats/Crl:CD(SD)
Number/sex/group or time point (main study): 15/sex/group for 0 and 10 mg/kg groups, 10/sex/group for 1 and 3 mg/kg groups
Route, formulation, volume: oral gavage in distilled water, 10 mL/kg
Satellite groups used for toxicokinetics or recovery: 10/sex/group used for TK
Age: ~8 wks
Weight: Males, 290-354g; Females, 211-247g
Unique study design or methodology (if any): None
Dose Justification: STD_{10} achieved, see Results

Observation and Times:

Clinical signs:	daily and before and after dosing
Body weights:	weekly
Food consumption:	weekly
Ophthalmoscopy/Audiology:	Not done
EKG:	Not done
Hematology:	before sacrifice
Clinical chemistry:	before sacrifice
Urinalysis:	Not done
Gross pathology:	at sacrifice
Organ weights:	at sacrifice
Histopathology:	at sacrifice
Toxicokinetics:	days 1 and 28 at 0.5, 1, 2, 4, 8, 12, and 24 hr post dose
Adequate Battery:	yes (X), no ( )
Peer review:	yes ( ), no (X)

Results:

Mortality: 3 ♀ and 3 ♂ 10 mg/kg animals were moribund sacrificed (♂ on day 26, ♀ on days 13 and 15). On day 16 five 10 mg/kg ♀ were assigned to recovery and the rest sacrificed.

Clinical signs: In 10 mg/kg animals clinical signs included hunched posture, tremors, thin appearance, ataxia, touch sensitivity, hypoactivity, red nasal discharge, few feces, nonformed feces, squinted eyes, irregular respiration, cold to touch body, pale paws, ears, body, and nose, sore/scab, and/or rough haircoat. The moribund animals had the same clinical signs as the other animals, only more severe. Clinical findings in 1 and 3 mg/kg were unremarkable.

Body weights: Body weights were within 10% of controls

Food consumption: Unremarkable

Ophthalmoscopy/Audiology: Not done

EKG: Not done

Hematology:

Samples for the 10 mg/kg ♀ on day 13 clotted and could not be analyzed

Samples for the other 10 mg/kg ♀ rats sampled on day 16 showed ↓lymphocytes (16%), RBC (15%), HGB (17%), and HCT (14%) and ↑ reticulocytes (~2X), neutrophils (~4X), and leucocytes (17.5X) compared to the day 29 controls. All parameters returned to normal by the end of recovery.

10 mg/kg ♂ saw a 4.2X increase in neurtrophils, 30% ↓ in lymphocytes, 8% ↓ in RBCs HCT and HGB at the end of dosing. Lymphocyte ↓ was not stat. sig. after recovery but was still down 26%. All other parameters above returned to normal by the end of recovery.

Reticulocites (% and absolute values) were increased slightly at the end of dosing in 10 mg/kg ♂ but ↓ 26% after recovery.

The moribund sac. ♂ had the same pattern of hematology effects but with greater severity.

Clinical chemistry:

	10 mg/kg ♂	**10 mg/kg ♀**
Cholesterol	33%↓	14%↓
AST	1.6X	2.7X
ALT	1.6X	2.8X
Albumin	27%↓	46%↓
Globulin	1.3X	1.7X
Urea nitrogen	1.3X	1.5X

All parameters normal post-recovery except ~10% increase in phosphate in 10 mg/kg ♂.

Urinalysis: Not done

Gross pathology:

5/7 10 mg/kg ♀ had large mandibular lymph nodes at end of dosing (0 for controls)

7/7 10 mg/kg ♀ had skin abrasions at end of dosing (0 for controls)

2/5 10 mg/kg ♀ had distended uteri at end of recovery (0 for controls)

2/5 10 mg/kg ♂ had large mandibular lymph nodes at end of recovery (0 for controls)

Organ weights:

Weights relative to brain weight are shown below.

	3 mg/kg ♂	**10 mg/kg ♀**
Liver	15%↓	
Spleen		55%↑
Thymus		40%↓
Ovary		44%↓

Organ weights were unremarkable post-recovery

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Histopathology:

Microscopic findings for the unscheduled sacrifices are listed in the sponsor's table below:

Organ	Finding
adrenal cortex	degenerative/necrosis
Heart	cardiomyopathy
Liver	random necrosis, centrilobular necrosis, periportal hypertrophy
Spleen	lymphocyte depletion/necrosis
Thymus	lymphocyte depletion/necrosis, lymphocytolysis, medullary germinal center proliferation, medullary degeneration
Kidney	tubule dilatation, papillary necrosis
glandular stomach	epithelial degeneration/necrosis
colon, cecum, and rectum	epithelial degeneration/necrosis, smooth muscle necrosis
mesenteric and mandibular lymph nodes	lymphocyte depletion/necrosis, lymphoid follicle apoptosis/necrosis, plasma cell hyperplasia, plasma cell apoptosis, plasma cell necrosis
skin/subcutis	acanthosis, ulcer, erosion, fibrosis, hyperkeratosis, epidermal necrosis
Ovary	increased corporeal luteal apoptosis/necrosis, follicular cysts
Vagina	increased epithelial cell apoptosis
femoral and sternal bone marrow	degeneration/necrosis, hyperplasia

Number of animals with significant findings at terminal sacrifice

	Control ♂/♀ n=10	3 mg/kg ♂ n=10	10 mg/kg ♂ n=7	3 mg/kg ♀ n=10	10 mg/kg ♀ n=7
Adrenal, Cortex, Degeneration/necrosis		1	1		3
Heart, cardiomyopathy, degenerative	1/0	3	1		1
Liver necrosis, hepatocyte, random		1			4
Liver hypertrophy, hepatocyte, periportal			1		4
Vacuolation, Hepatocyte			1		
Spleen, depletion/necrosis, lymphocytes					4
Thymus, lymphocytolysis			2		2
Thymus, necrosis/depletion, lymphocytes		1		1	3
Thymus, lymphocytolysis			2		2
Thymus, germinal center proliferation, medulla		3	3	3	1
Thymus, degeneration, medulla			3		3
Stomach, degeneration/necrosis			1		5
Lymph nodes, mesenteric, depletion/necrosis, lymphocytes			3		3
Lymph nodes, mesenteric, apoptosis/necrosis, lymphoid follicles			3		4
Lymph nodes, mesenteric, hyperplasia, plasma cell					4
Lymph nodes, mesenteric, apoptosis, plasma cell					4
Lymph nodes, mandibular, depletion/necrosis, lymphocytes			1		4
Lymph nodes, mandibular, apoptosis/necrosis, lymphoid follicles			2		1

Lymph nodes, mandibular , hyperplasia, plasma cell			2		7
Lymph nodes, mandibular , apoptosis, plasma cell					7
Lymph nodes, mandibular, necrosis, plasma cell					1
GI, infiltrate, lymphocytes	1/0				
Skin, acanthosis	0/1	1	4		7
Skin, ulcer					7
Ovary, necrosis and cysts					6
Vagina, apoptosis, epithelial cells	0/1			2	4
Marrow, necrosis			3		
Marrow, hyperplasia		1			2

Tissues unremarkable at recovery sacrifice.

Toxicokinetics:

Sex	Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	C_{max}/Dose	AUC_{0-24}	AUC_{0-24}/Dose	$t_{1/2}$ (h)
Day 1							
F	1	8	7	7	106	106	Not determined
M	1	4	5	5	77	77	7
F	3	4	37	12	453	151	5
M	3	6	24	8	258	86	5
F	10	6	141	14	1702	170	6
M	10	8	97	9	1123	112	Not determined
Day 16							
F	10	4	851	85	12,603	1260	5
Day 28							
F	1	4	13	13	157	157	9
M	1	4	10	10	102	102	6
F	3	2	55	19	602	201	7
M	3	6	29	10	330	110	7
M	10	6	357	36	2892	289	7

AUC seems approximately dose proportional.
The AUC and C_{max} are slightly higher in females than males

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/s/

SHAWNA L WEIS
05/29/2015

M A GOHEER
05/29/2015

WHITNEY S HELMS
05/29/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA

NDA Number: 206-192 **Applicant:** Genentech Inc. **Stamp Date:** December 11, 2014

Drug Name: Cobimetinib **NDA Type:** **505(b)(1)** new molecular entity (NME)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		CTD format
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		Electronic submission
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		Carcinogenicity – not done/not required Mutagenicity – done Teratogenicity – done Fertility – not required Juvenile studies – done (28-days in rats) Acute and repeat dose toxicity – done (13-weeks in rats and dogs) ADME – done Safety pharmacology – done (cardio, pulmonary, local tolerance)
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		Similar formulations were used in pivotal preclinical and clinical studies
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		Same route of administration
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	√		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		Sufficient for filing.
11	Has the applicant addressed any abuse potential issues in the submission?		√	Does not constitute a filing issue
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. This NDA is NME

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _YES__

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

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None**

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/s/

M A GOHEER
02/02/2015

WHITNEY S HELMS
02/03/2015