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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
BLA (supplement)	202429 (S-16)
Submission Date:	June 7, 2017 \\CDSESUB1\evsprod\NDA202429\202429.enx
PDUFA Date:	November 1, 2017
Brand Name:	Zelboraf®
Generic Name:	Vemurafenib
Formulation/Strength:	240 mg Tablet
Applicant:	Roche
Submission Type:	Efficacy Supplement
Proposed Dosing Regimen:	960 mg orally twice-daily without regard to food
Proposed Indications	Patients with Erdheim-Chester Disease with BRAF V600 mutation
OCP Review Team:	Sriram Subramaniam, Ph.D., Stacy Shord, Pharm.D., and Bahru Habtemariam, Pharm.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Hematology Products (DHP)

1 EXECUTIVE SUMMARY

Zelboraf (vemurafenib) is an orally available inhibitor of the mutated forms of the BRAF serine-threonine kinase, including BRAF V600E. Zelboraf received accelerated approval on August 17, 2011 for the treatment of patients with unresectable or metastatic melanoma (MM) with a BRAF V600E mutation. The approved dose is 960 mg orally twice daily (BID), with or without food.

The current review includes evaluation of supplement 16 submitted to support the proposed indication of vemurafenib for the treatment of patients with Erdheim-Chester Disease (ECD) harboring a BRAF V600 mutation.

The following key questions were addressed in this review of this efficacy supplement:

- Is the pharmacokinetics (PK) of vemurafenib similar in patients with ECD compared to other diseases?
- Is the proposed dosing regimen for the treatment of ECD supported by the exposure-response (E-R) relationships in Trial MO28072?

1.1 Recommendations

The Office of Clinical Pharmacology's Division of Clinical Pharmacology V reviewed the information contained in supplement 16. The supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

The recommended dose of 960 mg BID, with or without food is supported by the limited PK data that indicates that the PK is similar for patients with different diseases. No E-R can be explored in the ECD population, as PK samples were only collected from one patient with ECD.

1.2 Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments.

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Zelboraf (vemurafenib) is an orally available inhibitor of mutated forms of the BRAF serine-threonine kinase, including BRAF V600E. Zelboraf was previously reviewed under original NDA 202429 (DARRTS ID 2968791). The following is a summary of the clinical PK of vemurafenib in metastatic melanoma (MM):

- Vemurafenib exhibits linear PK at steady state between a dose of 240 mg and 960 mg. The mean (± SD) C_{max} is 62 ± 17 µg/mL and the mean (± SD) $AUC_{0\text{-}12h}$ is 601 ± 170 µg*h/mL. The median T_{max} is ~3 hours following multiple doses. The median accumulation ratio was 7.4 following twice daily administration and steady-state was achieved within 15 days to 22 days. The population apparent oral clearance was 31 L/day (%CV=32%) and the median terminal elimination half-life was 57 hours (5^{th} percentile, 30 hours; 95^{th} percentile, 120 hours).
- A high-fat meal increased vemurafenib AUC by ~5-fold and C_{max} by 2.5-fold, and delayed T_{max} by ~4 hours as compared to an overnight fasted state.

The observed and population PK data following a dose of 960 mg BID appears similar in patients with different diseases, including MM, non-small cell lung cancer (NSCLC) and ECD.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant proposes a dose of 960 mg BID without regard to food for the treatment of patients with ECD harboring a BRAF V600 mutation. This dosing regimen is the same as the dosing regimen listed in the Zelboraf labeling for the treatment of MM.

In general, the PK of vemurafenib at a dose of 960 mg BID is similar for patients with different diseases, including MM, NSCLC and ECD. The PK was collected as part of an ongoing open-label basket trial (MO28072) designed to evaluate the safety and efficacy of a dose of 960 mg BID, without regard to food, in patients diagnosed with BRAF V600 mutation-positive diseases, including 22 patients with ECD (Cohort 7a).

2.3 Outstanding Issues

No outstanding issues.

2.4 Summary of Labeling Recommendations

Labeling changes are not recommended by the Office of Clinical Pharmacology, as PK information is limited to only one patient with ECD.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Zelboraf received accelerated approval on August 17, 2011 for the treatment of unresectable or metastatic melanoma (MM) harboring a BRAF V600E mutation. The randomized Trial NO25026 showed that the co-primary endpoints, overall survival (OS) and progression free survival (PFS), were significantly ($p<0.0001$) longer for vemurafenib (960 mg BID without regard to food) compared to dacarbazine.

The current efficacy supplement includes a clinical study report (CSR) of Trial MO28072 to support the proposed indication:

- The primary efficacy endpoint, overall response rate (ORR), was 55% (95% CI: 32, 75) (l Complete response and 11 Partial responses) in patients with ECD (Cohort 7a: n=22) administered a dose of

960 mg BID, without regard to food. The duration of response was not evaluable with a median duration of follow-up of 26 months.

3.2 General Pharmacology and Pharmacokinetic Characteristics

The PK of vemurafenib in MM was previously described in the clinical pharmacology review of the original NDA submission (DARRTS ID 2968791). Please refer to this review for a description of the clinical pharmacology data. The current submission included an updated population PK model of vemurafenib and a graphical PK/PD analysis in various diseases; however, since PK samples were collected from only one patient with ECD, the PK and PK/PD analysis cannot be evaluated in patients with ECD.

3.3 Clinical Pharmacology Review Questions

3.3.1 Is the proposed dose acceptable?

Yes. The PK of vemurafenib is similar in patients with different diseases based on observed data within Trial MO28072 and a cross study comparison using observed and population PK data. The safety profile in patients with ECD was mostly similar compared to patients with other diseases despite the longer treatment duration for patients with ECD. The adverse reactions (ARs) in the ECD population were managed by dose modifications and supportive care. The dose was reduced to 720 mg or 480 mg for all patients; however, the ORR was consistent across the efficacy population. No additional dose exploration is recommended in this rare patient population.

Observed Data

The applicant is conducting an open label basket trial which includes the following cohorts: cohort 1 – NSCLC and cohort 7 multiple diseases (including ECD). A summary of the sparse PK samples collected from 26 patients with various diseases [n=14 non-small cell lung cancer (NSCLC), 1 ECD, & 11 others] was available from the CSR for Study MO28072. The samples were collected before the dose on multiple occasions including Cycle 1 Day 15 (C1D15), C2D1, C3D1 and C4D1.The mean pre-dose concentration at steady state ($C_{trough,ss}$) is similar for patients with different underlying BRAF V600 mutation positive diseases (**Error! Reference source not found.** and **Table 1:** Vemurafenib mean trough concentrations at steady state in different patient populations

Population (n of patients)	**Mean Steady-State Trough Concentrations (**µg/mL)
Pooled (22)	40 to 48
NSCLC (12)	33 to 55
Cohort 7 (10)	35 to 47
ECD (1)	39

Data Source: Tables 155, 156 & 157, CSR for Trial MO29072
NSCLC: Non-small cell lung cancer; ECD= Erdheim-Chester Disease; Pooled = NSCLC and Cohort 7, and Cohort 7 includes ECD population.

Figure 1).

Table 1: Vemurafenib mean trough concentrations at steady state in different patient populations

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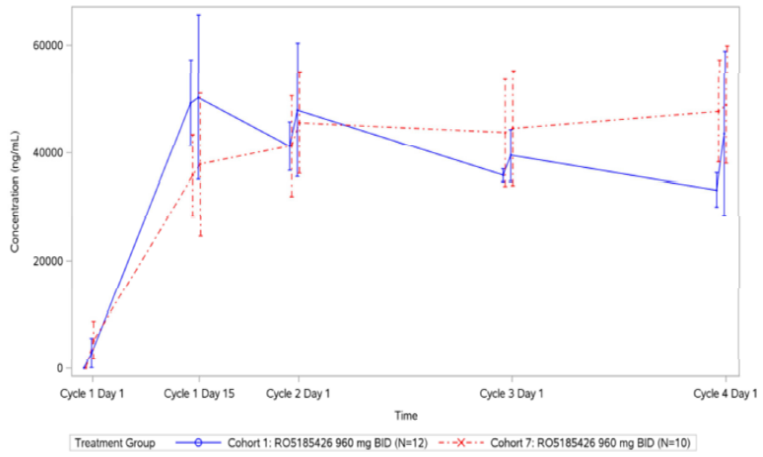
NSCLC: Non-small cell lung cancer; ECD= Erdheim-Chester Disease; Pooled = NSCLC and Cohort 7, and Cohort 7 includes ECD population.

Figure 1: Mean vemurafenib concentration versus time profiles for patients with non-small cell lung cancer and other diseases harboring a BRAF V600 mutation (Study MO28072**)**



Cohort 1: Non-small cell lung cancer (NSCLC)
Cohort 7: ECD/ Langerhans cell histiocytosis, anaplastic thyroid cancer, advanced-stage astrocytoma, early-stage astrocytoma, and other BRAF V600 positive diseases.

Population Analysis

The population analysis (see **APPENDIX**:) shows that the vemurafenib PK parameters are similar regardless of the underlying disease (**Table 2**).

Table 2: Predicted steady-state pharmacokinetic parameters following a dose of 960 mg BID by disease

Parameter	NSCLC (N=14)		ECD (N=1)		Others (N=11)	
	Geometric Mean (CV)	Median (Range)	Geometric Mean (CV)	Median (Range)	Geometric Mean (CV)	Median (Range)
$AUC_{SS,12h}$ (µg/mL*day)	26.9 (0.193)	28.8 [19-35.2]	23.9 (-)	23.9 [23.9-23.9]	28.2 (0.396)	27.1 [14.6-53.1]
T_{max} (day)	0.198 (0.121)	0.208 [0.167-0.237]	0.21 (-)	0.21 [0.21-0.21]	0.183 (0.103)	0.19 [0.153-0.204]
$t_{1/2}$ (day)	2.00 (0.309)	2.01 [1.04-3.27]	5.97 (-)	5.97 [5.97-5.97]	2.00 (0.253)	2.19 [1.16-2.9]
C_{max} (µg/mL)	54.8 (0.199)	58.9 [38.3-72.8]	48 (-)	48 [48-48]	57.8 (0.405)	55.6 [30.1-109]
C_{min} (µg/mL)	51.9 (0.184)	54. 8[37.1-65.9]	47.3 (-)	47.3 [47.3-47.3]	54.1 (0.382)	51.8 [27.7-101]

ECD= Erdheim-Chester Disease, NSCLC=non-small cell lung cancer, Other=non-ECD/NSCLC

Cross Study Comparison

A cross study comparison of pre-dose concentrations at steady state (**Table 3**) shows that the observed mean $C_{trough,ss}$ are similar regardless of the underlying disease: multiple diseases harboring a BRAF V600 mutation (Study MO28072), melanoma (NP22657) and papillary thyroid cancer (PTC: NO25530).

Table 3: Mean vemurafenib trough concentrations at steady state

	Study NP22657[a]				Study NO25530[b]				Study MO28072			
	N	Mean±SD (ng/mL)	CV%	Range	N	Mean±SD (ng/mL)	CV%	Range	N	Mean±SD (ng/mL)	CV%	Range
C1 D15	108	47550± 23140	49%	2110, 118000	22	56300± 21100	38%	12600, 104000	10	45100± 12200	27%	22700, 64400
C2 D1	122	41120± 23390	57%	0, 111000	22	52900± 25400	48%	14100, 115000	10	41100± 7510	18%	30700, 57100
C3 D1	109	452000± 21330	47%	30, 96600	22	57700± 23100	40%	18500, 109000	6	39700± 8870	22%	33800, 57300
C4 D1	109	50310± 19520	39%	0, 109000	17	50600± 20600	41%	166, 80000	6	39800± 10500	26%	28900, 59200

C = cycle; CV = coefficient of variation; D = day; SD = standard deviation. All studies used 960 mg BID dose.

Dose Modifications

The most commonly reported ARs in patients with ECD were: arthralgia, maculo-papular rash, alopecia, fatigue, QT prolongation, skin papilloma, hyperkeratosis, and diarrhea. The overall safety profile in patients with ECD is similar to the safety profile of patients with MM.

All patients with ECD had at least one dose reduction (DR) and one dose interruptions (DI) due to an adverse reaction (AR). The most common ARs leading to DR or DI in patients with ECD were maculo-papular rash, fatigue, and arthralgia, palmar-plantar erythrodysaesthesia, and increased lipase. The AR associated with a DR or DI in patients with ECD are similar to those associated with dose modification in patients with NSCLC or MM; however, more patients with ECD required a DR and DI due to ARs compared to patients with other diseases (**Table 4** and **Table 5**). Also, more patients with ECD (32%) discontinued study drug due to ARs compared to patients with NSCLC (10%) and MM (7%: Study MO25515). Nonetheless, these comparisons can be confounded by factors including limited sample size and longer duration of exposure to vemurafenib in the ECD population compared to the other diseases.

Table 4: Patients (%) with at least one dose reduction (DR) due to adverse reactions

Disease (n)	**DR to 720 mg**	**DR to 480 mg**	**DR to 240 mg**
ECD (n=22)	91%	64%*	0
NSCLC (n=62)	53%	16%	3%
MM (n=3219) †	19%	6%	<0.5%

*includes 2 patients with DR from 960 to 480 mg† Table 27, Study MO25515
ECD and NSCLC results based on analysis of dataset aex xpt
ECD= Erdheim-Chester Disease, NSCLC=non-small cell lung cancer, MM=metastatic melanoma

Table 5: Patients (%) with at least one dose interruption (DI) due to adverse reactions

Disease (n)	**1 DI**	**2 DI**	**≥3 DI**
ECD (n=22)	32%	36%	32%
NSCLC (n=62)	37%	21%	8%
MM (n=3219)†	28%	13%	NA

† Table 28, Study MO25515. NA=not available
ECD and NSCLC results based on analysis of dataset aex xpt
ECD= Erdheim-Chester Disease, NSCLC=non-small cell lung cancer, MM=metastatic melanoma

A dose was reduced for a total of 20 patients with ECD from the starting dose of 960 mg to 720 mg and the dose was reduced for 12 patients from a dose of 720 mg to 480 mg due to ARs. The dose for two additional patients was reduced to 480 mg from 960 mg due to ARs. The median treatment duration following a DR to 480 mg was 3-fold longer than following a DR to 720 mg (**Table 4** and **Table 6**). Nonetheless, the ORR does not appear to be affected for patients with a DR to 480 mg BID (n=14) as the ORR appears consistent with the total population. The duration of DI across number of DI ranged between 1 day to 29 days, with a median of 1 day to 10 days (**Table 7**).

Table 6: Summary results of dose reductions (DR) due to adverse reactions

Dose Reduction	720 mg BID	480 mg BID
%Patients	91% (n=20)	67% (n=14)
Median time to dose reduction (min, max)	33 days (9,421)	91.5 days (17, 502)
Median treatment duration (min, max)	77 days (4, 1325)	236 days (21,924)
ORR (95% CI)	n=8 37.5% (8.5, 75.5)	n=14 64.3% (35.1, 87.2)
DOR	NE	NE

ORR=best overall response rates, DOR=duration of response

Table 7: Summary results of dose interruptions (DI) for any reason

	First DI	Second DI	Third DI
% Patients	17%	27%	59%
Median time to dose interruption (min, max)	15 days (1, 190)	48 days (13, 492)	110 days (31,498)
Median duration for interruption (min, max)	6.5 days (1, 29)	10 days (1, 28)	1 day (1, 29)

3.3.2 Are there exposure-response relationships for efficacy and safety to support the proposed dose for the proposed indication?

No. E-R cannot be explored in the ECD population as PK sampling was limited to one patient with ECD. In the original NDA submission in the untreated MM population, a statistically significant exposure-response relationships was observed between PFS and vemurafenib exposure (C_{min}) ($p < 0.0001$), as well as between the risk of development of a squamous cell carcinomas and vemurafenib exposure (C_{min}) ($p <0.0001$) (DARRTS ID 2968791).

3.4 Are the bioanalytical measurements of vemurafenib reliable?

The PK of vemurafenib in Trial MO28072 was measured using the same validated assay reported in the original NDA. The method involved protein precipitation followed by high-performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) with a validated assay range of 25 ng/mL to 50,000 ng/mL. The assay accuracy and precision, and incurred samples reanalysis were within acceptable limits.

4 APPENDIX: PHARMACOMETRIC REVIEW

4.1.1. Applicant's Population PK Analysis

The applicant conducted population PK analyses using data from Trial MO28072 following oral administration of vemurafenib to confirm if a previously established population PK model of vemurafenib in patients with metastatic melanoma (MM) is able to describe the PK of vemurafenib in patients with non-small cell lung cancer (NSCLC), Erdheim-Chester Disease (ECD) and other diseases harboring a V600 BRAF mutation and to compute the PK parameters for these diseases within Trial MO28072. In addition, graphical analysis of exposure-efficacy (BOR and change in tumor size from baseline) and exposure-safety (serious AEs and Grade ≥3 AEs) in NSCLC and ECD in Trial MO28072 were compared.

Table 8:. Overview of trials and data included in the population PK analysis

Study No.	Study design and dosing regimens	Description of data
MO28072	An open-label, multiple cohort Phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers (Cohort 1=NSCLC, Cohort 7 included ECD). Dose: 960 mg BID in 28 day cycles	Sparse sampling for all patients enrolled under Amendment 7 (1/13/15) before dosing and 2-4 hours post-dose during Cycle 1, Days 1 and 15, and Cycles 2-4, Day 1. Sparse PK sampling were only collected from one patient with ECD

(Source: Applicant's Population PK/PD Report)

The population PK data set contains 147 measurable PK samples from 26 patients that received a dose of 960 mg BID. Data points that were not used in the analysis were 2 (1.3%) post-dose BQL observations and 1 (0.7%) positive pre-dose observation. PK samples were collected from only one patient with ECD.

The previously developed population PK model (Model 001) included a one compartment model with first-order absorption and first-order elimination. Only sex was identified as a significant covariate. The results from the population analysis showed that the differences in exposure (in terms of steady-state AUC, C_{max}, and C_{min} following 960 mg BID) between male and female are relatively small, indicating that there is no need to dose adjust based on sex. The results from the previous analysis also showed that the impact of food intake at the time of measurement may have an impact on the PK measurements as food intake was not strictly controlled across all studies. Different relative bioavailability values were estimated in the previous analysis based on differences in the study design to account for this effect. In the final model of the prior analysis all the parameters were fixed (including the effects of gender) and relative bioavailability was constant and equal to 1.

Following investigation of various model refinements during model development, the previously established model (Model 001) was found optimal and was used to compute exposure estimates.

The parameter estimates for Model 001 are summarized in **Table 9**. The model was validated through goodness of fit plots (**Figure 2**) and prediction corrected visual predictive check (**Figure 3**).

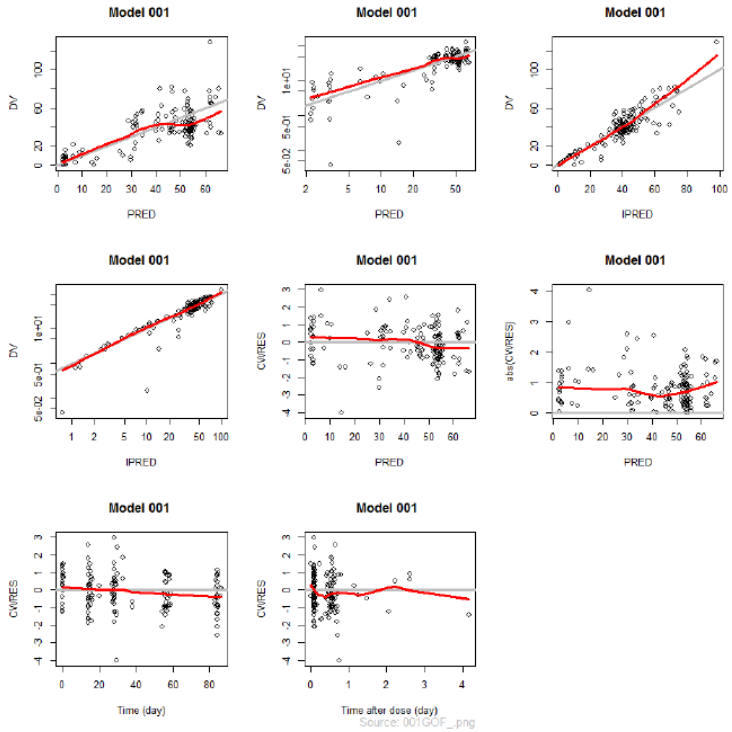
Table 9: Parameter estimates of Model 001

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

BPV – Between-patient variability, σ – Residual error, RSE – Relative standard error of estimate, SEX – Gender,
[a] F1 for Phase I study NP25163 and Phase II study NP22657 data,
[b] F1 for Phase I study NP25163 and Phase II study NP22657 data starting cycle 5 and after, and all Phase III study NO25026 cycles,
[c] Typical values estimated for CL/F and V/F were for female, and males were estimated to have 17% and 48% greater CL/F and V/F, respectively, than females.

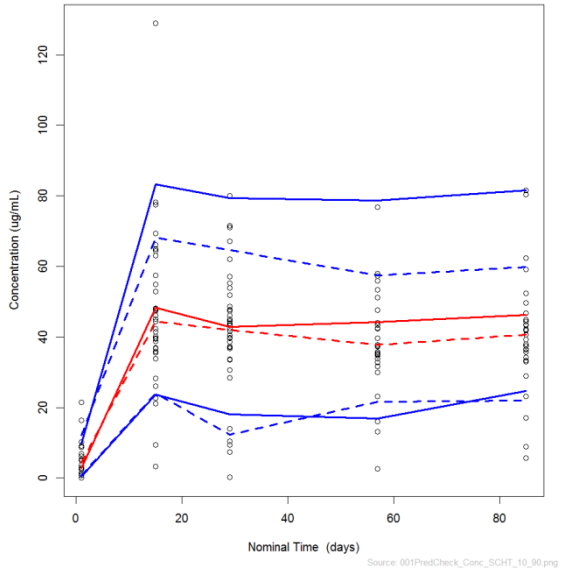
(Source: Applicant's Population PK and PK/PD Report, Table 1)

Figure 2: Goodness-of-Fit plots of the applicant's final Model



(Source: Applicant's Population PK and PK/PD Report, Figure 13)

Figure 3: Prediction Visual Predictive Check of the Final Model by Study

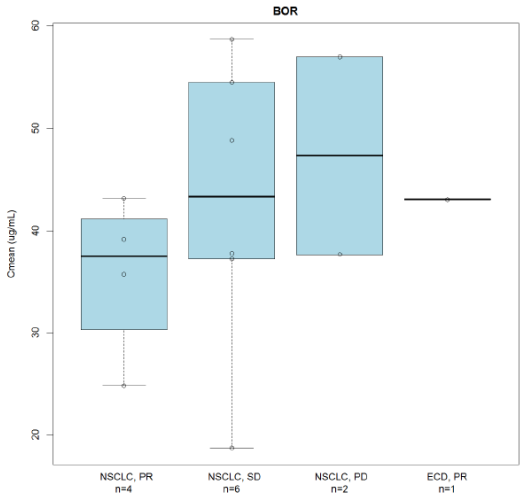


Key: The circles show the observed concentrations. The lines show median (red), and the 10th and 90th percentiles (blue) of the simulated (solid lines) and observed (dash lines) concentrations. The simulated values were computed from 10,000 trials with dosing, sampling, and covariate values of the analysis dataset.
(Source: Applicant's Population PK and PK/PD Report, Figure 23)

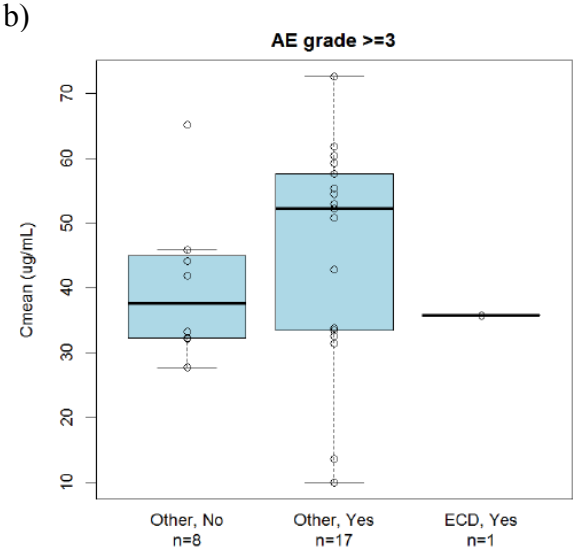
Graphical analyses of predicted exposure and efficacy relationship for BOR (**Figure 4a**) showed that the range of mean vemurafenib concentration over complete treatment period (C_{mean}) achieved across the response categories generally overlapped; similar exposure levels were achieved for patients with partial response and with stable or progressive disease. Graphical analyses of predicted exposure and safety relationship (**Figure 4a**) showed the C_{mean} of the one patient with ECD was similar to that of patients with other diseases who did not have any serious AEs and Grade ≥3 AEs.

Figure 4: Relationship between vemurafenib exposure and (a) Best overall response (BOR), (b) Grade ≥ 3 adverse events, and (c) Serious adverse events

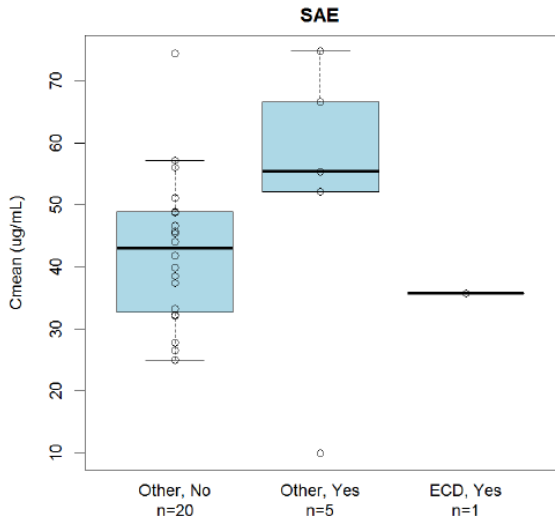
a)



b)



c)



C_{mean} is the mean concentration over the interval from the first dose to a) the time of BOR and, b & c) first event or last dose (if there were no events). NSCLC=Non-small cell lung cancer, ECD=Erdheim-Chester Disease, PR=partial response, SD=stable disease, PD=progressive disease, Other =non-ECD diseases, No=no events, and Yes=with events.
(Source: Applicant's Population PK and PK/PD Report, Figures 41 and 44)

Applicant's Conclusion:

- Vemurafenib concentrations in patients with NSCLC, ECD and other diseases following an oral dose of 960 mg BID were adequately described by the previously developed model in patients with melanoma.
- No differences in exposure for patients with NSCLC across different BOR response categories.
- The C_{mean} of the one patient with ECD with safety event was similar to patients with non-ECD diseases who did not have any serious AEs and Grade ≥ 3 AEs.

Reviewer's Comments:

The applicant's original population PK model developed in using the PK data from patients with MM was able to describe the PK of vemurafenib for patients with other disease types (refer to Table 2). At best, the submitted population PK analysis confirms the previously described structural model. Due to limited population, PK comparison across different population is not reliable. In addition, graphical PK/PD analysis is not useful considering the small sample size across different diseases, particularly, for the proposed ECD population.

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