

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202429Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
DIVISION DIRECTOR MEMO

NDA /Serial Number: 202429/N_000

Drug Name: Zelboraf® (Vemurafenib)

Applicant: Hoffmann-La Roche Inc.

Indication(s): Treatment of BRAF V600E mutation positive unresectable
or metastatic melanoma

Date(s): Submission Date: April 28, 2011
PDUFA Date: July 31, 2011

Review Priority: Priority Review

Biometrics Division: Division of Biometrics V (HFD-711)

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Medical Division: Division of Drug Oncology Products (HFD-150)

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Project Manager: Theresa Ferrara

Keywords: Targeted therapy, Adaptation, Overall survival, Melanoma

Introduction

This is Division Director's memo in addition to the primary statistical review by Dr. Qiang Xu, and secondary team leader memo by Dr. Shenghui Tang. I concur with the conclusions and recommendations of both Drs Xu and Tang. Additional comments are presented here to our approach in advising the applicant during the course of the Phase III trial to use adaptation and revise the statistical analysis plan based on the evidence available from other clinical trials of the same product.

Overview

In this application (submitted April 2011), the applicant is seeking the indication for vemurafenib as a treatment for patients with BRAF V600E mutation positive unresectable or metastatic melanoma.

In support of the claim, the applicant has submitted one pivotal randomized open-label study and two supporting trials: a Phase 1 dose-escalating trial and a Phase 2 open-label trial. The randomized study demonstrated an improvement in overall survival compared to an active control (DTIC). Please refer to the review by the primary reviewer for a detailed description and results of these trials.

Targeted Therapy

The applicant pursued a targeted approach by developing vemurafenib in patients whose tumors harbor BRAF V600E mutation based on the initial Phase 1 dose-escalation trial (trial PLX06-02 conducted between November 2006 to June 2010) in 55 patients (49 of whom had melanoma) and an extension phase which included 32 additional patients with metastatic melanoma who had BRAF V600E mutation. In the dose-escalation phase, the dose was escalated from doses of < 240 mg (30 patients, no responses) to 1120 mg twice daily, and in the extension phase 32 patients were treated at 960 mg dose twice daily. In the dose-escalation phase, 11 of 16 patients (69%) whose tumors harbored BRAF V600E mutation responded whereas 5 patients with metastatic melanoma whose tumors did not have the BRAF mutation did not respond to vemurafenib. In the extension phase 26 of 32 patients (81%) had a response with duration of response of > 8 months in 11 of the 32 patients. The results of this trial were published in August 2010 in *The New England Journal of Medicine*¹.

To confirm the level of activity observed in the dose-escalation phase in the targeted population, the applicant conducted a Phase 2 trial (trial NP22657 conducted between September 2009 to September 2010) in 132 patients with metastatic melanoma whose tumors harbored BRAF V600E mutation. The applicant shared with the Agency preliminary results suggesting an objective response rate of approximately 50% from this trial in August 2010. The final analysis as submitted in this application confirmed an objective response rate of 52% among the 132 patients.

The randomized, open label, controlled, multicenter Phase III trial was initiated in January of 2010 and enrollment was completed by October of 2010 in 675 patients with previously untreated melanoma with BRAF V600E mutation. Interim overall survival analysis conducted in January 2011 showed a statistically significant improvement in overall survival among patients receiving vemurafenib compared to patients receiving DTIC (HR = 0.37, p-value < 0.0001). This trial also demonstrated significant improvement in progression-free survival with the treatment of vemurafenib and confirmed a response rate of 48.4% in the vemurafenib treatment arm compared to 5.5% in the DTIC treatment arm.

Adaptation

The phase 3 randomized, controlled, multicenter clinical trial was originally designed (September 2009) with 680 patients (468 events) to detect a difference in median overall survival of 10.7 months in the vemurafenib arm vs. 8 months in the DTIC arm and HR of 0.75 with 80% power and two-sided 2.5% level of significance, accounting for 2 interim analyses with 50% and 75% of information. Overall survival was the primary efficacy endpoint.

In August of 2010 the Agency became aware of the preliminary results of the Phase 2 study as well as the published results of the Phase 1 study. At this time both studies showed impressive objective response rates of > 50% in the targeted population of patients with metastatic melanoma whose tumors harbored BRAF V600E mutation. It was also reported¹ that in the extension phase of the Phase 1 trial, the median progression-free survival among the 32 patients was greater than 7 months. Literature review² suggested that the objective response rates ranged from 11% to 24% in metastatic melanoma patients treated with a variety of chemotherapy agents. Given these results the Agency proactively communicated with the applicant multiple times to modify the statistical analysis plan of the phase 3 trial (which had accrued approximately 400 patients at that time and about 300 more patients had been screened to enter the study), adapting with the impressive observed activity of vemurafenib in the phase 1 and phase 2 studies. Specifically the Agency advised the applicant to (1) increase overall study alpha level to two-sided 5% from two-sided 2.5%, (2) set up alpha spending rule with higher probability to cross at interim analysis, (3) less conservative target HR (0.65 instead of 0.75) to be detected, and (4) add progression-free survival as a second primary endpoint. The applicant accordingly revised the statistical analysis plan to conduct final progression-free survival analysis with 187 events at which time an interim survival analysis was to be conducted with 98 deaths (50% information per modified estimates). Although patients were enrolled into the study within a very short period of time at an unexpected high rate of accrual and hence could not reduce the actual number of patients enrolled with the adaptation, the applicant was able to successfully conduct the analysis early in a planned manner with the timely adaptation of the clinical trial. The application was also reviewed by the Agency in an expedited manner and completed well before the PDUFA dead line.

As illustrated in this application, particularly in diseases where practically there is no effective treatment that prolongs survival, information regarding extraordinary activity of a treatment from studies outside of the confirmatory study, can guide in using adaptation in an on-going study.

Rajeshwari Sridhara, Ph.D.

Division Director

Date: August 11, 2011.

References:

1. Flaherty KT, et.al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med* (2010) 363: 809-19
2. Jensen EH et.al. Melanoma and other skin cancers. In 'Cancer Management: A multidisciplinary approach' edited by Pazdur et al, 9th edition, CMP United Business Media.

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/s/

RAJESHWARI SRIDHARA
08/11/2011



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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES— STATISTICAL REVIEWER'S ADDENDUM

NDA/BLA Serial Number: NDA
202429

Drug Name: Zelboraf[®] (Vemurafenib)

Indication(s): Treatment of BRAF V600 mutation positive unresectable or metastatic melanoma

Applicant: Hoffmann-La Roche Inc.

Date(s): Submit Date: April 28, 2011
PDUFA Date: October 28, 2011

Review Priority: Priority

Biometrics Division: Division of Biometrics V (HFD-711)

Statistical Reviewer: Qiang (Casey) Xu, Ph.D.

Concurring Reviewers: Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Director

Medical Division: Division of Drug Oncology Products (HFD-150)

Clinical Team: Yang-min Max Ning, M.D.
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John Johnson, M.D.

Project Manager: Theresa Ferrara

Keywords: Metastatic Melanoma, BRAF V600 Mutation Positive, Progression-Free Survival, Overall Survival, Kaplan-Meier Product Limit

This is an addendum to Qiang (Casey) Xu's statistical review (dated July 15, 2011).

Of the 14 subjects enrolled in Site 201192, the records for half of the enrolled subjects were reviewed during the site inspection. The main issue identified during this inspection was the failure to maintain complete/accurate case histories relating to measurements of target lesions for all seven subjects' records reviewed. Source CT scans for baseline assessments were not present at the site. In addition, personnel at the site were not able to accurately identify the target lesions measured from time point to time point during the study that were reported in the CRF; therefore, actual measurements of target lesions were also not able to be verified. Survival data from the site appears to have been accurately reported in the NDA.

In order to examine whether the reliability of the data would impact the primary efficacy results, this reviewer conducted sensitivity analyses by excluding patients from Site 201192. The results of the sensitivity analyses are presented in the table below.

Sensitivity Analyses on PFS and OS with Site 201192 Excluded

	<i>Vemurafenib</i>	<i>Dacarbazine</i>
PFS	267	269
Number of Events	101	179
Hazard Ratio		0.26
95% CI for HR		(0.20, 0.33)
p-Value (Log-Rank Test)		<0.0001
Kaplan-Meier Estimate of Median (months)	5.32	1.61
95% CI for Median	(4.83, 6.57)	(1.54, 1.74)
OS (Censored at Cross-Over)	329	332
Number of Deaths	75	118
Hazard Ratio		0.44
95% CI for HR		(0.33, 0.59)
p-Value (Log-Rank Test)		<0.0001
Kaplan-Meier Estimate of Median (months)	--	7.92
95% CI for Median	(9.59, --)	(7.26, 9.63)
OS (ITT Analysis: No Censoring at Cross-Over)	329	332
Number of Deaths	75	119
Hazard Ratio		0.47
95% CI for HR		(0.35, 0.62)
p-Value (Log-Rank Test)		<0.0001
Kaplan-Meier Estimate of Median (months)	--	8.80
95% CI for Median	(9.59, --)	(7.33, --)

With a total of 14 ITT patients from Site 201192 removed, the sensitivity analyses demonstrates consistent results with the primary efficacy analyses, which have been elaborated in Section 3.2 in Statistical Review and Evaluation. Therefore, the inspection problem in Site 201192 does not change the conclusion drawn previously in this review regarding the efficacy of vemurafenib in Study 25026.

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/s/

QIANG XU
07/28/2011

SHENGHUI TANG
07/28/2011

RAJESHWARI SRIDHARA
07/28/2011



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/BLA Serial Number: NDA
202429

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Applicant: Hoffmann-La Roche Inc.

Date(s): Submit Date: April 28, 2011
PDUFA Date: July 31, 2011

Review Priority: Priority

Biometrics Division: Division of Biometrics V (HFD-711)

Primary Reviewer: Qiang (Casey) Xu, Ph.D.

Secondary Reviewer: Shenghui Tang, Ph.D., Team Leader

Concurring reviewer: Rajeshwari Sridhara, Ph.D., Director

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Amy Mckee, M.D.
John Johnson, M.D.

Project Manager: Theresa Ferrara

Keywords: Metastatic Melanoma, BRAF V600 Mutation Positive, Progression-Free Survival, Overall Survival, Kaplan-Meier Product Limit

This is an original New Drug Application (NDA) submission seeking the indication for vemurafenib (Zelboraf[®]) for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The applicant has submitted results from one pivotal study, NO25026, a randomized, open-label, dacarbazine (DTIC) controlled, multicenter Phase III study in previously untreated patients with histologically confirmed metastatic melanoma (unresectable Stage IIIC or Stage IV) harboring BRAF V600 mutation as determined by the companion diagnostic test (cobas[®] 4800 BRAF V600 Mutation Test). The co-primary endpoints were overall survival (OS) and progression-free survival (PFS) with best overall response rate (BORR) and duration of response as key secondary endpoints. The data cutoff date for the primary efficacy analyses was Dec 30, 2010. One hundred eighteen deaths occurred with 43 in the vemurafenib group and 75 in the dacarbazine group. The hazard ratio for death was 0.37 (95% CI: 0.26, 0.55; log-rank p-value<0.0001). The KM estimates of median OS was 9.23 months (95% CI: 8.05, not reached) for vemurafenib and 7.75 months (95% CI: 6.28, 10.28) for dacarbazine. The findings were confirmed in an updated overall survival analysis with a data cutoff date of Mar 31, 2011. The updated hazard ratio for death was 0.44 (95% CI: 0.33, 0.59). A total of 286 PFS events occurred with 104 in the vemurafenib group and 182 in the dacarbazine group. The hazard ratio for progression or death was 0.26 (95% CI: 0.20, 0.33; log-rank p-value <0.0001). The KM estimates of median PFS was 5.32 months (95% CI: 4.86, 6.57) for vemurafenib and 1.61 months (95% CI: 1.58, 1.74) for dacarbazine. The confirmed investigator-assessed BORR in the vemurafenib group was 48.4% (95% CI: 41.6, 55.2) with a KM estimate of the median duration of response of 5.49 months (95% CI: 3.98, 5.72). The confirmed investigator-assessed BORR in the dacarbazine group was 5.5% (95% CI: 2.8, 9.3). Median response duration was not reached due to small number of responders.

The results from Study NO25206 were supported by Study NP22657, an open-label, multi-center, single agent, single-arm Phase II study in previously treated patients with metastatic melanoma harboring BRAF V600E mutation. The primary endpoint was BORR as assessed by an independent review committee (IRC). A total of 132 patients were enrolled. Study NP22657 showed an IRC assessed BORR of 52% (95% CI: 0.43, 0.61) with median response duration of 6.5 months (95% CI: 5.6, not reached).

For further details regarding the designs, data analyses, and results of both Study NO25206 and Study NP22657, please refer to the statistical review by Dr. Qiang (Casey) Xu, (July 15, 2011).

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Qiang (Casey) Xu) of this application. The cobas test was designed to detect the predominant V600E mutation with high sensitivity. Non-clinical performance studies have shown that the cobas test also detects BRAF V600D mutations and a proportion of BRAF V600K mutations. Sanger sequencing was performed retrospectively on all available tumor specimens obtained for patients screened for enrollment as of June 15, 2010. Among 220 randomized patients who were available for Sanger sequencing results, 164 were detected as V600E. The hazard ratio for OS from a subgroup analysis for the 164 patients with V600E was 0.58. The data submitted by the applicant

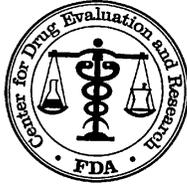
demonstrates overall survival benefit and supports approval. The exact indicated population for approval is deferred to the clinical team. A post-market commitment to obtain a survival update with a minimum of 24 month follow-up after randomization of the last patient is recommended.

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/s/

SHENGHUI TANG
07/15/2011

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07/15/2011



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Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: NDA
202429

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Date(s): Submit Date: April 28, 2011
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1. EXECUTIVE SUMMARY

This is a New Drug Application (NDA) seeking the indication for vemurafenib (Zelboraf[®]) for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The application is primarily based on a pivotal randomized Phase III study NO25026, supported by a Phase II single-arm study NP22657. Both studies achieved their primary objectives and demonstrated a clinically meaningful and statistically significant efficacy improvement through primary endpoints of overall survival (OS) and progression-free survival (PFS), and best overall response rate (BORR), respectively, in the studied patients. A brief summary of major efficacy findings and statistical issues are presented below.

Study NO25026 was a randomized, open-label, dacarbazine (DTIC) controlled, multicenter Phase III study in previously untreated patients with histologically confirmed metastatic melanoma (unresectable Stage IIIC or Stage IV) harboring BRAF V600 mutation as determined by the companion diagnostic test (cobas[®] 4800 BRAF V600 Mutation Test). A total of 675 patients were randomized. The co-primary endpoints were overall survival (OS) and progression-free survival (PFS) with best overall response rate (BORR) and duration of response as key secondary endpoints. The primary efficacy results based on the data cutoff date of Dec 30, 2010 are

- One hundred eighteen deaths occurred with 43 in the vemurafenib group and 75 in the dacarbazine group. The hazard ratio for death was 0.37 (95% CI: 0.26, 0.55; log-rank p-value < 0.0001), indicating a 63% decrease in the hazard of death in patients assigned to vemurafenib compared with patients assigned to dacarbazine. The KM estimates of median OS was 9.23 months (95% CI: 8.05, not reached) for vemurafenib and 7.75 months (95% CI: 6.28, 10.28) for dacarbazine.
- A total of 286 PFS events occurred with 104 in the vemurafenib group and 182 in the dacarbazine group. The hazard ratio for progression or death was 0.26 (95% CI: 0.20, 0.33; log-rank p-value < 0.0001), representing a 74% decrease in the hazard of progression or death in the vemurafenib group compared to the dacarbazine group. The KM estimates of median PFS was 5.32 months (95% CI: 4.86, 6.57) for vemurafenib and 1.61 months (95% CI: 1.58, 1.74) for dacarbazine.
- The confirmed BORR in the vemurafenib group was 48.4% (95% CI: 41.6, 55.2) with a KM estimate of the median duration of response of 5.49 months (95% CI: 3.98, 5.72). The confirmed BORR in the dacarbazine group was 5.5% (95% CI: 2.8, 9.3). Median response duration was not reached due to small number of responders.

Based on the data cutoff date of Mar 31, 2011, updated OS analyses, in which 50 patients who were assigned to dacarbazine were censored at the time of crossing over to vemurafenib, included a total of 199 deaths (78 in the vemurafenib group and 121 in the dacarbazine group). The updated hazard ratio for death was 0.44 (95% CI: 0.33, 0.59). The KM estimates of median

OS was 7.89 (95%CI: 7.26, 9.63) for dacarbazine, and the median OS for vemurafenib was not reached (95%CI: 9.59, not reached).

Study NP22657 was an open-label, multi-center, single agent, single-arm Phase II study in previously treated patients with metastatic melanoma harboring BRAF V600E mutation. The primary endpoint was BORR as assessed by an independent review committee (IRC). A total of 132 patients were enrolled. Study NP22657 showed an IRC assessed BORR of 52% (95% CI: 0.43, 0.61) with median response duration of 6.5 months (95% CI: 5.6, not reached).

The major statistical issue in the application is the short follow-up time for overall survival in Study NO25026. The median OS follow-up time in the vemurafenib group was 6.21 months (range: 0.39 - 13.86) as of March 31, 2011, the updated clinical cutoff date. As a result, the long-term OS benefit still remains unanswered. A longer period of follow-up time would also help to obtain a robust Kaplan-Meier estimate of median OS in the vemurafenib arm.

This reviewer, based on the totality of the results summarized above, confirms that the data supports approval. The exact indicated population for approval is deferred to the clinical team. A post-market commitment to obtain a survival update with a minimum of 24 month follow-up after randomization of the last patient is recommended (Appendix).

2. INTRODUCTION

2.1 Overview

Background

Metastatic melanoma is one of the most deadly cancers with the median survival for patients with stage IV melanoma ranging from 8 to 18 months after diagnosis.

There are currently 3 FDA approved drugs for the treatment of advanced melanoma. Dacarbazine (DTIC) was approved in 1975 based on clinical responses and is a commonly used chemotherapeutic agent either alone or in combination with other biologic or chemotherapy agents. IL-2 (Proleukin) was approved in 1998 also based on response rates without demonstrating overall survival benefit. Ipilimumab (Yervoy), a monoclonal antibody targeting CTLA-4, was recently approved in 2011 on the basis of a double-blind, randomized therapy comparing ipilimumab to ipilimumab in combination with Gp100 to Gp100 alone. The median overall survival in ipilimumab group and ipilimumab and Gp 100 group was 10 months as compared to 6 months in Gp100 alone group.

Oncogenic mutations in BRAF, predominantly V600E, have been observed in approximately 50% of metastatic melanomas. The BRAF mutations result in constitutive activation of BRAF kinase, causing dysregulated downstream signaling via MEK and ERK and leading to excessive cell proliferation and survival. Vemurafenib (also known as RO5185426 and PLX4032) is a compound that selectively inhibits oncogenic BRAF kinase.

Clinical Studies

In this application, the applicant proposed the use of vemurafenib for the treatment of BRAF V600 mutation-positive metastatic melanoma. The efficacy of vemurafenib was primarily demonstrated through Study NO25026 (BRIM3), supported by Study NP22657 (BRIM2). Study NO25026 was a randomized, open-label, multi-center phase III study comparing 960 mg bid vemurafenib with dacarbazine (DTIC) in previously untreated patients with histologically confirmed metastatic melanoma harboring BRAF V600 mutation. Study NP22657 was a single-arm, multi-center phase II study of vemurafenib in previously treated patients with BRAF V600 mutation-positive metastatic melanoma. Two studies are summarized in Table 1.

Table 1: Table of Studies Included in Analyses

<i>Study</i>	<i>Phase and Design</i>	<i>Study Population</i>	<i>Treatment Dose</i>	<i># of Subjects per Arm</i>	<i>Primary Endpoints</i>
NO25026	Phase 3 Vemurafenib vs. DTIC	Unresectable Stage IIIc or Stage IV BRAF-V600 Mutation-Positive Melanoma	960 mg bid	337 vs. 338	Progression-Free Survival and Overall Survival
NP22657	Phase 2 Vemurafenib	BRAF-V600 Mutation-Positive Metastatic Melanoma	960 mg bid	132	Best Overall Response Rate

Regulatory Communications and Related Amendments in Study NO25026

The original protocol of Study NO25026 (dated Sep 1, 2009) was powered for the sole primary endpoint of OS. Assuming that the hazard ratio of OS between the vemurafenib group and the DTIC group was 0.75 (median survival 10.7 vs. 8 months), a total of 468 deaths from 680 patients were required to provide 80% power at a two-sided significant level of 0.025. Two interim OS analyses were planned, each at 50% and 75% of the total information, respectively.

Positive efficacy results from Phase 1 and 2 studies of vemurafenib triggered a series communications between the applicant and the Agency, in which a possible underestimation of the efficacy of vemurafenib in the original design of Study NO25026 was discussed. Subsequently, the sponsor, concurred by the Agency, changed the protocol and added Amendment C (first implemented Nov 1, 2010) before the interim analysis for OS. The major changes in Amendment C were as follows:

- Added PFS as a co-primary endpoint, and increased the two-sided alpha level for the study from 0.025 to 0.05 (0.045 for OS and 0.005 for PFS)
- Decreased the expected OS hazard ratio from 0.75 to 0.65, leading to a reduction in the required number of deaths from 468 to approximately 196
- Scheduled the final PFS analysis at the time of OS interim analysis at 50% of the total number of deaths
- Removed the OS interim analysis at 75% of the total deaths
- Alpha allocated for the interim OS analysis was changed from 0.0008 (O'Brien-Fleming alpha spending boundary based on the old design setting with alpha level of

- 0.025) to 0.028 (Pocock alpha spending boundary based on the new design setting with alpha level of 0.045)
- Allowed patients on DTIC to cross over to vemurafenib if the p-value of the interim OS analysis was less than 0.05

All statistical analyses performed in this review follow the revised protocol and SAP. Details regarding the sample size and statistical analysis methods used in this study are elaborated in Section 3.2.1.

Major Statistical Issues in Study NO25026

The major statistical issue in Study NO25026 is the short follow-up time for overall survival. The median OS follow-up time in the vemurafenib group was 6.21 months (range: 0.39, 13.86) as of March 31, 2011. As a result, the long-term OS benefit still remains unanswered.

2.2 Data Sources

Materials reviewed for this application include the submitted clinical study reports, raw and derived datasets, original and amended protocols, statistical analysis plans, documents of regulatory communications, and the applicant's presentation slides.

Electronic submission including the study reports and datasets based on the cutoff date of Dec 30, 2010 is located in

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Updated electronic submission including the study reports and datasets based on the cutoff date of Mar 31, 2011 is located in

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SAS program code was also submitted for key endpoint derivation and statistical analyses.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted both raw and derived analysis datasets from Study NO25026 and Study NP22657 in high quality. Variables were clearly formatted and labeled. From raw tabulation, the primary endpoints and the main secondary endpoints of each study were reproduced by this reviewer based on the programming algorithm defined by the applicant.

Documentations of statistical analysis methods were included with sufficient details for this reviewer to reproduce the applicant's key efficacy results.

3.2 Evaluation of Efficacy

The applicant in this application demonstrated the efficacy of vemurafenib primarily based on Study NO25026 with results from Study NP22657 as supportive evidence. Therefore, this review in the following subsections will focus on presenting the design and results of the pivotal trial NO25026, followed by a brief summary of the phase 2 study NP22657.

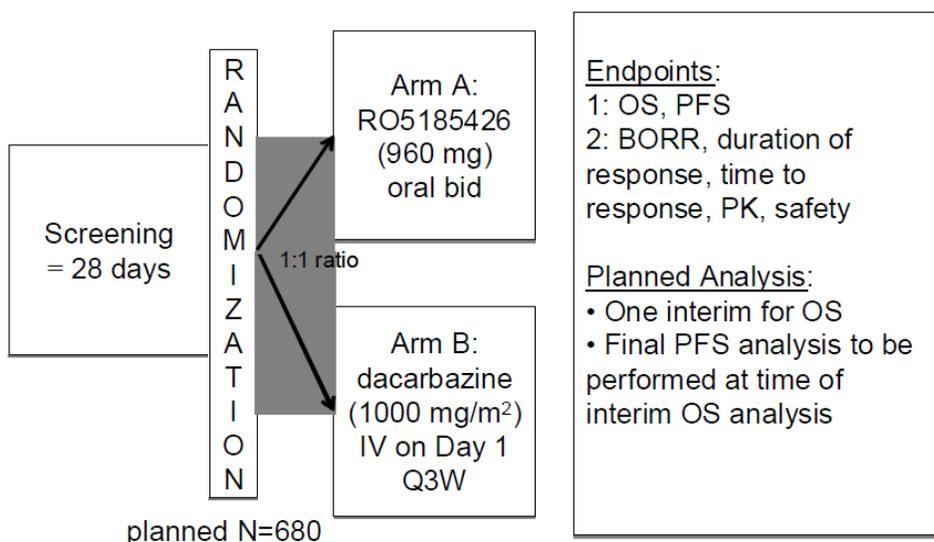
3.2.1 Efficacy in Study NO25026

3.2.1.1 Study Design and Endpoints

Study NO25026 was a randomized, open-label, DTIC controlled, multicenter Phase III study in previously untreated patients with histologically confirmed metastatic melanoma (unresectable Stage IIIC or Stage IV) harboring BRAF V600 mutation as determined by the companion diagnostic test (cobas® 4800 BRAF V600 Mutation Test). Patients were randomized in a 1:1 ratio to either oral vemurafenib bid at a dose of 960 mg or DTIC administered intravenously 1000 mg/m² on Day 1 every 3 weeks (Figure 1).

The primary objective of this study was to evaluate the efficacy of vemurafenib as a monotherapy compared to dacarbazine in terms of PFS and OS in the studied population with key secondary objectives to assess the efficacy based on BORR, time to response, duration of response, and characterize the PK profile and safety profile of vemurafenib.

Figure 1 Design and Endpoints of Study NO25026



Stratification factors at randomization included: metastatic disease stage classification, ECOG performance status, LDH level, and geographic region.

BORR = best overall response rate; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics.

* From the applicant's CSR Figure 1.

All patients were required to have a baseline brain CT and/or MRI to assess for brain metastasis, and subsequent scans were done as clinically indicated. Radiological tumor assessments of chest, abdomen, and pelvis was done at screening, every 6 weeks for the first 12 weeks, every 9 weeks

thereafter, and at final visit. There was a +/- 7 day window for tumor assessments. Patients were followed for concomitant medication and AEs up to 28 days after the last dose in all patients. All SCC events occurring at any time during the study or follow-up period (every 3 months until patient death, withdrawal of consent, or lost to follow-up) were collected and reported as a serious adverse event (SAE) to the sponsor.

3.2.1.2 Statistical Analysis Plan

Analyses reported in the applicant's CSR followed SAP dated Nov 4, 2010, which incorporated Amendment C as noted in Section 2.1. The primary data cutoff date was Dec 30, 2010.

Sample Size

Approximately 680 patients were planned to be randomized to receive either vemurafenib or DTIC. A total of 196 deaths were required to provide 80% power to detect a hazard ratio of 0.65 comparing vemurafenib to dacarbazine (median survival 12.3 vs. 8 months) at type I error of 0.045 (two-sided). One interim analysis was scheduled at 50% information. Lan-DeMets alpha spending method of the Pocock type boundary was employed to control the alpha level, and statistical significance for OS would be claimed at the interim analysis if the log-rank p-value (two-sided) was ≤ 0.028 .

A total of 187 PFS events were required to provide 90% power to detect a hazard ratio of 0.55 for vemurafenib relative to DTIC (median PFS 4.5 vs. 2.5 months) at type I error of 0.005 (two-sided). No interim analysis was planned for PFS.

Overall Survival

OS was defined as the time from randomization to death from any cause. For patients who were alive at the time of analysis data cutoff, OS time was censored at the last date the patient was known to be alive prior to the cutoff date. Survival time for patients with no post-baseline survival information was censored on the date of randomization. Patients in the ITT population who were randomized on or before Dec 15, 2010 were evaluable for OS according to the SAP.

The primary analysis of OS was a comparison of the two treatment groups using an unstratified log-rank test. The OS hazard ratio and the associated 95% CI were computed using a Cox regression model. Median OS was estimated using the Kaplan-Meier method, with 95% CI calculated using the method of Brookmeyer and Crowley. The Kaplan-Meier estimate of 6-month OS and the associated 95% CI was provided.

Progression-Free Survival

The final analysis for PFS was performed at the time of the interim efficacy analysis for OS. PFS was defined as the time from randomization to the date of disease progression (based on tumor assessment date) or death from any cause, whichever occurred first. Patients who had neither progressed nor died were censored on the date of last evaluable tumor assessment prior to the

clinical cutoff date. PFS for patients who had no post-baseline assessment and who did not have an event were censored on the date of randomization.

The population evaluable for PFS was originally defined as all ITT patients randomized at least 7 weeks prior to the OS interim analysis data cutoff date. Prior to the interim analysis of OS, the applicant recognized that the interval of 7 weeks did not allow sufficient time as intended for the first tumor assessment to occur, as per the protocol the first tumor assessment was to be scheduled 6 weeks from start of treatment rather than 6 weeks from randomization. Therefore, the 7-week interval was changed to a 9-week interval to account for up to 2 weeks between randomization and the start of treatment. All patients randomized on or before Oct 27, 2010 were considered evaluable for the analysis of PFS.

The primary analysis of PFS was a comparison of the two treatment groups using an unstratified log-rank test. The PFS hazard ratio and the associated 95% CI were computed using a Cox regression model. Median PFS was estimated using the Kaplan-Meier method, with 95% CI calculated using the method of Brookmeyer and Crowley. The Kaplan-Meier estimate of 6-month PFS and the associated 95% CI was provided.

Best Overall Response Rate

Best overall response (confirmed) was defined as a complete response (CR) or partial response (PR) which was confirmed per RECIST version 1.1. The best overall response of CR or PR was determined on the basis of confirmed response at the next tumor assessment.

The population evaluable for best overall response rate (BORR, confirmed) was defined as ITT patients who were randomized at least 14 weeks before the data cutoff date. Therefore, all patients randomized on or before Sep 22, 2010 were considered evaluable for the analysis of BORR.

The BORR and the associated 95% Clopper-Pearson CI were calculated for each treatment group. The difference in BORR between treatment groups and the associated 95% Hauck-Anderson CI were calculated. BORR was compared between treatment groups using a Chi-squared test with Schouten correction.

Duration of Response

Duration of response was evaluated for patients who satisfied the criteria for best overall responses (confirmed). Duration of response was defined as the time from the date of the earliest qualifying response to the date of disease progression or death from any cause. For patients who were alive without progression following the qualifying response, duration of response was censored on the date of last evaluable tumor assessment before the data cutoff date.

Time to Response

Time to response was evaluated for patients who satisfied the criteria for best overall response (confirmed). Time to response was defined as the time from randomization to the date of the

earliest qualifying response. Time to response was summarized using descriptive statistics (median, 25% and 75% quartiles minimum, maximum). No formal hypothesis testing was performed for time to response.

3.2.1.3 Applicant's Results

Patient Disposition, Demographic and Baseline Characteristics

A total of 675 patients were randomized in Study NO25026 between Jan 4, 2010 and Dec 16, 2010 with 337 patients in the vemurafenib arm and 338 in the DTIC arm. Four hundred and eight (60%) patients were enrolled in centers in Western Europe, 172 (25%) in North America, 77 (11%) in Australia/New Zealand, and 18 (3%) in Israel.

There were 48 patients randomized to DTIC who withdrew from the study prior to treatment compared to 2 patients in the vemurafenib arm (Table 2). One patient randomized to DTIC received vemurafenib instead due to an error in communication from the IVRS service provider to the clinical site. As of the primary clinical cutoff date of Dec 30, 2010, 223 (66%) patients treated with vemurafenib and 83 (29%) patients treated with DTIC were still receiving protocol therapy. The major reason for treatment discontinuation was disease progression in both arms (89 in the vemurafenib group vs. 170 in the DTIC group).

As described in Section 3.2.1.2, patients in the ITT population who were randomized on or before Dec 15, 2010 were evaluable for OS; randomized on or before Oct 27, 2010 were evaluable for PFS; and randomized on or before Sep 22, 2010 were evaluable for BORR. Table 2 also summarizes the efficacy analysis populations by randomized treatment group according to the definitions presented in Statistical Analysis Plan.

Table 2 Analysis Sets and Patient Disposition in Study NO25026

	<i>Vemurafenib</i>	<i>Dacarbazine</i>
Randomized	337	338
Evaluable for OS	336	336
Evaluable for PFS	275	274
Evaluable for BORR	219	220
Treated	336 ¹	289
Refused Treatment/Withdrew Consent	0	37
Other Reasons	2 ²	11 ³
Still on Treatment	223	83
Discontinued Randomized Treatment	113	206
Disease Progression	89	170
Death	6	11
Lost to Follow Up/Patient Decision	6	12
Adverse Event	12	10
Other	0	3 ⁴

¹ 1 patient was randomized to Dacarbazine but was mistakenly given Vemurafenib

² 1 patient was discontinued from trial due to anemia prior to starting treatment; 1 patient was randomized in error and did not have BRAF mutation.

³ 5 patients had progressive disease prior to starting treatment; 2 patients found to have brain metastasis and were not treated; 1 patient with pulmonary embolus found prior to starting treatment; 1 patient with no measurable disease and was not treated; 2 patients have no records available.

⁴ 2 patient stopped per PI discretion; 1 patient stopped after it was discovered that patient was randomized in error (No BRAF mutation but patient received 1 dose of dacarbazine).

Table 3 summarizes patient demographic and baseline disease characteristics for all randomized patients. Demographic characteristics were generally similar between treatment groups. The proportions of males in the vemurafenib and dacarbazine groups were 59% and 54%, respectively. The majority of patients (99%) of patients were White. There were 93 (28%) and 68 (20%) patients in the vemurafenib and dacarbazine groups aged ≥ 65 years, respectively. Most of the patients (60.4%) were enrolled from Western Europe.

Most patients had M1c disease stage (66% vemurafenib, 65% dacarbazine). All patients had ECOG performance status of 0 or 1. Around 42% of the patients had elevated LDH level. The time since metastatic melanoma diagnosis was less than 6 months in 57% of the vemurafenib patients and 64% of the dacarbazine patients with median of 3 months in each arm.

Table 3 Demographics and Baseline Disease Characteristics in Study NO25026

	<i>Vemurafenib</i> <i>N=337</i> <i>n (%)</i>	<i>Dacarbazine</i> <i>N=338</i> <i>n (%)</i>
Sex		
Female	137 (40.7)	157 (46.4)
Male	200 (59.3)	181 (53.6)
Race		
White	333 (98.8)	338 (100)
Hispanic	2 (0.6)	0
Other	2 (0.6)	0
Age		
Mean (range)	55.2 (21-86)	52.6 (17-86)
< 65 yrs	244 (72.4)	270 (79.9)
≥ 65 yrs	93 (27.6)	68 (20.1)
Geographic Region		
Australia/New Zealand	39 (11.6)	38 (11.2)
North America	86 (25.5)	86 (25.4)
Western Europe	205 (60.8)	203 (60.1)
Others	7 (2.1)	11 (3.3)
ECOG Performance Status		
0	229 (68.0)	230 (68.0)
1	108 (32.0)	108 (32.0)
Disease Stage		
Unresectable Stage IIIC	20 (5.9)	13 (3.8)
M1a	34 (10.1)	40 (11.8)
M1b	62 (18.4)	65 (19.2)
M1c	221 (65.6)	220 (65.1)

Serum Lactate Dehydrogenas		
LDH Elevated	142 (42.1)	142 (42.0)
LDH Normal	195 (57.9)	196 (58.0)
Time Since Metastatic diagnosis		
< 6 months	191 (56.7)	216 (63.9)
≥ 6 months	97 (28.8)	84 (24.9)
Brain Metastasis		
Yes	0	2 (0.6)
No	333 (98.8)	332 (98.2)

Key Efficacy Results

Co-Primary Endpoint: Overall Survival

As of the data cutoff date of Dec 30, 2010, there were 672 ITT patients evaluable for the analysis of OS with a total of 118 deaths of which 43 occurred in the vemurafenib group and 75 in the dacarbazine group. The median follow-up time in the vemurafenib group was 3.75 months (range 0.3 – 10.8) and in the dacarbazine group was 2.33 months (range 0 – 10.3).

Unstratified log-rank test of OS demonstrated a statistically significant difference in the duration of survival favoring the vemurafenib group ($p < 0.0001$, the actual alpha allocation for this interim analysis was 0.032 by the Pocock alpha spending boundary). The unstratified hazard ratio for death for vemurafenib relative to dacarbazine was 0.37 (95% CI: 0.26, 0.55), representing a 63% decrease in the hazard of death for patients in the vemurafenib group compared to patients in the dacarbazine group (Table 4). Figure 2 shows the Kaplan-Meier estimates for OS.

Reviewer's Comments: *If the O'Brien-Fleming Boundary had been used for the interim OS analysis in the revised SAP, the p-value of the unstratified log-rank test would also have crossed the significant level of 0.006 at the observed information based on the required total number of deaths.*

At the time of analysis, the Kaplan-Meier estimate of median OS for the vemurafenib group was 9.23 months (95% CI: 8.05, not reached) and 6 patients were at risk at the time of the estimated median. For the dacarbazine group, the Kaplan-Meier estimate of median OS was 7.75 months (95% CI: 6.28, 10.28) and 10 patients were at risk at the time of the estimated median.

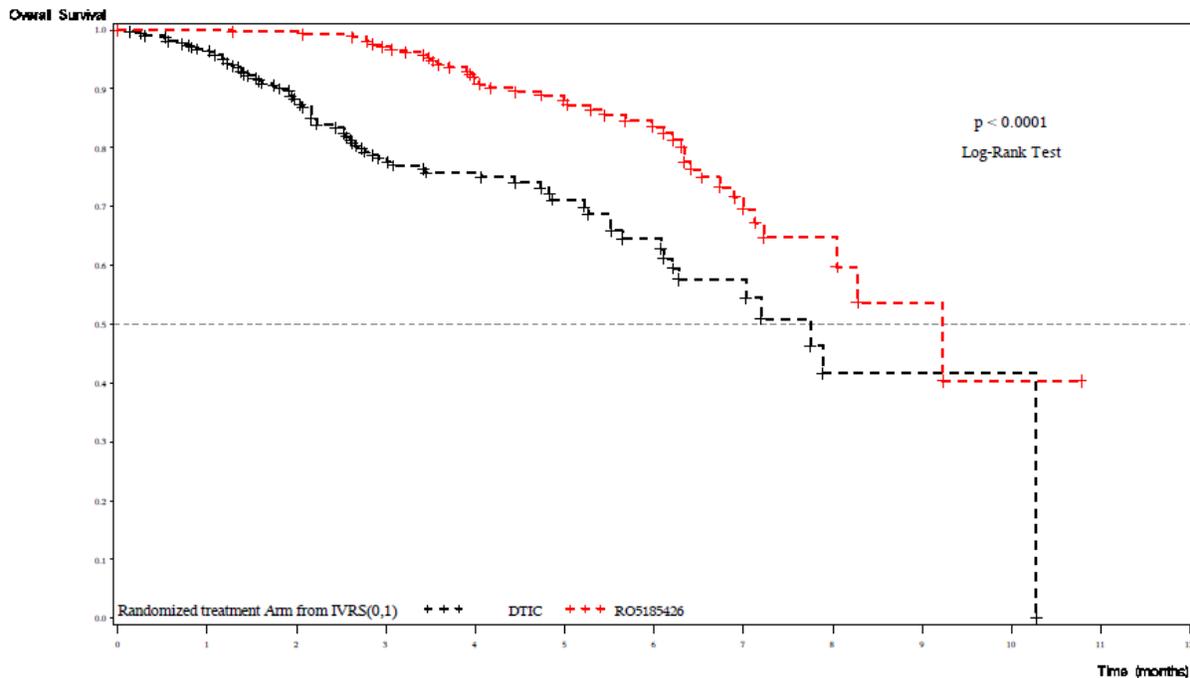
Reviewer's Comments: *Due to small number of patients at risk when Kaplan-Meier curves reach median, the estimated median OS and median difference of OS between the vemurafenib group and dacarbazine group are not robust. Simulations conducted by this reviewer showed that in such scenario, the estimated hazard ratio was close to the true value based on the observed information; however, difference in median survivals among the simulated samples whose median survivals were reached in two arms in general tended to underestimate the real values.*

Table 4 Analysis of Overall Survival in Study NO25026

	<i>Vemurafenib</i> N=336	<i>Dacarbazine</i> N=336
Number of Deaths	43	75
Number of Censored Patients	293	261
Time to Event (months)		
Median	9.23	7.75
(95% CI for Median)	(8.05, --)	(6.28, 10.28)
Range	0.26 – 10.78	0.03 – 10.28
6-Month Survival Rate	0.84	0.64
(95% CI for rate)	(0.78, 0.89)	(0.56, 0.73)
p-Value (Log-Rank Test)		<0.0001
Hazard Ratio		0.37
(95% CI for HR)		(0.26, 0.55)

Stratified analyses with stratification factors including metastatic classification (unresectable Stage IIIc, M1a, M1b, M1c), LDH (normal, elevated), and ECOG performance status (0, 1) showed similar results as the unstratified analyses. The p-value of stratified log-rank test was < 0.0001, and the stratified hazard ratio was 0.36 (95%CI: 0.24, 0.53).

Figure 2 Kaplan-Meier Estimates of OS in Study NO25026



At the planned interim analysis of the OS, the DSMB for Study NO25026 determined that the p-value from the log-rank test for OS ($p < 0.0001$) crossed the efficacy boundary in favor of

vemurafenib. The DSMB recommended release of the results of this study due to compelling efficacy.

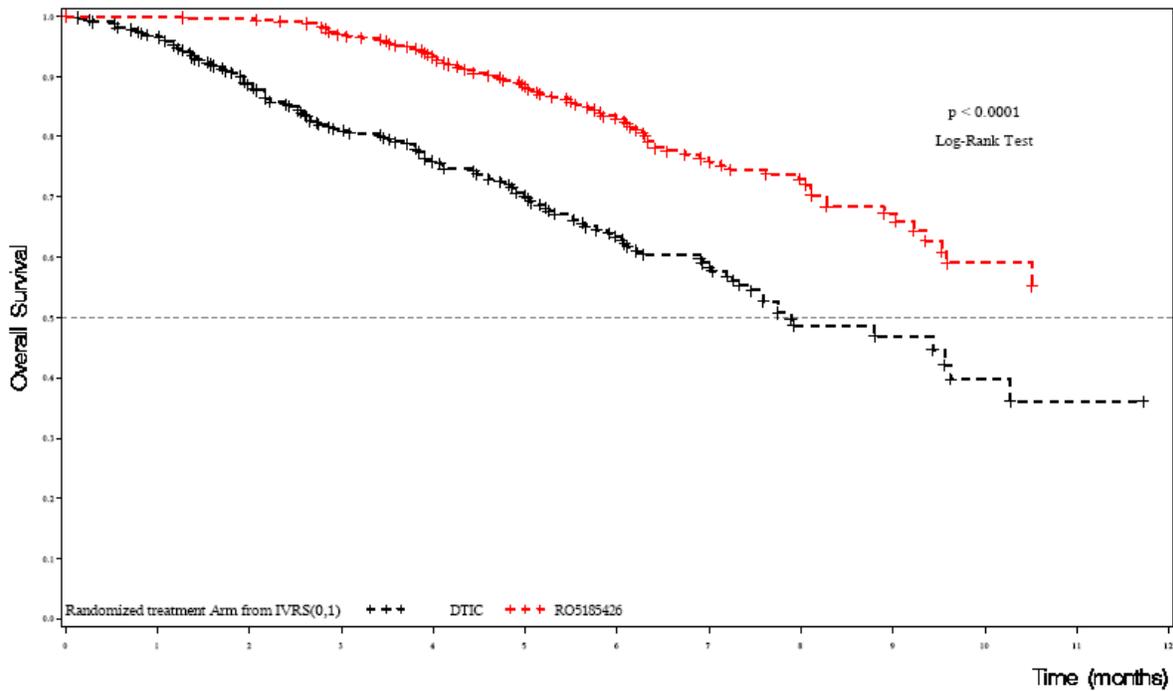
Updated Overall Survival

The applicant updated results of overall survival based on the cutoff date of Mar 31, 2011.

The updated median follow-up time for vemurafenib was 6.21 months (range 0.39 – 13.86), and for dacarbazine was 4.70 months (range 0.03 – 11.73). Fifty patients assigned to dacarbazine had crossed over to the treatment of vemurafenib.

Updated OS analyses submitted by the applicant censored the patients who switched treatment to vemurafenib at the time of crossing over. A total of 199 deaths (78 in the vemurafenib group and 121 in the dacarbazine group) were included in this analysis. The updated hazard ratio for death was 0.44 (95% CI: 0.33, 0.59). The KM estimates of median OS was 7.89 (95% CI: 7.26, 9.63) for dacarbazine, and the median OS for vemurafenib was not yet reached (95% CI: 9.59, not reached) (Figure 3).

Figure 3 Kaplan-Meier Estimates of OS in Study NO25026 (Updated)



Reviewer's Comments: Additional 3-month follow-up time is not enough to obtain robust KM estimates of median OS in both groups.

This reviewer conducted a sensitivity analysis (Section 3.2.1.4) in which patients in DTIC crossing over to vemurafenib were not censored at the time of switching treatments, instead if the patients were still alive, were censored at the last date known to be alive prior to the cutoff date.

Co-Primary Endpoint: Progression Free Survival

A total of 549 ITT patients (275 in the vemurafenib group and 274 in the dacarbazine group) were evaluable for the analysis of PFS with 286 patients having experienced disease progression or had died: 104 in the vemurafenib group and 182 in the dacarbazine group.

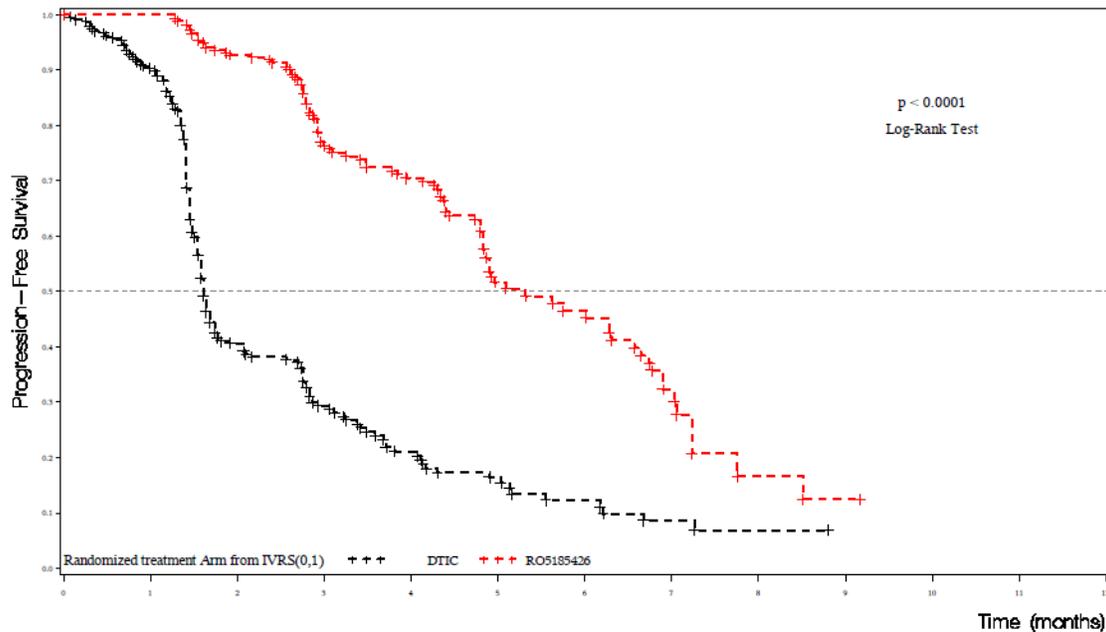
Unstratified log-rank test of PFS demonstrated a statistically significant difference in PFS favoring the vemurafenib group ($p < 0.0001$, compared with the significance level of 0.005). The unstratified hazard ratio for progression or death for vemurafenib relative to dacarbazine was 0.26 (95% CI: 0.20, 0.33), representing a 74% decrease in the hazard of progression or death for patients in the vemurafenib group compared with patients in the dacarbazine group (Table 5). The p-value of stratified log-rank test was < 0.0001 , and the stratified hazard ratio was 0.22 (95% CI: 0.17, 0.29).

The Kaplan-Meier estimate of median PFS for patients in the vemurafenib group was 5.32 months (95% CI: 4.86, 6.57) and for patients in the dacarbazine group was 1.61 months (95% CI: 1.58, 1.74) (Figure 4).

Table 5 Analysis of Progression-Free Survival in Study NO25026

	<i>Vemurafenib</i> <i>N=275</i>	<i>Dacarbazine</i> <i>N=274</i>
Number of Events	104	182
Number of Censored Patients	171	92
Time to Event (months)		
Median	5.32	1.61
(95% CI for Median)	(4.86, 6.57)	(1.58, 1.74)
Range	0.03 – 9.17	0.03 – 8.80
6-Month Event-Free Rate	0.47	0.12
(95% CI for rate)	(0.38, 0.55)	(0.07, 0.18)
p-Value (Log-Rank Test)	<0.0001	
Hazard Ratio	0.26	
(95% CI for HR)	(0.20, 0.33)	

Figure 4 Kaplan-Meier Estimates of Progression-Free Survival in Study NO25026



Secondary Endpoints: Confirmed Best Overall Response, Duration of Response, and Time to Response

As of the data cutoff date, 439 patients (219 in the vemurafenib group and 220 in the dacarbazine group) were evaluable for the analysis of BORR. A total of 106 of 219 patients (48.4%; 95% CI: 41.6%, 55.2%) in the vemurafenib group and 12 of 220 patients (5.5%; 95% CI: 2.8%, 9.3%) in the dacarbazine group had a response that was confirmed. The difference in overall response rates was 42.95% (95% CI: 35.4%, 50.5%) in favor of vemurafenib with p-value of Chi-squared test with Shouten correction less than 0.0001 (Table 6). Two of 219 patients in the vemurafenib group had a complete response (CR) (0.9%; 95%CI: 0.1%, 3.3%); no patients in the dacarbazine group had a CR.

Nine patients in the vemurafenib group and 52 patients in the dacarbazine group had no response assessment at the time of this analysis as more patients in the dacarbazine group did not receive any of the assigned treatment compared to the vemurafenib group. The confirmed BORR rates in treated patients were 48.8% (106 of 217 patients) and 6.3% (12 of 191 patients) in the vemurafenib group and the dacarbazine group, respectively, with difference in response rates of 42.57% (95%CI: 34.8, 50.3).

Table 6 Analyses of Confirmed Best Overall Response in Study NO25026

	<i>Vemurafenib</i> <i>N=219</i>	<i>Dacarbazine</i> <i>N=220</i>
Responders	106 (48.4%)	12 (5.5%)
(95% CI for Response Rate)	(41.6, 55.2)	(2.8, 9.3)
Difference in Response Rates	42.95	
(95% CI for Difference)	(35.4, 50.5)	
p-Value (Chi-squared Test)	<0.0001	
Complete Response (CR)	2 (0.9%)	0 (0%)
(95% CI for CR)	(0.1, 3.3)	(0.0, 1.7)
Partial Response (PR)	104 (47.5%)	12 (5.5%)
(95% CI for PR)	(40.7, 54.3)	(2.8, 9.3)
Response Duration		
Median (months)	5.49	--
(95% CI for Median)	(3.98, 5.72)	(4.60, --)
Range	1.22 – 7.62	1.18 – 5.55
Time to Response		
Median (months)	1.45	2.72
Range	1.0 – 5.5	(1.6, 5.8)

Table 6 also summarizes the analysis of duration of response among responders (106 in the vemurafenib group and 12 in the dacarbazine group). The Kaplan-Meier estimate of the median duration of response was 5.49 months in the vemurafenib group (95% CI: 3.98, 5.72) and was not reached in the dacarbazine group (95% CI: 4.60, not reached).

Among the 106 vemurafenib patients with a confirmed response, the median time to response was 1.45 months (range: 1.0 to 5.5). Among the 12 dacarbazine patients with a confirmed response, the median time to response was 2.72 months (range: 1.6 to 5.8).

3.2.1.4 Reviewer's Results

This reviewer confirmed data derivation and statistical analyses in Study NO25026 submitted by the applicant. Study results at the interim analysis of OS demonstrated clinically and statistically significant improvement in the vemurafenib group compared to the dacarbazine group in terms of the primary endpoints of OS and PFS and the key secondary endpoints of BORR and duration of response.

Over the course of review, this reviewer identified three potential issues which will be discussed below.

Analysis Subsets

In the applicant's analyses, certain cutoff dates of randomization were used to define subsets of patients evaluable for OS and PFS: Dec 15, 2010 for the patients evaluable for OS and Oct 27, 2010 for the patients evaluable for PFS.

This reviewer re-analyzed the data in the full ITT population for the co-primary endpoints of OS and PFS based on the clinical cutoff date of Dec 30, 2010 as an exploratory analysis. As expected, in the full ITT population, additional PFS events were found: 2 more in vemurafenib patients and 16 more in dacarbazine patients. The PFS hazard ratio estimate from the 675 ITT patients was 0.25 (95% CI: 0.20, 0.32; log-rank test p-value < 0.0001), which was similar to the applicant's findings (Table 7).

There was no additional death founded in the full ITT patients. As a result, the results of OS remained almost identical to the applicant's as presented in the previous section.

Table 7 Results of OS and PFS in the ITT patients in Study NO25026

	<i>Vemurafenib</i>	<i>Dacarbazine</i>
ITT Patients	337	338
Overall survival (co-primary endpoint)		
Number of Deaths	43	75
Hazard Ratio	0.37	
95% CI for HR	(0.26, 0.55)	
p-Value (Log-Rank Test)	<0.0001	
6-Month Event-Free Rate	84%	64%
95% CI for 6-Month Rate	(77%, 89%)	(56%, 72%)
Kaplan-Meier Estimate of Median (months)	9.23	7.75
95% CI for Median	(8.05, not reached)	(6.21, 10.28)
PFS (co-primary endpoint)		
Number of PFS Events	106	198
Hazard Ratio	0.25	
95% CI for HR	(0.20, 0.32)	
p-Value (Log-Rank Test)	<0.0001	
6-Month Event-Free Rate	46%	12%
95% CI for 6-Month Rate	(38%, 55%)	(7%, 18%)
Kaplan-Meier Estimate of Median (months)	5.32	1.61
95% CI for Median	(4.83, 6.31)	(1.54, 1.68)

ITT Analysis of OS in the Presence of Crossovers

The DSMB for Study NO25026 recommended release of the results of this study due to compelling efficacy based on review of results presented January 14, 2011 at the time of the planned interim analysis of OS. The patients assigned to dacarbazine were allowed to switch to vemurafenib.

This analysis was based on updated OS data where 50 patients randomized to dacarbazine had switched to vemurafenib. As a sensitivity analysis, these 50 patients were censored at the last date known to be alive if the patients were still alive before the cutoff date of Mar 31, 2011. A total of 200 deaths were included in this analysis (78 in the vemurafenib group and 122 in the dacarbazine group). The hazard ratio was 0.47 (95% CI: 0.35, 0.62) (Table 8).

Table 8 Analysis of Updated Overall Survival with Crossovers

	<i>Vemurafenib</i> N=337	<i>Dacarbazine</i> N=338
Number of Deaths	78	122
Number of Censored Patients	259	216
Time to Event (months)		
Median	--	8.80
(95% CI for Median)	(9.59, --)	(7.33, 10.28)
Range	0.39 – 13.86	0.03 – 11.73
6-Month Survival Rate	0.83	0.64
(95% CI for rate)	(0.78, 0.87)	(0.58, 0.70)
Hazard Ratio		0.47
(95% CI for HR)		(0.35, 0.62)

Follow-up for Overall Survival with Cross-Over

Although vemurafenib demonstrated significant gain of efficacy through submitted datasets, with median OS follow-up time of 3 months and 5.5 months in the primary and updated analyses, respectively, the long-term survival benefit could not be determined. There are concerns among clinical reviewers that the acquired resistance and acquired RAS mutations occurring in new lymph node lesions after a prolonged use of vemurafenib may cause detriment in OS benefit. Unfortunately, the submitted datasets cannot help to answer this question.

Confounded by the dacarbazine patients crossing over to the vemurafenib group, OS results with longer follow-up may not be able to truly reflect the biological effect of vemurafenib compared with dacarbazine. The estimate of OS hazard ratio will be inflated to a certain level, depending on the underlying true effect of vemurafenib. However, longer follow-up time will help to get robust KM estimate of median OS for vemurafenib.

3.2.2 Summary of Efficacy in Study NP22657

This was an open-label, multi-center, single agent, single-arm Phase II study in previously treated patients with metastatic melanoma harboring BRAF V600E mutation by the cobas 4800 BRAF V600 Mutation Test. Patients were continually dosed with oral vemurafenib 960 mg bid until progression of disease, unacceptable toxicity, withdrawal of consent, or other reason as determined by the investigator.

The primary endpoint was BORR as assessed by an independent review committee (IRC) using RECIST version 1.1 criteria for metastatic melanoma with duration of IRC response, time to response, PFS and OS as key secondary endpoints.

Radiological tumor assessments to assess the extent of disease were obtained at screening (within a 28-day period), Day 1 of every other cycle (every 6 weeks), and at the final visit. Tumor assessments were completed +/- 7 days of the scheduled visit. If there was suspicion of disease progression based on clinical or laboratory findings at anytime before the next scheduled assessment during the treatment phase, an unscheduled tumor assessment was performed.

A total of 132 patients were enrolled across a total of 15 centers (12 in the United States and 3 in Australia). Among them, 81 patients (61.4%) were male. One hundred and thirty patients (98.5%) were white. The median age was 51.5 (range 17 – 82) with 107 patients (81.1%) less than 65 years of age.

All patients had histologically confirmed Stage IV melanoma and an ECOG performance status of 0 (46%) or 1 (54%). A majority of patients (61%) had M1C disease at the time of study entry. The median time since metastatic diagnosis was 13.6 months (range 1.4 - 194.8). Sixty-five patients (49%) had at least 2 prior therapies.

The median duration of follow-up was 6.87 months (range 0.59 - 11.27 months). The BORR assessed by the IRC among all 132 treated patients was 52% (69 responders; 95% CI: 0.43, 0.61) with 66 PRs (50%; 95%CI: 0.41, 0.59) and 3 CRs (2.3%; 95%CI: 0.005, 0.065). The SD rate was 30% (39 patients; 95% CI: 0.22, 0.38).

Out of 69 responders, 30 patients (44%) had progression (29 patients) or died (1 patient). Median duration of response as estimated by the Kaplan–Meier method was 6.5 months (95% CI: 5.6, not reached), ranging from 1.4 to 9 months. The median time to response was 1.4 months (range 1.2 – 5.5 months).

PFS assessed by the IRC ranged between 0 to 10.2 months with a median duration of 6.1 months (95% CI: 5.5, 6.9). OS ranged between 0.6 and 11.3 months, and median OS had not been reached (95%CI: 9.5, not reached).

***Reviewer’s Comments:** The analyses of PFS and OS are considered exploratory since it is difficult to interpret results of time-to-event endpoints in a single-arm study.*

3.3 Evaluation of Safety

Safety issues in this application were reviewed by Dr. Amy McKee. Please refer to Dr. McKee’s review for detailed safety evaluation and interpretation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

All analyses in this section were based on the primary cutoff date of Dec 30, 2010. Subgroup analyses in Study NO25026 by gender, age, race, geographic region and BRAF mutation status are summarized in this section to study the consistency of treatment effect of vemurafenib in advanced melanoma patients.

4.1 Gender, Race, Age, and Geographic Region

Table 9 summarizes PFS and OS results by gender, age, and geographic region. Since only 4 patients in NO25026 (all in the vemurafenib arm) were non-white, subgroup analysis by race will not be presented.

Subgroup analyses on PFS and OS showed that the effect of vemurafenib was consistent across various defined subpopulations.

Table 9 OS and PFS results in NO25026 by Age, Gender, and Geographic Region

	OS ¹			PFS ²		
	n	HR	95% CI	n	HR	95% CI
Age						
< 65 years	512	0.40	(0.25, 0.62)	421	0.26	(0.20, 0.34)
>=65 years	160	0.33	(0.16, 0.67)	128	0.26	(0.15, 0.45)
Gender						
Male	379	0.30	(0.18, 0.51)	309	0.25	(0.18, 0.34)
Female	293	0.49	(0.28, 0.86)	240	0.26	(0.18, 0.38)
Geographic region						
North America	172	0.44	(0.20, 0.93)	147	0.30	(0.19, 0.47)
Western Europe	405	0.33	(0.20, 0.53)	328	0.24	(0.17, 0.32)
Australia/NewZealand	77	0.59	(0.20, 1.78)	61	0.28	(0.13, 0.61)

¹ Based on ITT patients randomized by Dec 15, 2010

² Based on ITT patients randomized by Oct 27, 2010

4.2 Other Special/Subgroup Populations

The cobas test was designed to detect the predominant V600E mutation with high sensitivity. Non-clinical performance studies have shown that the cobas test also detects BRAF V600D mutations and a proportion of BRAF V600K mutations. Sanger sequencing was performed retrospectively on all available tumor specimens obtained for patients screened for enrollment as of June 15, 2010.

Among the randomized patients, a subgroup of 220 patient specimens (111 vemurafenib patients, 109 dacarbazine patients) were available for Sanger sequencing results, 164 were detected as V600E, and 56 were non-V600E including 19 V600K, 1 V600E2, 1 other rare V600 mutation, 8 wild type, and 27 being identified as “No Sequence”. Table 10 shows the hazard ratio estimates of OS and PFS by Sanger BRAF mutation status, in which results of combined non-V600E patients were presented due to small sample size in each non-V600E subcategory. These analyses were considered exploratory since the subgroup patients may not preserve the balance in baseline characteristics as randomized patients.

Table 10 OS and PFS results by BRAF Mutation Status

	OS			PFS		
	n	HR	95% CI	n	HR	95% CI
BRAF Mutations						
V600E	164	0.58	(0.33, 1.02)	164	0.34	(0.23, 0.50)
Other	56	0.44	(0.17, 1.15)	56	0.48	(0.25, 0.90)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study NO25026 demonstrated a clinically and statistically significant efficacy of vemurafenib compared to dacarbazine in terms of co-primary endpoints of OS and PFS and key secondary endpoints of BORR and duration of response in patients with advanced melanoma. The main efficacy results based on the primary cutoff date of Dec 30, 2010 are summarized below.

- The hazard ratio for death was 0.37 (95% CI: 0.26, 0.55; log-rank p-value<0.0001), indicating a 63% decrease in the hazard of death in patients assigned to vemurafenib compared with patients assigned to dacarbazine. The KM estimates of median OS was 9.23 months (95% CI: 8.05, --) for vemurafenib and 7.75 months (95% CI: 6.28, 10.28) for dacarbazine. The DSMB of Study NO25026 determined that the p-value from the log-rank test crossed the efficacy boundary favoring vemurafenib and recommended release of the results of this trial.
- The final analysis of PFS was performed at the time of the interim analysis of OS. The hazard ratio for progression or death was 0.26 (95% CI: 0.20, 0.33; log-rank p-value <0.0001), representing a 74% decrease in the hazard of progression or death in the vemurafenib group compared to the dacarbazine group. The KM estimates of median PFS was 5.32 months (95% CI: 4.86, 6.57) for vemurafenib and 1.61 months (95% CI: 1.58, 1.74) for dacarbazine.
- The confirmed BORR in the vemurafenib group was 48.4% (95%CI: 41.6, 55.2) with a KM estimate of the median duration of response of 5.49 months (95% CI: 3.98, 5.72). The confirmed BORR in the dacarbazine group was 5.5% (95%CI: 2.8, 9.3). Median response duration was not reached due to small number of responders.
- Consistent efficacy of vemurafenib on primary endpoints was observed across examined subgroups defined by gender, age, geographic region and BRAF mutation status.

Based on the data cutoff date of Mar 31, 2011, updated OS analyses in which 50 patients assigned to dacarbazine were censored at the time of crossing over to vemurafenib included a total of 199 deaths (78 in the vemurafenib group and 121 in the dacarbazine group). The updated hazard ratio for death was 0.44 (95%CI: 0.33, 0.59). The KM estimates of median OS was 7.89 months (95%CI: 7.26, 9.63) for dacarbazine, and the median OS for vemurafenib was not reached (95%CI: 9.59, not reached).

The ITT results which took account of the impact of crossover were similar due to limited number of crossover patients and short follow-up after crossover. A total of 200 deaths were included in the ITT analysis (78 in the vemurafenib group and 122 in the dacarbazine group). The hazard ratio was 0.47 (95% CI: 0.35, 0.62). The KM estimates of median OS was 8.80 months (95% CI: 7.33, 10.28) for dacarbazine, and the median OS for vemurafenib remained unchanged.

The cobas test was designed to detect the predominant V600E mutation with high sensitivity. Non-clinical performance studies have shown that the cobas test also detects BRAF V600D mutations and a proportion of BRAF V600K mutations. Among 220 randomized patients who were available for Sanger sequencing results, 164 were detected as V600E. The hazard ratio for OS from a subgroup analysis for the 164 patients with V600E was 0.58 (95% CI: 0.33, 1.02).

The efficacy of vemurafenib demonstrated in Study NO25026 was supported by the findings in Study NP22657, which showed an IRC assessed BORR of 52% (95% CI: 0.43, 0.61) with median response duration of 6.5 months (95% CI: 5.6, not reached).

Although Study NO25026 showed that vemurafenib significantly improved OS, however, the long-term OS benefit still remained unanswered based on current datasets. A longer period of follow-up time will provide more information regarding the long-term OS improvement of vemurafenib and help to obtain robust KM estimates of median OS for vemurafenib.

5.2 Conclusions and Recommendations

The pivotal study NO25026 achieved its primary objective and demonstrated a clinically meaningful and statistically significant improvement in the co-primary endpoints of OS and PFS in studied patients. The data submitted by the applicant supported approval. The exact indicated population for approval is deferred to the clinical team. A post-market commitment to obtain a survival update with a minimum of 24 month follow-up after randomization of the last patient is recommended (Appendix).

APPENDIX

To determine the length of follow-up recommended for the post market commitment, this reviewer conducted a simulation study with two settings in which the time to death in the first setting in the vemurafenib arm and in the dacarbazine arm followed exponential distribution with median survival of 20 and 8 months, respectively, i.e., HR=0.4; and in the second setting, the survival time followed exponential distribution with median survival of 17.8 and 8 months, respectively, i.e., HR=0.45.

For both settings, the other simulation elements including recruitment rate and number of patients were set up according to Study NO25026. Patients were assumed to be followed till either death or the end of follow-up, and there was no drop out.

The results for patients in the vemurafenib arm from the first setting and second setting are presented in Tables A.1 and A.2, respectively. The reviewer used two measures to make decision: (1) probability of having median survival reached at the end of follow-up, and (2) bias in the estimated median survival of the study with median reached.

Table A.1 Results for Vemurafenib (Setting One - Median Survival=20 months)

	Follow-UP (months)					
	0	3	6	12	18	24
Probability (%)	5.3	7.4	9.7	31.5	95.6	100
Median Survival (months)	7.4	10.1	12.9	17.7	19.9	20.0

Table A.2 Results for Vemurafenib (Setting Two - Median Survival=17.8 months)

	Follow-UP (months)					
	0	3	6	12	18	24
Probability (%)	6.1	8.6	13.8	54.5	100	100
Median Survival (months)	7.4	10.1	12.6	16.7	17.8	17.8

Both tables demonstrate that the likelihood of having median survival estimates increases with longer follow-up. If assuming that the hazard ratio is 0.4, we will have 100% chance to observe median survival at the end of 24 months follow up. If the hazard ratio is 0.45, then 18-month follow-up will be enough.

Furthermore, longer follow-up also helps us to obtain more accurate estimates of median survival. With short follow-up, the obtainable median survival tends to underestimate the clinical benefit in the vemurafenib arm. For the first setting, 24-month follow-up is expected to provide an unbiased estimate of median survival of 20 months.

In summary, based on the simulations results, combining the consideration of safety profile, this reviewer recommends a minimum of 24-month follow-up for the post market commitment.

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/s/

QIANG XU
07/15/2011

SHENGHUI TANG
07/15/2011

RAJESHWARI SRIDHARA
07/15/2011

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202429

Applicant: Roche

Stamp Date: 4/27/2011

Drug Name: Vemurafenib

NDA/BLA Type: NDA

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.		X		
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.		X		
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.		X		
Appropriate references for novel statistical methodology (if present) are included.		X		
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		X		
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Qiang (Casey) Xu 5/24/2011

Reviewing Statistician Date

Supervisor/Team Leader Date

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/s/

QIANG XU
05/24/2011

SHENGHUI TANG
05/24/2011