

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204369Orig1s000

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 204369
Supplement #: 00
Drug Name: Stivarga (Regorafenib)
Indication(s): The treatment of patients with [REDACTED] (b) (4)
[REDACTED]
Applicant: Bayer HealthCare Pharmaceuticals
Received Date: August 30, 2012
PDUFA Date: February 28, 2013
Review Type: Priority
Biometrics Division: Division of Biometrics V
Statistical Reviewer: Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers: Kun He, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Division Director
Medical Division: Division of Oncology Products 2
Clinical Team: Jenny Chang, Pham.D., Clinical Reviewer
Amir Shahlaee, M.D., Clinical Reviewer
Suzanne Demko, Clinical Team Leader
Patricia Keegan, M.D., Division Director
Project Manager: Monica Hughes, M.S.

Keywords: Stratified log-rank test, Kaplan-Merier method, Cox regression

Table of Contents

1	EXECUTIVE SUMMARY	3
2	INTRODUCTION	4
2.1	OVERVIEW.....	4
2.2	DATA SOURCES	4
3	STATISTICAL EVALUATION	4
3.1	DATA AND ANALYSIS QUALITY	4
3.2	EVALUATION OF EFFICACY	4
3.2.1	<i>Study Design and Endpoints</i>	4
3.2.2	<i>Statistical Methodologies</i>	6
3.2.3	<i>Patient Disposition, Demographic and Baseline Characteristics</i>	7
3.2.4	<i>Results and Conclusions</i>	9
3.3	EVALUATION OF SAFETY	14
3.4	BENEFIT-RISK ASSESSMENT	14
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	14
4.1	GENDER, RACE, AGE, AND GEOGRAPHIC REGION	14
4.2	OTHER SPECIAL/SUBGROUP POPULATIONS	15
5	SUMMARY AND CONCLUSIONS	15
5.1	STATISTICAL ISSUES	15
5.2	COLLECTIVE EVIDENCE.....	16
5.3	CONCLUSIONS AND RECOMMENDATIONS	16

1 EXECUTIVE SUMMARY

The applicant submitted a type 9 New Drug Application (NDA) with data from Study 14874 (GRID) entitled ‘A randomized, double-blind, placebo-controlled study of regorafenib plus best supportive care (BSC) versus BSC alone in patients with metastatic and/or unresectable GIST after prior treatment with at least imatinib and sunitinib’ and other studies to seek an approval of regorafenib for the proposed indication ‘treatment of patients with (b) (4)

This review focuses on evaluation of efficacy results from GRID.

In GRID, a total of 199 patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib and sunitinib were randomized in a 2:1 ratio to receive regorafenib plus best supportive care (BSC) or placebo plus BSC. The randomization was stratified by line of therapy (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world).

The primary endpoint was progression free survival (PFS), assessed by blinded central radiology review (BCRR), according to modified Response Evaluation Criteria in Solid Tumors criteria (RECIST 1.1). The primary analysis was a stratified log-rank test on the intent-to-treated (ITT) population, consisting of all randomized patients. Based on 145 PFS events assessed by BCRR, the PFS result demonstrated that the patients had statistically significant improvement in PFS when treated with regorafenib plus BSC than those treated with BSC alone (stratified log-rank p-value <0.0001). The estimated median PFS was 4.8 months (95%CI: 3.9, 5.7) in the regorafenib plus BSC arm versus 0.9 months (95%CI: 0.9, 1.1) in the BSC arm. The hazards ratio of PFS was 0.27 (95%CI: 0.19, 0.39) in favor of the treatment with regorafenib plus BSC. The interim overall survival (OS) analysis result failed to show that there was statistical difference in overall survival between patients treated with regorafenib plus BSC and treated with BSC alone (stratified log-rank p-value=0.1989).

Whether the results from Study GRID provide a favorable benefit to risk ratio to support an approval of regorafenib for the proposed indication will be determined by the clinical review team.

2 INTRODUCTION

2.1 Overview

In this NDA, the applicant submitted the data from Study 14674 (GRID) and other studies to seek an approval of regorafenib for a proposed indication for patients with (b) (4)

GRID was a phase 3, randomized, double-blind, placebo-controlled study in patients with metastatic and/or unresectable GIST and progressed after therapy with at least imatinib and sunitinib. The primary objective of the study was to compare the treatments in terms of progression-free survival (PFS), per blinded central radiology review, according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).

The first visit of the first patient was on January 04, 2011 and the first treatment of the last patient was in August 2011. Study GRID was conducted at 57 study centers in 17 countries. North America comprised 18% of the study population with 13% from the US and 52% from Canada.

One of the secondary objectives of the study was comparison of OS between the two randomized treatment arms. There was a planned OS interim analysis at the time of the final PFS analysis. The final OS analysis will be conducted when 160 deaths have been observed.

2.2 Data Sources

Data used for this review were from the electronic submission received on August 30, 2012. The link was "<\\CDSESUB1\EVSPROD\NDA204369\204369.enx>"

3 STATISTICAL EVALUATION

This section mainly focuses on statistical evaluation of efficacy results from Study GRID.

3.1 Data and Analysis Quality

The quality of submitted data allowed this reviewer to reproduce the primary analysis and other submitted efficacy results. Also, the statistical analysis plan (SAP) was provided in the NDA submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

GRID was a randomized, double-blind, placebo-controlled, multi-center, crossover phase III study. The patient inclusion criterion included Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, at least imatinib and sunitinib as the prior treatment regimens, with objective disease progression or intolerance to imatinib, as well as disease progression while on sunitinib therapy, and at least one measurable lesion according to modified RECIST 1.1. Patients randomized in GRID were allowed to crossover after experiencing disease progression.

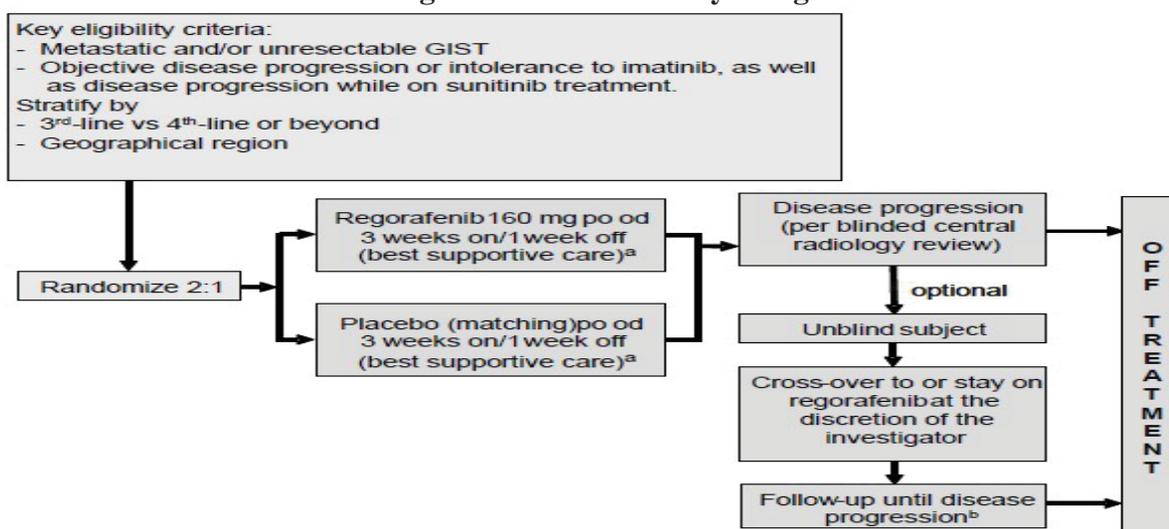
A total of 199 patients with advanced GIST who had received at least imatinib and sunitinib as prior treatments were randomized in a 2:1 ratio, using a telephone Interactive Voice Response System (IVRS), to receive one of the two following treatments:

Experimental Arm: Regorafenib 160 mg once daily (od), 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks, plus BSC

Control (Placebo) Arm: Placebo (same regimen as regorafenib) plus BSC

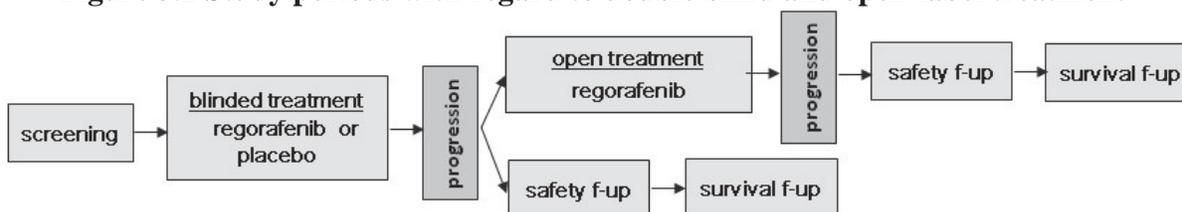
The randomization was stratified by line of therapy (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world). Figure 3.1 and 3.2 show the overall study design of GRID.

Figure 3.1 Overall Study Design



[Source: Clinical Study Report Figure 7.1]

Figure 3.2 Study periods with regard to double blind and open-label treatment



[Source: Clinical Study Report Figure 7.2]

Per the protocol and the statistical analysis plan, the primary endpoint PFS was defined as the time from date of randomization to date of first observed radiological progression by blinded central radiology review (BCRR) or death due to any cause. The required tumor assessments were performed every 4 weeks (+/- 7 days) for the first 3 months, every 6 weeks (+/- 7 days) for the subsequent 3 months (through month 6 on study), and every 8 weeks (+/- 7 days) until the end of study drug administration (>6 months on study). Intervening unscheduled tumor assessments could be performed at any time, if clinically indicated, throughout the study.

For the patient who did not have radiological progression by BCRR or death at the time of analysis, PFS was censored at the last date of radiological assessment. For the patient who did not have tumor assessments after baseline, and

- did not die, PFS was censored at day 1
- died before the latest possible scheduled date for the second tumor assessment (10 weeks after randomization), death was considered as a PFS event
- died later than 10 weeks after randomization, death was not considered as a PFS event and PFS was censored after week 10

For the patient who changed therapy to something other than the study medication prior to observing progression, PFS was censored at the date of the last scan performed prior to the change of therapy. For the patient who had progression after 2 consecutive missed or non-evaluable assessments, PFS was censored at the date of the last evaluable scan before the 2 missing assessments.

For the patient who discontinued or withdrew early from the study without documented radiological progression, PFS was censored on the date of the last evaluable tumor assessment unless the patient died no later than after the next 2 imaging assessment periods after the last evaluable assessment. In this case, death was considered a PFS event.

The secondary endpoints in the study included time to progression (TTP) and overall survival (OS). TTP was defined as the time (days) from date of randomization to date of first observed radiological progression. OS was defined as the time from date of randomization to date of death due to any cause. OS for the patient who was not known to have died was censored at their last date of being known to be alive or at the database cutoff date, whichever came first.

3.2.2 Statistical Methodologies

Per the protocol and the SAP, the primary analysis of PFS would be a log-rank test stratified by two randomized stratified factors at two-sided alpha level of 0.01. The BCRR assessments of radiological data would be used for the primary analysis of PFS. The Kaplan-Meier method would be used to estimate parameters such as medians for PFS analysis on each treatment group. Hazard ratios would be estimated using the Cox proportional hazards model stratified by two randomized stratified factors with assigned treatment as the only covariate, and reported with 2-tailed 98% confidence intervals (CIs).

The same statistical analysis methods would be applied to the secondary endpoint TTP and OS analyses, with a gatekeeping procedure specified in the SAP in the order of testing TTP first and OS next, i.e., OS would be tested only if the one-sided p-value for testing TTP was 0.025 or less. There were two planned OS analyses: an OS interim analysis at the time of final PFS analysis and final OS analysis when a minimum of 160 deaths would be observed. An O'Brien-Fleming alpha spending function approach would be used to determine the significance thresholds based on the actual number of events.

GRID was originally designed to randomize 170 patients in order to observe 122 PFS events, assumed that the true PFS hazard ratio was 0.5 with 6 weeks of the median PFS for BSC

treatment. A required 122 events would provide 90% power to detect statistically significant difference in PFS between two arms at a 2-sided alpha level of 0.01. The sample size of 170 patients with 136 death events also would provide 80% power to detect statistically significant difference in OS between two arms at a 2-sided alpha level of 0.05, assumed that the true OS hazard ratio was 0.60 and median OS for BSC treatment was 6 months.

Per applicant, enrollment for GRID occurred much faster than anticipated, with 42 new patients entering screening in the final week of recruitment, the final number of patients randomized was 199 (29 more patients than originally planned). The applicant amended the protocol of Study GRID (amendment 3, integrated protocol version 4.0, dated on September 27, 2011) to increase of the number of PFS events required for primary analysis from 122 to 144. The applicant submitted the protocol version 4.0 and SAP version 1.0 on February 7, 2012. Because of increase of required number of events for the primary analysis of PFS, the power to detect an improvement in PFS would be increased from 90% to 94%. Therefore, the number of targeted survival events was also increased from the originally planned number of 136 to 160. The increase number of OS events would increase power from 80% to 84% at a one-sided of 0.025.

Reviewer's Comments:

- 1. There were several rounds of communication between FDA and the applicant regarding of the applicant's submitted protocol of Study GRID version 4.0 (the integrated protocol with the amendment 3) and SAP version 1.0. In the Advice/Information Request letter dated on March 20, 2012, FDA stated that the primary analysis in the study protocol 14874 (GRID) should be performed based on the originally planned 122 PFS events despite the fact that 29 additional patients were enrolled. However, FDA stated that if the applicant strongly preferred to change the primary analysis from 122 PFS events to 144 PFS events, FDA would consider the primary objective fulfilled only if tests at both 122 and 144 PFS events were statistically significant.*
- 2. There were two versions (version 1.0 and version 1.1) of statistical analysis plan (SAP) for Study GRID in the NDA submission. Version 1.0 was dated on January 25, 2012, the date prior to January 26, 2012, the date of datalock for the final analysis. Version 1.1 of SAP was dated on March 22, 2012, the date after the date of datalock. Since SAP should be finalized before datalock for the final analysis, FDA considers the submitted SAP version 1.0 as the final SAP for GRID.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were 240 patients enrolled and screened in GRID. Among the 240 patients, 41 patients (17.1%) failed screening, and 199 patients (82.9%) were randomized. Table 3.1 summarizes the disposition for the intent-to-treated (ITT) population as January 26, 2012, the data cutoff date.

Table 3.1 Patient Disposition (ITT)

	Regorafenib + BSC	Regorafenib + BSC
Randomized, n (%)	66 (100.0)	133 (100.0)
Study drug never administered	0	1 (0.8)
Started double blind treatment	66 (100.0)	132 (99.2)
Ongoing with double blind treatment at database cutoff date	3 (4.5)	53 (39.8)
Terminated double blind treatment but no open label treatment	7 (10.6)	38 (28.6)
Receiving open label treatment	56 (84.8)	41 (30.8)
Ongoing with open label treatment at database cutoff date	33 (50.0)	24 (18.0)

[Source: Clinical Study Report Table 8-2]

The demographics and baseline characteristics of ITT population are summarized in Table 3.2.

Table 3.2 Demographics and Baseline Characteristics (ITT)

	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)
Gender, n (%)		
Male	42 (63.6)	85 (63.9)
Female	24 (36.4)	48 (36.1)
Age, year		
Median (range)	61 (25- 87)	60 (18- 82)
Age Group, n (%)		
<65	46 (69.7)	90 (67.7)
>=65	20 (30.3)	43 (32.3)
Race/ethnic group, n (%)		
White	45 (68.2)	90 (67.7)
Asian	16 (24.2)	34 (25.6)
ECOG performance status, n (%)		
0	37 (56.1)	73 (54.9)
1	29 (43.9)	60 (45.1)
Duration of treatment with imatinib, n (%)		
< 6 months	4 (6.1)	18 (13.5)
> = 6 and <18 months	7 (10.6)	26 (19.5)
> =18 months	55 (83.3)	89 (66.9)
Prior anti-cancer drug group, n (%)		
3rd line	39 (59.1)	74 (55.6)
4th line and	27 (40.9)	59 (44.4)
Mutation biomarkers (historical data), n (%)		
Not Assessed/Available	30 (45.5)	73 (54.9)
Any Assessed Information	36 (54.5)	60 (45.1)
KIT Exon 11 mutation	17 (47.2)	34 (56.7)
KIT Exon 9 mutation	6 (16.7)	9 (15.0)

[Source: Clinical Study Report Table 8-10]

Reviewer’s Comments:

3. As shown in Table 3.2, the demographic and major baseline disease characteristics except duration of treatment with imatinib appear balanced between the two treatment arms.

3.2.4 Results and Conclusions

3.2.4.1 Results of Primary Endpoint

The data was locked for the final PFS on January 26, 2012. The same censoring rules as for PFS, except for those related to death events, were applied to TPP. The primary analysis of PFS was based on BCRR assessment. Table 3.3 summarizes the applicant’s primary analysis of PFS.

Table 3.3 Applicant’s Results of Progression Free Survival (ITT)

	BCRR 144 Events		BCRR 122 Events	
	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)
Number of Events (%)	63 (95.5)	81 (60.9)	59 (89.4)	63 (47.4)
Number Censored (%)	3 (4.5)	52 (39.1)	7 (10.6)	70 (52.6)
Median PFS in months (95% CI)	0.92 (0.92, 1.05)	4.82 (4.01, 5.68)	0.90 (0.90, 1.05)	4.24 (2.79, 6.54)
P-value (stratified* log rank)	<0.0001		<0.0001	
Hazard Ratio* (95% CI)	0.27 (0.185 – 0.39)		0.22 (0.14 – 0.35)	

*stratified by two randomized stratified factors: line of treatment (3rd-line versus 4th-line or beyond), geographical region (Asia vs. rest of world); a hazard ratio of less than 1 indicates that the treatment with regorafenib plus BSC is associated with lower risk of progression or death compared to the treatment with placebo plus BSC.

Reviewer’s Comments:

4. As shown in Table 3.3, both PFS analyses based on 144 and 122 PFS events demonstrated that the treatment of Regorafenib plus BSC significantly prolonged PFS compared to placebo plus BSC.
5. During the review process, it was found that the PFS for one patient (Patient ID 200021002) should not be censored because this patient died less than two months after being randomized. Per the applicant, the PFS was censored for this patient because the patient was unblinded prior to death according to the censored rule in SAP version 1.1. FDA considers SAP version 1.0 as the final SAP; and FDA does not agree with the censored rule that censoring PFS for patients who were unblinded prior to progression or death. This reviewer performed PFS analyses by changing the PFS for this patient from censoring at the date of the tumor assessment prior to the unblinded date to the date of death. Table 3.4 summarizes the reviewer’s PFS analyses based on 145 events and 123 events. Based on the communication between FDA and the applicant mentioned in Reviewer’s Comments 1, FDA considered the analysis based on BCRR assessed 145 PFS events as the primary analysis.

Table 3.4 Primary Analysis of Progression Free Survival (ITT)

	BCRR 145 Events		BCRR 123 Events	
	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)
Censored (%)	3 (4.5)	51 (38.4)	7 (10.6)	69 (51.9)
Events (%)	63 (95.5)	82 (61.6)	59 (89.4)	64 (48.1)
Progression	62	76	58	58
Death	1	5	1	5
Median PFS in months (95% CI)	0.9 (0.9, 1.1)	4.8 (3.9, 5.7)	0.9 (0.9, 1.1)	4.2 (2.8,6.5)
P-value (stratified* log-rank)	<0.0001		<0.0001	
Hazard Ratio* (95% CI)	0.27(0.19, 0.39)		0.27(0.19, 0.40)	

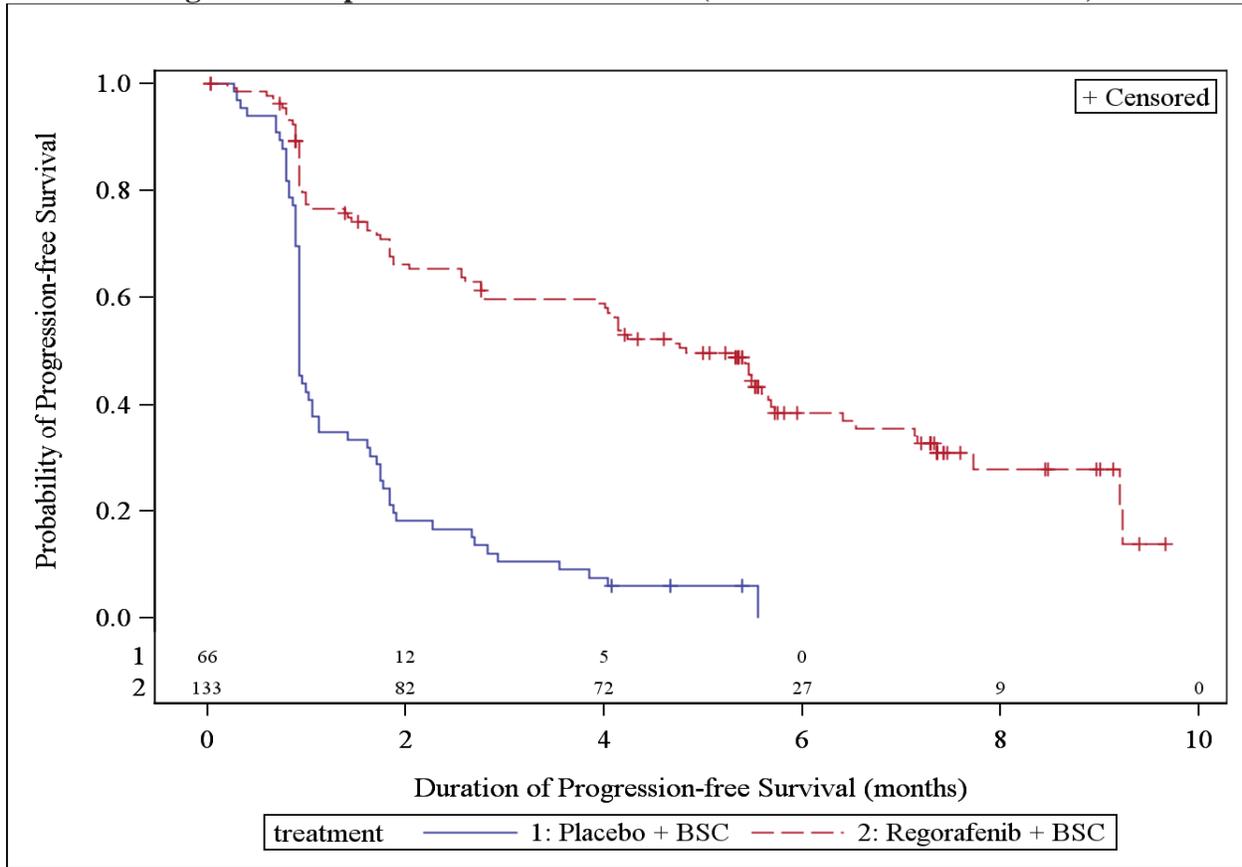
*stratified by two randomized stratified factors: line of treatment (3rd-line vs. 4th-line or beyond), geographical region (Asia vs. rest of world); a hazard ratio of less than 1 indicates that the treatment with regorafenib plus BSC is associated with lower risk of progression or death compared to the treatment with placebo plus BSC.

Reviewer’s Comments:

6. As shown in Table 3.4, the PFS analyses demonstrated that the treatment of regorafenib plus BSC statistically prolonged PFS compared to the treatment with placebo plus BSC.

Figure 3.3 displays Kaplan-Meier curves of PFS based on 145 BCRR assessed PFS events.

Figure 3.3 Kaplan-Meier curves of PFS (ITT with BCRR 145 Events)



Since PFS results depend on the length of assessment schedule and frequency of assessment, any imbalances in the tumor assessment schedule and frequency between the two arms may introduce systematic bias in the evaluation of PFS. Per FDA’s request, the applicant submitted the summary results of time from randomization to tumor assessments as displayed in Table 3.5.

Table 3.5 Summary of Time to Tumor Assessment from Randomization

Days from randomization to	Number of Patients		Median		25th Percentile		75th Percentile	
	Placebo + BSC (n=66)	Regor* + BSC (n=133)	Placebo + BSC (n=66)	Regor* + BSC (n=133)	Placebo + BSC (n=66)	Regor* + BSC (n=133)	Placebo + BSC (n=66)	Regor* + BSC (n=133)
Assessment 1	65	129	28.0	27.0	24.0	23.0	28.0	28.0
Assessment 2	35	101	54.0	56.0	52.0	52.0	56.0	57.0
Assessment 3	13	90	84.0	84.0	82.0	79.0	86.0	85.0
Assessment 4	8	75	123.0	126.0	115.5	123.0	125.0	131.0
Assessment 5	3	61	164.0	166.0	142.0	162.0	169.0	169.0
Assessment 6	0	30	0	222.0	0	212.0	0	224.0

*Regor=Regorafenib

Reviewer’s Comments:

7. *As shown in Table 3.5, it appears that the lengths of assessment schedule between two arms are balanced.*

The applicant also provided PFS data based on investigator (INV) assessment in the NDA submission. Table 3.6 summarizes the reviewer’s discordance analysis.

Table 3.6 Discordance of PFS Assessment by INV and IR

INV Reading, n (%)	Placebo + BSC			Regorafenib + BSC		
	BCRR Reading			BCRR Reading		
	PD	No PD	Total	PD	No PD	Total
PD	50 (100)	0 (0)	50	40 (91)	4 (9)	44
No PD	12 (80)	3 (20)	15	37 (44)	48 (56)	85

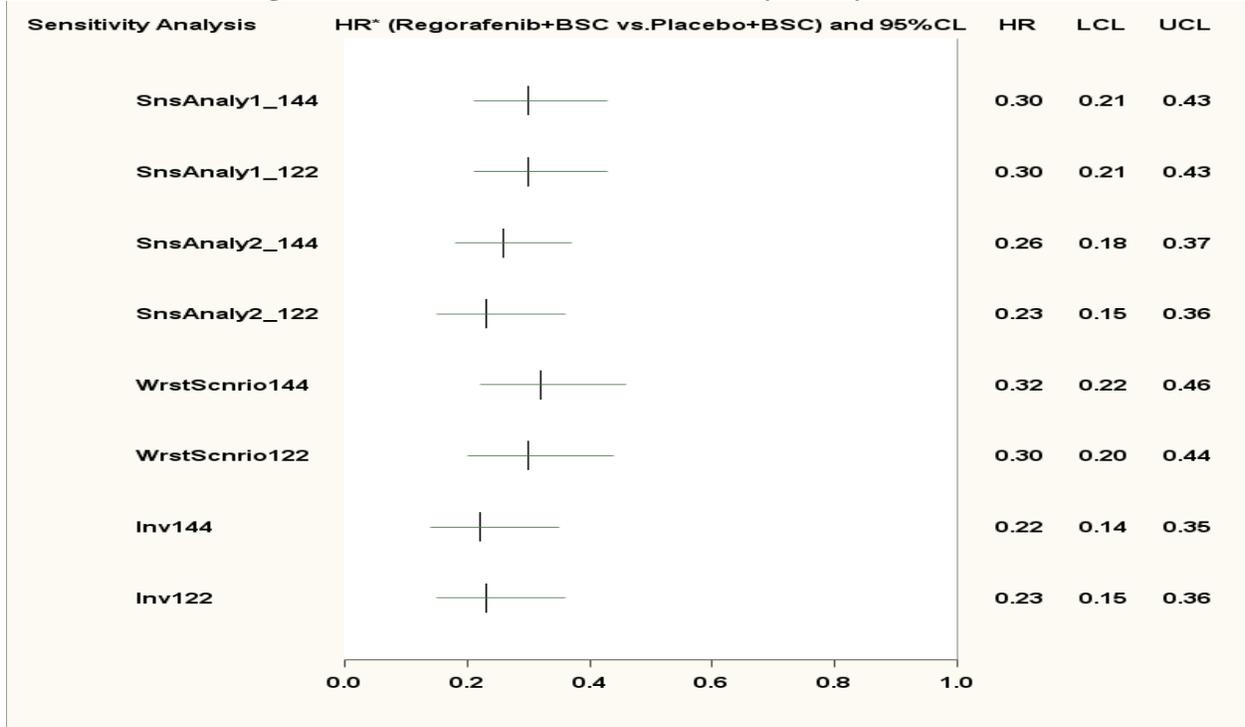
Reviewer’s Comments:

8. *As shown in Table 3.6, the percentages of disagreement between INV and BCRR in the status of PD (no PD by INV reading) are higher in both arms, particularly in placebo arm. The percentage of patients who were determined to have PD by BCRR is higher than those determined by INV.*

In order to assess the robustness of the observed PFS treatment effect, this reviewer conducted two sensitivity analyses (denoted as SnsAnaly1_144 and SnsAnaly1_122 in Figure 3.4) by using INV and BCRR assessed data (see the description from Appendix in the end of the review). Also, the applicant conducted several sensitivity analyses results, including using unstratified log-rank test on BCRR’s data based on 144 and 122 PFS events (denoted as SnsAnaly2_144 and SnsAnaly2_122 in Figure 3.4), and using stratified log-rank test based on INV assessments data (denoted as Inv_144 and Inv_122 in Figure 3.4). Per FDA requested, the applicant conducted a “worse-case” scenario sensitivity analysis (denoted as WrstScnrio_144 and WrstScnrio_122 in

Figure 3.4 and see the description from Appendix in the end of the review). Based on this reviewer's and the applicant's sensitivity analyses results, this reviewer created the forest plot shown in Figure 3.4.

Figure 3.4 Frost Plots of PFS Sensitivity Analyses Results



*a hazard ratio of less than 1 indicates that the treatment with regorafenib plus BSC is associated with lower risk of progression or death compared to the treatment with placebo plus BSC.

Reviewer's Comments:

9. As shown in Figure 3.4, the sensitivity analyses results are consistent with the primary analysis results.

3.2.4.2 Results of Secondary Endpoints

Endpoint of time to progression (TTP) was pre-specified as a secondary endpoint evaluated in Study GRID. Table 3.7 summaries the TTP analysis based on BCRR assessment.

Table 3.7 Analysis of Time to Progression (ITT)

	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)
Number of Events (%)	62 (93.9)	76 (57.1)
Number Censored (%)	4 (6.1)	57 (42.9)
Median TTP in months (95% CI)	0.92 (0.92, 1.12)	5.42 (4.11, 5.72)
P-value (stratified log rank)	<0.0001	
Hazard Ratio* (95% CI)	0.25 (0.17, 0.36)	

*a hazard ratio of less than 1 indicates that the treatment with regorafenib plus BSC is associated with lower risk of progression compared to the treatment with placebo plus BSC.

Reviewer’s Comments:

- 10. The censoring rules applied in TTP analysis were the same as the ones in PFS analysis, except for those related to death events. TTP was censored at the date of the last evaluable tumor assessment prior to the death date for the patient who died.
- 11. As shown in Table 3.7, there was a statistically significant difference in delay progression between the regorafenib plus BSC and placebo plus BSC arms.

In GRID, overall survival was another secondary endpoint with TTP that were pre-specified to test for the labeling purpose after the result of the primary endpoint PFS shows statistically significant difference in favor treatment with regorafenib plus BSC. A planned interim analysis was conducted at the time of final PFS analysis. There were 46 death events when the interim analysis was conducted. Table 3.8 summaries the interim OS analysis.

Table 3.8 Interim Analysis of Overall Survival

	Placebo + BSC (n=66)	Regorafenib + BSC (n=133)
Number of Events (%)	17 (25.8)	29 (21.8)
Number Censored (%)	49 (74.2)	104 (78.2)
Median OS in months (95% CI)	NA*	NA*
P-value (stratified log rank)	0.1989	
Hazard Ratio** (95% CI)	0.772 (0.423, 1.408)	

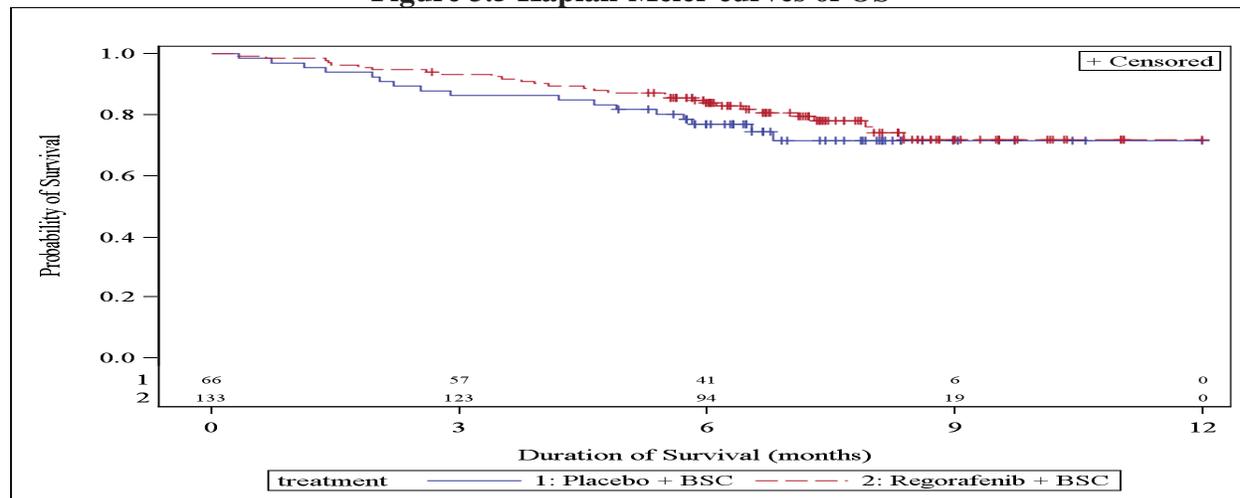
*NA=Not available due to immature OS data; **a hazard ratio of less than 1 indicates that the treatment with regorafenib plus BSC is associated with lower risk of progression or death compared to the treatment with placebo plus BSC.

Reviewer’s Comments:

- 12. Using O'Brien-Fleming alpha spending function approach based on actual number of events 46, the nominal significance level for the OS interim analysis is 0.0002. As shown in Table 3.8 and Figure 3.5, there was no statistically significant difference in survival between the regorafenib plus BSC and placebo plus BSC arms.

Figure 3.5 displays Kaplan-Meier curves of OS.

Figure 3.5 Kaplan-Meier curves of OS



3.3 Evaluation of Safety

Please refer to Dr. Amir Shahlaee’s review for safety evaluation of regorafenib.

3.4 Benefit-Risk Assessment

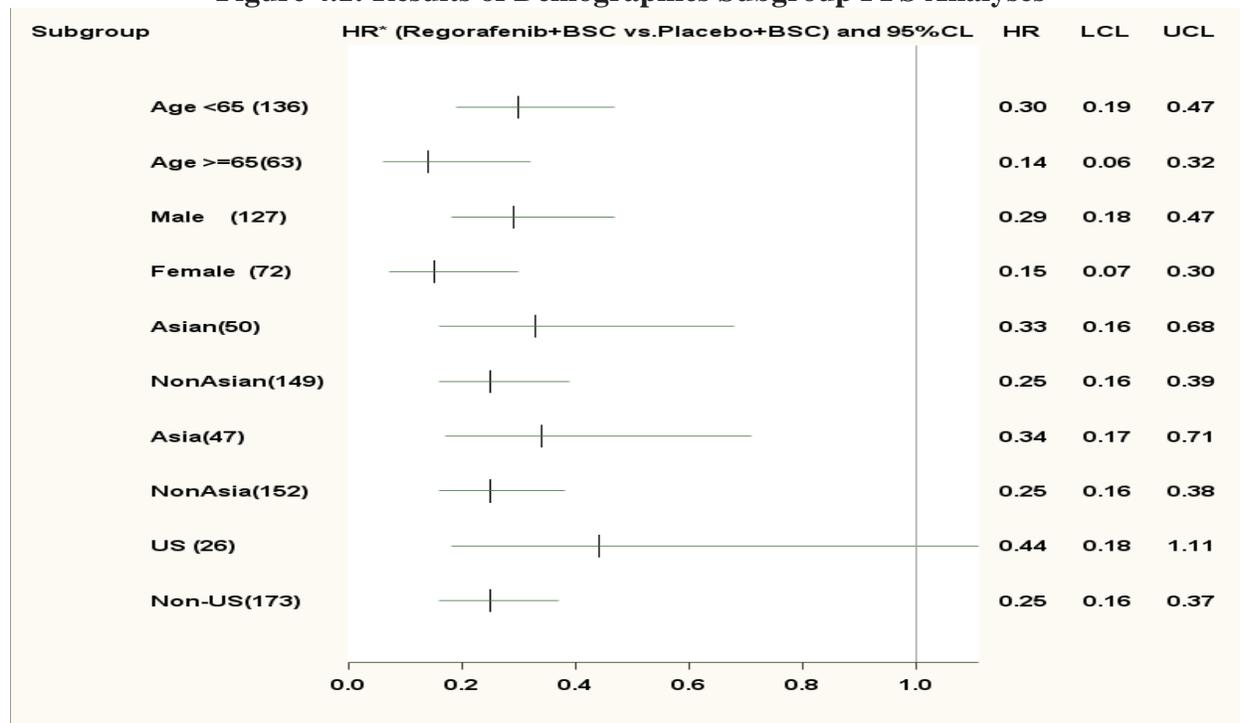
The results of Study GRID show statistically significant improvement in progression-free survival in patients with metastatic and/or unresectable GIST whose disease had progressed despite prior treatments with at least imatinib and sunitinib when treated with regorafenib plus BSC compared to the treatment with BSC alone. Whether the results from GRID provide a favorable benefit to risk ratio to support an approval of regorafenib for the proposed indication will be deferred to the clinical review team.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This reviewer conducted PFS analyses in the subgroup defined by age (greater than 65 versus less than or equal to 65 years), gender and region (Asia vs. Rest of World and US vs. non-US). Figure 4.1 displays the forest plot of PFS analyses in the demographic subgroups.

Figure 4.1: Results of Demographics Subgroup PFS Analyses



*A hazard ratio of less than 1 indicates that the treatment with regorafenib plus BSC is associated with lower risk of progression or death compared to the treatment with placebo plus BSC.

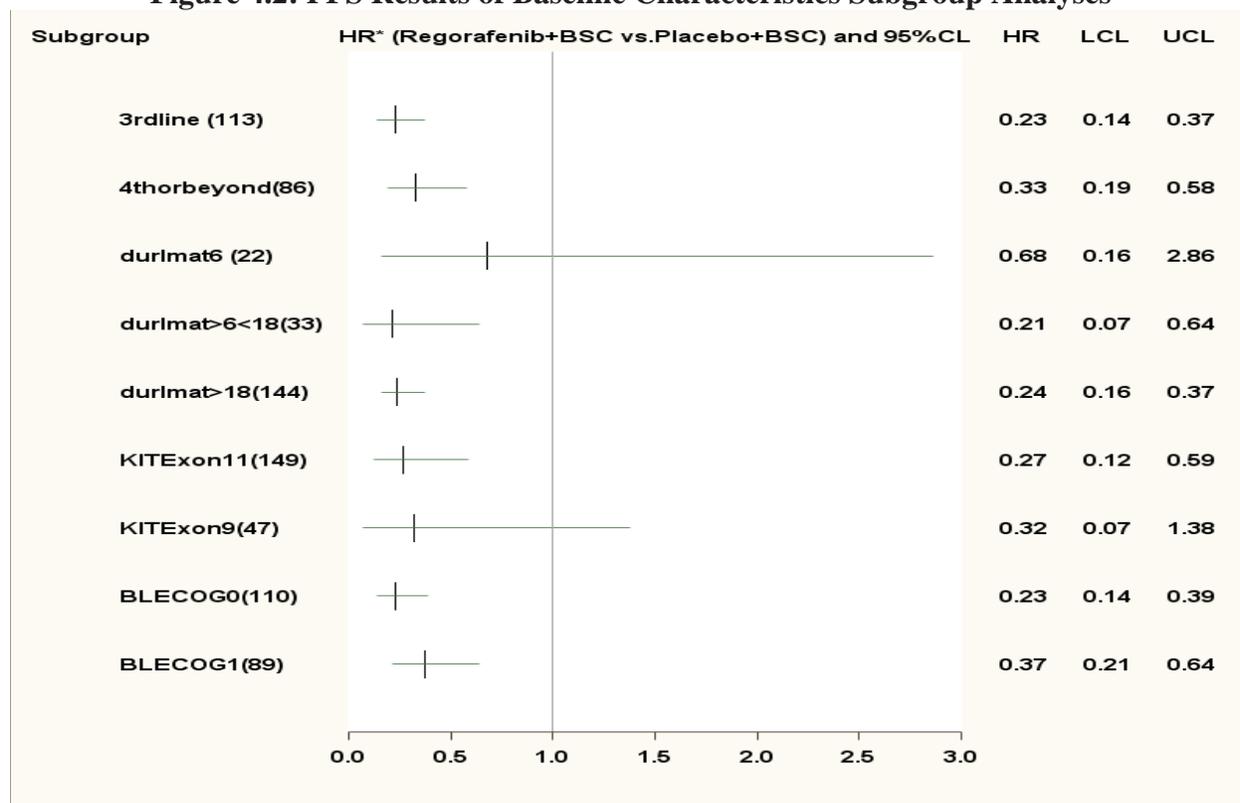
Reviewer’s Comments:

13. As shown in the Figure 4.1, most PFS analyses in demographic subgroups are consistent with the primary analysis. The subgroup analyses results are considered exploratory.

4.2 Other Special/Subgroup Populations

This reviewer conducted the PFS analyses in subgroups defined by major baseline disease characteristics. The major baseline characteristics used to define the subgroups are ECOG performance status at baseline, line of treatment, Duration of treatment with imatinib, and mutation biomarkers (KIT Exon 11 mutation or KIT Exon 9 mutation). Figure 4.2 displays the forest plot of the PFS analyses of the subgroups based on major baseline characteristics.

Figure 4.2: PFS Results of Baseline Characteristics Subgroup Analyses



Abbreviations: durlmat6/>6<18/>18= subgroup of patients whose duration with imatinib<6months/>6months<18months/>18 months; KITExon9/11=subgroup of patients whose Mutation biomarkers were KIT Exon 9/11 mutation; KITExon11=subgroup of patients whose Mutation biomarkers were KIT Exon 11 mutation; BLECOG0/1=subgroup of patients whose baseline ECOG performance status were 0/1.

Reviewer's Comments:

14. As shown in the Figure 4.2, most PFS analyses in major baseline characteristic subgroups are consistent with the primary analysis. The results of the baseline disease characteristic subgroup analyses are considered exploratory.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This reviewer found no major statistical issue that impacted the overall conclusions.

5.2 Collective Evidence

Based on the data from the submitted Study GRID, the primary analysis result of PFS demonstrated that patients with metastatic and/or unresectable GIST whose disease had progressed despite prior treatments with at least imatinib and sunitinib had statistically significant improvement in PFS when treated with regorafenib plus BSC instead of BSC alone (stratified log-rank p-value <0.0001). Based on 145 PFS events assessed by BCRR, estimated median PFS was 4.8 months (95%CI: 3.9, 5.7) for the patients treated with regorafenib plus BSC versus 0.9 months (95%CI: 0.9, 1.1) for the patients treated with BSC alone. The hazards ratio of PFS was 0.27 (95% CI: 0.19, 0.39) in favor of the treatment with regorafenib plus BSC. The results of interim OS analysis based on interim OS data failed to show that there was statistically significant improvement in survival between two treatments (stratified log-rank p-value=0.1989). The final OS analysis will be conducted when 160 deaths have been observed.

5.3 Conclusions and Recommendations

Based on PFS analyses from Study GRID, this reviewer concludes that treatment with regorafenib plus BSC statistically delays time to progression or death for patients with metastatic and/or unresectable GIST whose disease had progressed despite prior treatments with at least imatinib and sunitinib compared to the treatment with BSC alone. Whether the results from GRID provide a favorable benefit to risk ratio to support an approval of regorafenib for the proposed indication will be determined by the clinical review team.

APPENDIX

Description of PFS sensitivity analyses (Figure 3.2) in Section 3.2.4.1

Sensitivity analysis 1 (Snsanaly1)

Sensitivity analysis 1 was conducted by taking using minimum PFS data of INV and BCRR as described as the followings:

PFS time = minimum (INV assessed PFS time, BCRR assessed PFS time)

Censored indicator = minimum (censored indicator based on INV assessment, BCRR censored based on BCRR assessment)

Where censored indicator = 0 when a patient had a PFS event otherwise censored indicator=1

“Worse-case” scenario sensitivity analysis

According to the applicant’s document “introduction-to-adevttes-pfs-sensitivity.pdf” (submitted on October 26, 2012); the “worse-case” scenario sensitivity analysis was conducted as the followings:

- Only unscheduled tumor assessment dates that contributed to a PFS event were moved. According to the protocol tumor assessments are taken every 4 weeks +/- 7 days for the first 3 months, every 6 weeks +/- 7 days from 3-6 months, and every 8 weeks +/- 7 days after that. If the difference of a PFS event (or censored data) date and the previous evaluable tumor assessment is outside of the windows specified above, an algorithm has been created to move the PFS date as follows:
 - If the PFS date was in the 1st, 2nd or 3rd tumor assessment then the PFS date was moved 28 days earlier for Regorafenib arm or 28 days later for Placebo arm.
 - If the PFS date was in the 4th, 5th or 6th tumor assessment then the PFS date was moved 42 days earlier for Regorafenib arm or 42 days later for Placebo arm.
 - If the PFS date was after the 6th tumor assessment then the PFS date was moved 56 days earlier for Regorafenib arm or 56 days later for Placebo arm.
- If the PFS date was a death date then the PFS date remains unchanged.

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

/s/

XIAOPING JIANG
01/31/2013

KUN HE
01/31/2013
Accepted as a complete review.

RAJESHWARI SRIDHARA
02/01/2013

STATISTICS FILING CHECKLIST FOR NDA204369

NDA Number: 204369

Applicant: Bayer HealthCare

Stamp Date:

August 30, 2012

**Drug Name:
Stivarga(regorafenib)**

NDA Type: 9

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.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

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.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			×	
Appropriate references for novel statistical methodology (if present) are included.			×	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	×			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

File name: Statistics Filing Checklist for NDA204369

STATISTICS FILING CHECKLIST FOR NDA204369

Xiaoping (Janet) Jiang, Ph.D.	10/09/2012
Reviewing Statistician	Date
Kun He, Ph.D.	10/09/2012
Team Leader	Date

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

/s/

XIAOPING JIANG
10/09/2012

KUN HE
10/09/2012