CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig1s000

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 #:	NDA 205552
Supplement #:	
Drug Name:	Ibrutinib
Indication(s):	(b) (4) Mantle Cell Lymphoma
Applicant:	Pharmacyclics
Date(s):	Submission Date: May 31, 2013 PDUFA due Date: February 28, 2014 Review Completion Date: 28 October, 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Yun Wang, PhD
Concurring Reviewers:	Lei Nie, PhD, Acting Team Leader Rajeshwari Sridhara, PhD, Division Director
Medical Division:	Office of Hematology and Oncology Product
Clinical Team:	Karen McGinn, MD Angelo De Claro, MD
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Keywords: Mantle Cell Lymphoma, Overall Response Rate, Duration of Response

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1 EXECUTIVE SUMMARY

(b) (4)

(b) (4) the applicant seeks the approval of ibrutinib for treatment of mantle cell lymphoma (MCL) patients who received at least one prior regimen.

This NDA original-1submission is based on two clinical studies (Study PCYC-1104-CA and Study PCYC-04753) in 124 subjects in which ibrutinib was evaluated as a single agent at different doses for the treatment of MCL patients. Study PCYC-1104-CA with 115 subjects treated with ibrutinib at dose of 560 mg is considered pivotal for the evaluation of efficacy and forms the basis for this statistical review. Study PCYC-04753 enrolled 9 MCL patients into different doses and only provided preliminary efficacy results of ibrutinib. Therefore, study PCYC-04753 was not included in this statistical review.

In Study PCYC-1104-CA, the overall response rate (ORR) was 65.8% (95% CI [56.2%, 74.5%]) with median duration of response (DOR) of 17.5 months (lower 95% confidence limit (CI) of 15.8 months, and upper 95% CI not evaluable).

Study PCYC-1104-CA was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

The response data from PCYC-1104-CA demonstrate durable treatment effect of ibrutinib for relapsed and refractory mantle cell lymphoma patients.

2 INTRODUCTION

2.1 Overview

Ibrutinib is a selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of B-cell malignancies. By combining fast covalent binding to BTK with rapid in vivo elimination, ibrutinib provides a unique approach to improve selectivity for BTK in vivo relative to reversibly inhibited off-target kinases.

The proposed indication submitted in this NDA original-1 application is for the treatment of patients with (b) (4) MCL who have received at least one prior regimen.

Bortezomib (Velcade) is currently approved for treatment of patients with MCL based on an open-label, single-arm, multicenter study of 155 patients with progressive disease who had received at least 1 prior therapy. Based on that study, overall response rate (complete response (CR), unconfirmed CR (CRu), and partial response) to bortezomib was 31% (95% CI: 24%-39%), with duration of response of 9.3 months (95% CI: 5.4 -13.8 months); Complete response rate (CR + CRu) to bortezomib was 8% (95% CI: 4% - 13%).

Study PCYC-1104-CA was a Phase 2, open-label, nonrandomized, and multicenter study designed to evaluate the efficacy and safety of ibritinib monotherapy (560 mg daily) in the relapsed/refractory MCL patients who relapsed after 1 to 5 prior treatment regimens. The primary efficacy endpoint was overall response rate (ORR) based on investigator assessments

(INV). The secondary efficacy endpoints were duration of response (DOR), time to response (TTR), progression-free survival (PFS), and overall survival (OS).

A total of 115 patients with MCL were enrolled between 08 February 2011 and 21 March 2012 from 18 sites in the US and EU. The data cut-off date was 26 December 2012. Among the enrolled 115 patients, 111 patients received at least one dose of ibrutinib and constituted the all treated population for efficacy analyses for MCL indication.

The original protocol for Study PCYC-1104-CA was dated 28 September 2010, and the last version was Amendment 4 dated 03 January 2013.

Throughout this review, for Study PCYC-1104-CA, patients in bortezomib-naïve cohort are referred as "Bortezomib-naïve" arm in the text, the tables/figures, patients in bortezomib-exposed cohort are referred as "Bortezomib-exposed" arm in the text, the tables/figures, whereas all patients combined together are referred as "Total" arm in the text, the tables/figures.

TABLE 1: LIST OF ALL STUDIES INCLUDED IN ANALYSIS

Study	**Phase and Design**	**Treatment Period**	**Follow-up Period**	**# of Subjects per Arm**	**Enrollment period Geographic region**
PCYC-1104-CA	Phase 2, open-label, nonrandomized, multicenter study designed to evaluate the efficacy and safety of ibritinib monotherapy (560 mg daily) in the relapsed/refractory MCL patients who relapsed after 1 to 5 prior treatment regimens	Treatment until progressive disease (PD), death, or any other reason listed in the protocol for mandatory withdrawal.	After treatment discontinuation, subjects were followed for PD every 3 months until PD or start of new anti-MCL therapy. After that, patients will be followed every 3 months for survival until death or study closure.	N=115	08 February 2011 – 21 March 2012 18 sites in the US and EU

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: \\CDSESUB1\evsprod\NDA205552\205552.enx

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the Study PCYC-1104-CA.

3.1 Data and Analysis Quality

The overall response data for Study PCYC-1104-CA were derived and saved in analysis dataset "ADRS" for both IRC and investigator assessments. This NDA original-1 application provided source data for deriving overall response from individual disease assessments. The statistical reviewer can verify overall response for most patients in Study PCYC-1104-CA. However the statistical and clinical reviewers determined that:

- Three complete response (CR) claimed by the applicant for patients 032-004, 032-021, 217-002 were actually partial response (PR).
- One CR claimed by the applicant for patient 032-006 was stable disease (SD).
- One PR claimed by the applicant for patient 217-009 was stable disease (SD).

Therefore, the number of CR derived by the FDA reviewers was 4 less and the number of the overall response (CR+PR) was 2 less than those derived by the applicant. The responses derived by the FDA reviewers were used in this statistical review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Study PCYC-1104-CA was a Phase 2, open-label, nonrandomized, and multicenter study designed to evaluate the efficacy and safety of ibritinib monotherapy (560 mg daily) in the relapsed/refractory MCL patients who relapsed after 1 to 5 prior treatment regimens.

The primary objective of this study was to evaluate the efficacy of ibrutinib in subjects with relapsed/refractory MCL. Subjects enrolled in Study PCYC-1104-CA were grouped into 2 cohorts based on prior bortezomib exposure: a bortezomib-naïve cohort (subjects who received <2 cycles of prior treatment with bortezomib) and a bortezomib-exposed cohort (subjects who received ≥2 cycles of prior treatment with bortezomib).

In both cohorts, one interim futility analysis was performed based on the stopping rules from Simon 2-stage optimal design. For the bortezomib-naïve cohort, Simon 2-stage optimal design was used to test the null hypothesis that ORR would be ≤20%. Twenty-five subjects were to be included in the first stage, and, if there were at least 6 objective responses, a total of 65 subjects were to be enrolled in this cohort. A sample size of 65 subjects at final analysis would provide 91% power to test a difference of 20% versus 40% using a one-sided 0.01 significance level. For the bortezomib-exposed cohort, Simon 2-stage optimal design was used to test the null hypothesis that ORR would be ≤15%. Twenty-five subjects were to be included in the first stage, and, if there were at least 5 objective responses, a total of 50 subjects were to be enrolled in this cohort. A sample size of 50 subjects at final analysis would provide at least 80% power to test a difference of 15% versus 35% using a one-sided 0.01 significance level.

The sample size of 115 is based on justification described above for bortezomib-naïve and bortezomib-exposed cohort respectively.

3.2.1.2 Efficacy Endpoints

The primary efficacy endpoint was overall response rate (ORR), defined as the percent of subjects who achieved either a partial response (PR) or complete response (CR), according to the revised International Working Group (IWG) criteria for non-Hodgkin's Lymphoma (NHL), as assessed by investigators.

The secondary efficacy endpoints included:

- Duration of response (DOR), measured from the time CR or PR was first recorded to the time when progressive disease was objectively documented
- Time to response (TTR), defined as the interval between the date of first dose and the date of initial documentation of a response.
- Progression-free survival (PFS), measured from the time from first study drug administration until lymphoma progression or death as a result of any cause.
- Overall survival (OS), measured from the time of first study drug administration until the date of death.

3.2.2 Statistical Methodologies

The overall response rate and the corresponding exact 95% confidence interval (CI) will be presented. Median duration of response and the corresponding 95% CI calculated using Kaplan-Meier method will be presented as well.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis population

The intent-to-treat (ITT) population includes all subjects who met all eligibility criteria and was enrolled in the study.

All treated population includes all enrolled patients who received at least one dose of study drug. This population was used for summarizing subject disposition, demographics, baseline disease characteristics and all efficacy analysis.

Study PCYC-1104-CA enrolled 115 subjects with relapsed or refractory MCL, 50 to bortezomib-exposed cohort and 65 to bortezomib-naïve cohort, from 18 sites in US and EU. Four subjects (two from each cohort) never received study drug and were excluded from all treated population.

Subject disposition

In study PCYC-1104-CA, at the time of study cutoff of 26 December 2012, 46 of 111 subjects remained on treatment in the study (Table 2). The most common reason for discontinuation was disease progression (44.1% for all patients). The second most common reason for treatment discontinuation was adverse event (8.1% for all patients).

TABLE 2: SUBJECT DISPOSITION, ALL TREATED POPULATION

	Bortezomib-naïve N=63 n (%)	**Bortezomib-exposed N=48 n (%)**	**Total N=111 n (%)**
Subject still on treatment	24 (38.1)	22 (45.8)	46 (41.4)
Subject discontinued study treatments	39 (61.9)	26 (54.2)	65 (58.6)
Primary reason for treatment discontinuation			
Disease progression	32 (50.8)	17 (35.4)	49 (44.1)
Adverse event	4 (6.3)	5 (10.4)	9 (8.1)
Withdrew consent	2 (3.2)	2 (4.2)	4 (3.6)
Physician's decision	1 (1.6)	2 (4.2)	3 (2.7)

[Source: study PCYC-1104-CA CSR Pages 38 Table 1]

Subject demographics and baseline disease characteristics

Demographics and baseline characteristics for study PCYC-1104-CA are summarized in Table 3. Most subjects were ≥ 65 years old (63.1%), male (76.6%) and White (91.9%).

Baseline disease characteristics for study PCYC-1104-CA are summarized in Table 4.

TABLE 3: DEMOGRAPHICS AND BASELINE CHARACTERISTICS, ALL TREATED POPULATION

	Bortezomib-naïve N=63	**Bortezomib-exposed N=48**	**Total N=111**
Age (years)			
Mean (SD)	66.9 (8.6)	67.4 (8.6)	67.1 (8.6)
Median (Min, Max)	66 (46, 83)	69 (40, 84)	68 (40, 84)
Category, n (%)			
< 65	25 (39.7)	16 (33.3)	41 (36.9)
≥ 65	38 (60.3)	32 (66.7)	70 (63.1)
Sex, n (%)			
Male	46 (73.0)	39 (81.3)	85 (76.6)
Female	17 (27.0)	9 (18.8)	26 (23.4)
Race, n (%)			
White	60 (95.2)	42 (87.5)	102 (91.9)
Black or Africa American	2 (3.2)	3 (6.3)	5 (4.5)
Other	1 (1.6)	3 (6.3)	4 (3.6)
ECOG performance Status, n (%)			
0	28 (44.4)	23 (47.9)	51 (45.9)
1	25 (39.7)	23 (47.9)	48 (43.2)
≥ 2	10 (15.9)	2 (4.2)	12 (10.8)

SD: standard deviation; ECOG: Eastern Cooperative Oncology Group
[Source: Study PCYC-1104-CA CSR Page 39 Table 3 and statistical reviewer's analysis]

TABLE 4: BASELINE DISEASE CHARACTERISTICS, ALL TREATED POPULATION

	Bortezomib-naïve N=63	**Bortezomib-exposed N=48**	**Total N=111**
Time from diagnosis to first dose (Months)			
Mean (SD)	45.8 (45.5)	59.2 (39.6)	51.6 (43.4)
Median (Min, Max)	29.0 (2.5, 213.2)	48.3 (6.6, 223.3)	42.4 (2.5, 223.3)
Tumor bulk (largest diameter), n (%)			
< 5 cm	37 (58.7)	31 (64.6%)	68 (61.3%)
≥ 5 cm	26 (41.3)	17 (35.4%)	43 (38.7%)
≥ 10 cm	6 (9.5)	3 (6.3%)	9 (8.1%)
Simplified MIPI Score, n (%)			
Low risk (0-3)	9 (14.3)	6 (12.5)	15 (13.5)
Intermediate risk (4-5)	24 (38.1)	18 (37.5)	42 (37.8)
High risk (6-11)	30 (47.6)	24 (50.0)	54 (48.6)
Prior number of regimens			
Mean (SD)	2.6 (1.4)	3.3 (1.3)	2.9 (1.4)
Median (Min, Max)	2.0 (1.0, 5.0)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)
Category, n (%)			
< 3	32 (50.8)	18 (37.5)	50 (45.0)
≥ 3	31 (49.2)	30 (62.5)	61 (55.0)
Refractory disease, n (%)			
Yes	27 (42.9)	23 (47.9)	50 (45.0)
No	36 (57.1)	25 (52.1)	61 (55.0)
Advanced disease, n (%)			
Yes	49 (77.8)	31 (64.6)	80 (72.1)
No	14 (22.2)	17 (35.4)	31 (27.9)

	Bortezomib-naïve N=63	Bortezomib-exposed N=48	Total N=111
Blastoid histology, n (%)			
Yes	10 (15.9)	7 (14.6)	17 (15.3)
No	53 (84.1)	41 (85.4)	94 (84.7)
Prior high intensity therapy, n (%)			
Yes	23 (36.5)	16 (33.3)	39 (35.1)
No	40 (63.5)	32 (66.7)	72 (64.9)
Prior lenalidomide therapy, n (%)			
Yes	9 (14.3)	18 (37.5)	27 (24.3)
No	54 (85.7)	30 (62.5)	84 (75.7)
Prior stem cell transplant, n (%)			
Yes	8 (12.7)	4 (8.3)	12 (10.8)
No	55 (87.3)	44 (91.7)	99 (89.2)

SD: standard deviation;
[Source: Study PCYC-1104-CA CSR Page 40 – 43 Tables 4, 5 and 8 and statistical reviewer's analysis]

Protocol deviation

In study PCYC-1104-CA, a total of 12 subjects [10.8%] had major protocol deviations defined in the study protocol.

TABLE 5: SUBJECTS WITH MAJOR PROTOCOL DEVIATIONS, ALL TREATED POPULATION

	Bortezomib-naïve N=63 n (%)	Bortezomib-exposed N=48 n (%)	Total N=111 n (%)
Subjects with at least 1 major protocol violation	9 (14.3)	3 (6.3)	12 (10.8)
Violated inclusion/exclusion criteria	7 (11.1)	2 (4.2)	9 (8.1)
Other	2 (3.2)	1 (2.1)	3 (2.7)

[Source: Study PCYC-1104-CA CSR Page 45 Table 10]

3.2.4 Results and Conclusions

3.2.4.1 Results of Overall response

ORR per investigator was used to evaluating efficacy. Based on FDA analysis, ORR per investigator was 65.8% with median duration of response of 17.5 months for all patients (Table 6). The applicant reported an ORR of 67.6% (95% CI: 58.0% – 76.1%) with the same duration of response as calculated by FDA. Results of ORR per IRC are summarized in Table 7. Results of ORR per investigator and per IRC are consistent.

Reviewer's comment: The number of CR derived by the FDA reviewers based on investigator assessment was 4 less and the number of the overall response (CR+PR) was 2 less than those derived by the applicant.

TABLE 6: RESULTS OF ORR PER INVESTIGATOR, ALL TREATED POPULATION

	Bortezomib-naïve N=63 n (%)	**Bortezomib-exposed N=48 n (%)**	**Total N=111 n (%)**
Overall response rate (CR + PR), n (%)	42 (66.7)	31 (64.6)	73 (65.8)
Complete response (CR), n (%)	10 (15.9)	9 (18.8)	19 (17.1)
Partial Response (PR), n (%)	32 (50.8)	22 (45.8)	54 (48.7)
95% CI for ORR (%)	(53.7, 78.1)	(49.5, 77.8)	(56.2, 74.5)
Duration of response (DOR)	N=42	N=31	N=73
Number of subjects progressed or died, n (%)	17 (40.5)	6 (19.4)	23 (31.5)
Median DOR (Months) (95% CI)	15.8 (5.6, NE)	NE	17.5 (15.8, NE)

CI: confidence interval; NE: not evaluable.
[Source: Statistical reviewer's analysis]

TABLE 7: RESULTS OF ORR PER IRC, ALL TREATED POPULATION

	Bortezomib-naïve N=63 n (%)	**Bortezomib-exposed N=48 n (%)**	**Total N=111 n (%)**
Overall response rate (CR + PR), n (%)	45 (71.4)	31 (64.6)	76 (68.5)
Complete response (CR), n (%)	12 (19.0)	11 (22.9)	23 (20.7)
Partial Response (PR), n (%)	33 (52.4)	20 (41.7)	53 (47.8)
95% CI for ORR (%)	(58.7, 82.1)	(49.5, 77.8)	(59.0, 77.0)
Duration of response (DOR)			
Number of subjects progressed or died, n (%)	15 (33.3)	8 (25.8)	23 (30.2)
Median DOR (Months) (95% CI)	NE (7.1, NE)	19.6 (NE, NE)	19.6 (NE, NE)

CI: confidence interval; NE: not evaluable.
[Source: Statistical reviewer's analysis]

3.2.4.2 Analysis results for other efficacy endpoints

The analysis results of time to response (TTR), PFS and OS endpoints are summarized (Table 8).

Reviewer's comment: Other efficacy endpoints analyses presented in Table 8 are exploratory because PFS and OS analysis are not interpretable in single-arm study and TTR analysis is based on responders only.

TABLE 8: SUMMARY OF OTHER EFFICACY ENDPOINTS, ALL TREATED POPULATION

Endpoints	statistic	Bortezomib-naïve N=63 n (%)	Bortezomib-exposed N=48 n (%)	Total N=111 n (%)
PFS (Months)				
	Number (%) of subjects censored	27	27	54
	Number of subjects progressed/died	36	21	57
	Median (95% CI)	7.4 (5.3, 19.2)	16.6 (8.3, NE)	13.9 (7.0, NE)
TTR (Months)				
	Number of responders	42	31	73
	Mean (SD)	2.5 (1.9)	2.5 (2.3)	2.5 (2.0)
	Median (Min, Max)	1.9 (1.4, 11.1)	1.8 (1.6, 13.7)	1.9 (1.4, 13.7)
OS (Months)				
	Number (%) of subjects censored	39	31	70
	Number of subjects died	24	17	41
	Median (95% CI)	NE (10.0, NE)	NE (11.9, NE)	NE (13.2, NE)

PFS: progression-free survival; TTR: time to response; OS: overall survival; CI: confidence interval; SD: standard deviation; NE: not evaluable.
[Source: Study PCYC-1104-CA CSR Page 66 Table 21, Page 64 Table 20, Page 68 Table 23, and Statistical reviewer's analysis]

3.2.4.3 Conclusions for efficacy

Study PCYC-1104-CA demonstrated durable treatment benefit of ibrutinib for patients with relapsed and/or refractory mantle cell lymphoma.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.4 Benefit-risk assessment

Since the pivotal study supporting this NDA original-1 application was single-arm study, the benefit/risk can not be assessed based on comparative analyses. Whether the submission demonstrated an overall favorable risk-benefit profile on ibrutinib is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race and Region

Table 9 summarizes the subgroup analyses of overall response rate by gender, age and region for the study PCYC-1104-CA. The ORR results by subgroups of gender, age and region are consistent with the ORR results for all patients.

TABLE 9: ORR PER INVESTIGATOR – SUBGROUP ANALYSES BY GENDER, AGE, AND REGION, ALL TREATED POPULATION

Subgroup	Bortezomib-naïve N=63 r/n (%)	Bortezomib-exposed N=48 r/n (%)	Total N=111 r/n (%) (95% CI (%))
Gender			
Male	33/46 (71.7)	26/39 (66.7)	59/85 (69.4) (58.5, 79.0)
Female	9/17 (52.9)	5/9 (55.6)	14/26 (53.9) (33.4, 73.4)
Age			
< 65 yrs	15/25 (60.0)	12/16 (75.0)	27/41 (65.9) (49.4, 80.0)
≥ 65 yrs	27/38 (71.1)	19/32 (59.4)	46/70 (65.7) (53.4, 76.7)
Region			
USA	23/36 (63.9)	26/42 (61.9)	49/78 (62.8) (51.1, 73.5)
EU	19/27 (70.4)	5/6 (83.3)	24/33 (72.7) (54.5, 86.7)

r: number of response, n: number of subjects in a subgroup; CI: confidence interval.
[Source: Statistical reviewer's analysis]

Reviewer's comments:

- Most patients (92%) in Study PCYC-1104-CA were White. Therefore, subgroup analyses of ORR by race were not performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The study PCYC-1104-CA was a single-arm study, no comparative evaluation of treatment effect of ibrutinib can be performed.

5.2 Collective evidence

Based on the overall response data from Study PCYC-1104-CA, ibrutinib provided durable treatment effect for patients with relapsed or refractory mantle cell lymphoma. However, because study PCYC-1104-CA was a single-arm study, the treatment effects of ibrutinib can only be descriptively summarized.

5.3 Conclusions and Recommendations

This NDA original-1 application was based on one pivotal multicenter Phase II studies (PCYC-1104-CA) to evaluate the treatment effect of ibrutinib for patients with relapsed/refractory MCL.

Study PCYC-1104-CA demonstrated durable overall response benefit of ibrutinib for relapsed or refractory mantle cell lymphoma patients who received at least one prior regimen. The final decision on the benefit-risk evaluation of ibrutinib is deferred to the clinical review team.

5.4 Labeling recommendations

Reviewer's comment:

- Overall response results by subgroups should not be included in the labeling.
- In single-arm study, time-to-event endpoints are not interpretable. Only descriptive results of DOR can be included in labeling.

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/s/

YUN WANG
10/28/2013

LEI NIE
10/28/2013

RAJESHWARI SRIDHARA
10/28/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205552 **Applicant:** Pharmacyclics **Stamp Date: May 31, 2013**

Drug Name: Ibrutinib **NDA/BLA Type:** 505(b)(1)

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.

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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	This NDA is based on single-arm trials with ORR as the primary endpoints. Any subject dropped out without response will be treated as non-responders. No investigation of effect of dropouts on statistical analysis will be performed.

Comment:

Yun Wang **August 6, 2013**

Reviewing Statistician Date

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA

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/s/

YUN WANG
08/14/2013

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