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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: BLA 205858

Supplement #: 0

Drug Name: Zydelig™ (Idelalisib, CAL-101)

Indication(s): Patients with Indolent B-Cell Non-Hodgkin Lymphoma Refractory to Rituximab and Alkylating Agents

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1 EXECUTIVE SUMMARY

This review is to provide statistical evaluation of an original NDA submission seeking the approval of Idelalisib in subjects with previously treated Indolent B-Cell Non-Hodgkin Lymphomas. The submission consists of the results of a phase 2 study, GS-1101-09, for oral therapy of Idelalisib (IDELA (CAL-101)).

GS-1101-09 is an ongoing Phase 2, single-arm, study of Idelalisib in subjects with previously treated Indolent B-Cell Non-Hodgkin Lymphomas (iNHL), refractory to both rituximab and alkylating agent containing therapy. The starting dose was Idelalisib 150 mg twice per day (BID) and the treatment was continued until tumor progression or unacceptable toxicity. The study was conducted by North American (59% patients from US) and European investigators. The primary objective of this study was to evaluate tumor regression as determined by objective response rate (ORR) by Independent Review Committees (IRC); the secondary objectives were to determine duration of response, lymph node response rate, time to response, progression-free survival, and overall survival.

GS-1101-09 was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

The observed primary endpoint of objective response rate (ORR) assessed by IRC was 54.4%, 68 patients out of 125 treated patients had responses (intent-to-treat (ITT)) with 95% CI of (45.3, 63.3). However, the complete response (CR) was observed only 7 patients (5.6%) and partial response in 61 patients (48.8%). The median duration of objective response rate assessed by IRC was 12.5 months with a lower bound of 95% CI of 6.5 months. However, 5 patients' durations of objective response (OR) were less than 1 month, cumulatively, 52.9 % patients' duration of OR were less than 6 months. There were 23 patients (33.8%) who had progressive disease or death among 68 patients who achieved ORR.

A breakdown of the four disease categories among 125 iNHL patients were follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM), and marginal zone lymphoma (MZL). The number of subjects enrolled with FL, SLL, LPL/WM, and MZL were 72 (57.6%), 28 (22.4%), 15 (12.0%), and 10 (8.0%), respectively. The FDA excluded 2 SLL patients. The number of SLL patients was 26 patients. (b) (4)

The ORRs for FL and SLL were 54.2% and 57.7%, respectively. The median ORR duration for FL was not reached with a lower bound of 95 % CI of 4.5 months. The median ORR duration for SLL was 11.9 months with 95% CI of (3.7, 14.7). The ORRs for FL and SLL were consistent to the overall ORR observed in the study. However, these subgroup analyses were post-hoc analyses. There were no pre-planned sample size calculations in order to rule out certain lower percentage of responses in the subgroup disease categories.

Based on the observed objective response rates and durations of median objective response rate of study GS-1101-09, it may be reasonably likely to predict that Idelalisib has clinical benefit in

patients with previously treated FL and SLL, refractory to both rituximab and alkylating agent containing therapy.

2 INTRODUCTION

2.1 Overview

Idelalisib is a targeted selective competitive inhibitor of the adenosine triphosphate binding site of the phosphatidylinositol 3-kinase (PI3K) p110 δ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin.

Indolent non-Hodgkin lymphoma (iNHL) is a subtype of NHL that is slowly progressive over time. Among the indolent non-Hodgkin lymphoma (iNHL) subtypes, B-cell iNHL subtypes are follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM), and marginal zone lymphoma (MZL). Overall, the 5-year relative survival rate for patients with NHL is 63%. Current treatment options include radiotherapy, chemotherapy, combined radiotherapy, and chemotherapy, rituximab either alone or in combination with chemotherapy, radioimmunotherapy, and hematopoietic stem cell transplantation. Although some patients are cured with current treatment modalities, the majority of B-cell NHL patients will eventually relapse and require additional treatments.

Study GS-1101-09 was sponsored by Gilead Sciences, Inc. (Seattle, WA). This trial was conducted in North America (59% patients from US) and Europe.

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The dose was administered 150 mg BID orally until disease toxicity or unacceptable toxicity. Subjects were followed at 2-week intervals through the first 12 weeks of treatment, at 4-week intervals from 12 to 24 weeks of treatment, at 6-week intervals from 24 to 48 weeks of treatment, and at 12-week intervals thereafter for efficacy assessment.

The primary objective of this study was to determine the ORR by both the investigators and the independent review committees (IRC). Secondary objectives included determination of the duration of response (DOR), lymph node response rate, changes in tumor size, time to response (TTR), progression-free survival (PFS), and overall survival (OS).

Table 1 : List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
<i>Study 101-09</i>	<i>Phase 2</i>	<i>Until progression</i>		<i>125</i>	<i>B-cell iNHL</i>

The indication that applicant proposed was for the treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL).

2.2 Data Sources

The study report and data were provided electronically; the location/names of study report, analysis datasets (ADAM) including SDTM datasets and SAS programs are as follows;

Study Reports:

<\\CDSESUB1\evsprod\NDA205858\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\fl-sll-lpl-mzl\5352-stud-rep-uncontr\101-09>

Dataset;

<\\CDSESUB1\evsprod\NDA205858\0000\m5\datasets\101-09\analysis\adam\datasets>

Program;

<\\CDSESUB1\evsprod\NDA205858\0000\m5\datasets\101-09\analysis\adam\programs>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer was able to reproduce the primary analysis dataset, and in particular the primary endpoint, from the original data source. The sponsor provided SDTM and ADAM datasets.

3.2 Evaluation of Efficacy

Study 101-09 evaluated the efficacy of Idelalisib for the treatment in subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents.

3.2.1 Study Design and Endpoints

Study 101-09 is an ongoing Phase 2, single-arm, efficacy, safety, PK, and pharmacodynamic study of Idelalisib in the treatment of patients with previously treated iNHL that was refractory both to rituximab and to alkylating-agent-containing chemotherapy. Patients included with histologically confirmed diagnosis of B-cell iNHL (FL, SLL, MZL, and LPL/WM), radiographically measurable lymphadenopathy or extranodal lymphoid malignancy, and lymphoma that was refractory to rituximab and to an alkylating agent with definition as lack of response to, or progression within 6 months of completion of therapy were included in the trial. The study was conducted at a total of 54 study sites in North America and Europe. Patients were to receive oral Idelalisib 150 mg BID until tumor progression or unacceptable toxicity.

The primary endpoint was objective response rate (ORR) assessed by an independent review committee (IRC). The secondary endpoints were duration of response (DOR), lymph node response rate, changes in tumor size, time to response (TTR), progression-free survival (PFS),

and overall survival (OS). Responses were assessed by both the investigator and an independent review committee (IRC).

The IRC included four primary independent board-certified radiologists who evaluated the radiographic images in two reader pairs, a board-certified adjudicating radiologist who resolved any differences between readers, and two independent board-certified oncologists. The radiologists' findings, along with prospectively defined clinical data for each subject (including bone marrow examinations and lymph node or other tissue biopsies), were then reviewed by a board-certified oncologist. A final assessment was based on the combined input of the radiology and clinical review.

Tumor response was evaluated at baseline, 8, 16, and 24 weeks of therapy, and every 12 weeks thereafter according to standard criteria. Long-term post-treatment follow-up is being obtained for all subjects, including those who prematurely withdrew from study treatment at approximately 6-month interval up to year 2 and at approximately 12-month interval up to year 5.

3.2.2 Statistical Methodologies

Sample Size Determination

The planned sample size of 100 patients was calculated assuming null hypothesis, IRC-reviewed ORR of $\leq 20\%$ and alternative hypothesis of $\geq 39\%$ (~ 40%). Simon's optimal 2-stage design was used enrolling 31 patients in the Stage 1. If ≥ 9 patients had a tumor response in the stage 1, then the study was to continue and enroll additional 69 patients. A planned sample size of 100 provides more than 90% power with a 1-sided significance level of < 0.005 . The enrollment period was planned within 15 months and the follow-up period was planned over 6 months. The primary efficacy analysis was performed approximately 8 months after the last subject was enrolled.

Statistical Methodology

The primary analysis population set included all patients who were enrolled and received at least 1 dose in the study. This primary analysis population set was to be used for the efficacy endpoints analyses except lymph node response rate (LNR). LNR was analyzed based on the primary analysis population who had both baseline and at least one evaluable post-baseline tumor assessment.

The objective response rate (ORR) was defined as the proportion of patients with complete response (CR) or partial response (PR). The ORR per IRC and its two-sided 95% exact confidence interval were calculated using the exact binomial distribution method.

The DOR was defined as the interval from the first documentation of CR or PR (or minor response (MR) for subjects with WM) to the earlier of the first documentation of progression of disease (PD) or death from any cause, whichever comes first.

The LNR was defined as the proportion of subjects who achieved a $\geq 50\%$ decrease from baseline in the sum of the product of the perpendicular diameters of measurable index lesions (SPD) of index lymph nodes.

The TTR was defined as the interval from the start of Idelalisib treatment to the first documentation of CR or PR (or MR for subjects with WM).

The PFS was defined as the interval from the start of Idelalisib treatment to the earlier of the first documentation of PD or death from any cause.

Missing Data and Outliers

The missing data were not imputed unless methods for handling missing data were specified. No data were excluded from the analyses, including any outliers. If there is a significant degree of non-normality for a continuous endpoint, analysis may be performed on log-transformed data or using nonparametric methods, as appropriate.

If laboratory data are less than the lower limit of quantitation, then a value will be imputed 1 unit less than the limit of quantitation (e.g., <50 to 49) and if it is above the upper limit of quantitation, then a value will be imputed 1 unit above the limit of quantitation (e.g., >50 to 51) for the calculation of descriptive statistics.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

One hundred and twenty five patients are currently enrolled in the study. In Stage 1, 31 patients (15 follicular lymphoma, 11 small lymphocytic lymphoma, 4 lymphoplasmacytoid lymphoma, and 1 marginal zone lymphoma) were enrolled and completed 16-week tumor assessment. The investigator-assessed objective response rate reached the pre-defined interim analysis criterion to continue Stage 2. An additional 94 patients were enrolled in Stage 2.

The first patient's screened date and the last patient's screened date were April 26, 2011, and October 12, 2012, respectively. The data cutoff date was June 25, 2013.

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The patient disposition for all 125 patients (ITT population) is summarized in Table 2.

Table 2 : Population Disposition

Disposition	N=125 n (%)
Treatment Ongoing	40 (32.0)
Treatment Completed	49 (39.2)
Due to Disease Progression	41 (32.8)
Due to Death	8 (6.4)
Treatment Discontinued	36 (28.8)
Adverse Events	25 (20.0)
Withdrew Consent	4 (3.2)
Investigator Request	7 (5.6)

Subject disposition on long-term follow-up is summarized in Table 3.

Table 3 : Population Disposition for Long-term Follow-up

Long-term follow-up	ITT population (N=125) n (%)
Entered long-term follow-up	59 (47.2)
Ongoing	42 (33.6)
Discontinued	17 (13.6)
Withdrew Consent	1 (0.8)
Death	16 (12.8)
Other	1 (0.8)
Completed 6-month	38 (30.4)
Completed 12-month	11 (8.8)

A total of 6 protocol deviations had occurred at the cutoff data date, June 25, 2012. For 3 patients' severe adverse events (SAE) were not reported within 24 hours, 2 subjects' blood samples were drawn before the signing of consent, and one patient did not receive 2 cycles of bendamustine as required by the protocol to meet the alkylating agent refractory criteria. The per-protocol population included 119 patients after excluding 6 patients with protocol deviation.

The efficacy analyses were based on all 125 enrolled patients (ITT population). Patients demographic and baseline characteristics are summarized with all 125 patients in Table 4.

Table 4 : Demographic and Baseline Characteristics

	N=125 n (%)
Age (years)	
Mean (SD)*	62 (11.4)
Median (Min, Max)	64 (33, 87)
<65	69 (55.2)
≥65	56 (44.8)
Race	
White/Caucasian	110 (88.7)
Asian	3 (2.4)
Black	2 (1.6)
American Indian	1 (0.8)
Other	8 (6.5)
Missing	1 (0.8)
Gender	
Male	80 (64.0)
Female	45 (36.0)
BMI (kg/m ²)	N=124
Median (Min, Max)*	25.9 (17.2, 51.1)
LDH (U/L)	N=121
≤ ULN (Normal)	83 (66.4)
>ULN (Abnormal)	38 (30.4)
Hemoglobin (g/L)	
≥LLN (125)	61 (48.8)
100 - <LLN (Grade 1)	45 (36.0)
80- <100 (Grade 2)	18 (14.4)
< 80 (≥ Grade 3)	1 (0.8)
Platelets (x10 ⁹ /L)	
≥LLN (130)	82 (65.6)
75 - <LLN (Grade 1)	33 (26.4)
50 - <75 (Grade 2)	6 (4.8)
25 - <50 (Grade 3)	3 (2.4)
<25 (Grade 4)	1 (0.8)
Neutrophils(x10 ⁹ /L)	N=124
≥LLN (1.96)	94 (75.2)
1.5 - <LLN (Grade 1)	13 (10.4)
1.0 - <1.5 (Grade 2)	11 (8.8)
0.5 - <1.0 (Grade 3)	6 (4.8)
<0.5 (Grade 4)	1 (0.8)
Lymphocytes(x10 ⁹ /L)	N=124
≥LLN (1.96)	65 (52.0)
0.8 - <LLN (Grade 1)	6 (4.8)
0.5 - <0.8 (Grade 2)	30 (24.0)
0.2 - <0.5 (Grade 3)	20 (16.0)
<0.2 (Grade 4)	3 (2.4)
Missing	1 (0.8)

*: Mean (SD) : mean and standard deviation.

The median age was 64 years with range of 33 and 87. The majority of patients were White (88.7%), female (64.0%), with baseline LDH normal levels (66.4%), hemoglobin level \geq LLN (48.8%), platelets level \geq LLN (65.6%) and Neutrophils($\times 10^9/L$) \geq LLN (75.2%). Half of patients had Lymphocytes($\times 10^9/L$) \geq LLN (52%).

The disease history at baseline is summarized in Table 5.

Table 5 : Disease History

	ITT population (N=125)
FL, n (%)	72 (57.6)
Grade 1	21/72 (29.2)
Grade 2	39/72 (54.2)
Grade 3	12/72 (16.7)
Current FL Prognostic Index score, n (%)	
Low (≤ 1)	15/72 (20.8)
Intermediate (2)	18/72 (25.0)
High (≥ 3)	39/72 (54.2)
SLL, n (%)	28 (22.4)
LPL/WM, n (%)	10 (8.0)
MZL, n (%)	15 (12.0)
Splenic	1/15 (6.7)
Nodal	5/15 (33.3)
Extranodal	9/15 (60.0)
Time since initial diagnosis (years)	
Median (Min, Max)	5.3 (0.4, 18.4)
Ann Arbor Stage at Diagnosis, n (%)	
I	8 (6.4)
II	5 (4.0)
III	21 (16.8)
IV	87 (69.6)
Missing	4 (3.2)

The patient's prior therapy is summarized in Table 6.

Table 6 : Prior Therapy

	ITT population (N=125)
No. of prior regimens (N=125)	
Median (Min, Max)	4 (2, 12)
No. of treated, n, (%)	
2 regimen	33 (26.4)
3 regimen	19 (15.2)
4 regimen	30 (24.0)
5 regimen	18 (14.4)
≥ 6 regimen	25 (20.0)
No. of refractory	
1 regimen	26 (20.8)
2 regimen	64 (51.2)
3 regimen	22 (17.6)
≥ 4 regimen	13 (10.4)
Prior therapy, n, (%)	
Rituximab	125 (100)
Cyclophosphamide	111 (88.8)
Anthracycline	80 (64.0)
Purine Analog	42 (33.6)
Bendamustine	81 (64.8)
Refractory to Bendamustine	61 (75.3)
Prior radiation therapy, n (%)	36 (28.8)
Prior autologous stem cell transplant, n (%)	14 (11.2)
Bulky Disease, n (%)	
Tumor Diameter <7	92 (73.6)
Tumor Diameter ≥7	33 (26.4)
Kanorfsky performance score	
Mean (SD)	90.1 (9.6)
ECOG score, n (%)	
0	56 (44.8)
1	45 (36.0)
2	6 (4.8)
Missing	18 (14.4)

The median number of prior regimens received was 4; 58.4% of patients were treated with 4 or more prior regimens. Among alkylating agents, 88.8% patients had received cyclophosphamide; 64.8% patients had received bendamustine. A total of 36 subjects (28.8%) had been treated with radiation at some point prior to the study. Fourteen subjects (11.2%) had received an autologous stem cell transplantation. The patient with tumor diameter <7cm was 73.6%. The mean Karnofsky score was 90.1. The patient with ECOG score of 0 was 52.3%.

Reviewer's comment:

Based on Bendamustine labeling, while in Study 101-09, 99% of enrolled subjects were refractory to an alkylator, but in the Bendamustine trial, (b) (4) were refractory to an alkylator; In Study 101-09, 90% of enrolled subjects were refractory to last therapy, and in the Bendamustine trial, (b) (4) were refractory to the last therapy. Subjects enrolled in Study 101-09 appear to have more refractory disease.

3.2.4 Results and Conclusions

Primary Endpoint:

The primary efficacy analysis was the ORR (Cheson 2007) as assessed by IRC based on ITT population (125 patients). The FDA's primary endpoint results assessed by IRC and investigators are summarized in Table 7.

Table 7 : FDA's Primary Endpoint Results of ORR Assessed by IRC and Investigator

	ITT Population (N=125)	
	IRC n (%)	Investigator n (%)
Objective Response (ORR)	68 (54.4)	69 (55.2)
CR	7 (5.6)	7 (5.6)
PR	61 (48.8)	62 (49.6)
Exact 95% CI for ORR	(45.3, 63.3)	(46.1, 64.1)

The FDA analysis of primary endpoint of objective response rate assessed by IRC was 54.4% (68 patients out of 125 ITT patients) with a 95% CI of (45.3, 63.3) after excluding one MR with WM patient and two PR SLL patients who did not meet the inclusion criteria. The complete response rate was 5.6% (7 patients); partial response rate was 48.8% (61 patients). The FDA's ORR assessed by investigator was 55.2% (69 patients) with a 95% CI of (46.1, 64.1). The complete response rate was 5.6% (7 patients); partial response rate was 49.6% (62 patients).

Reviewer's comments:

- *The applicant's results are largely consistent with FDA's. The applicant's reported results are as follows; A total of 71 patients out of 125 ITT patients (56.8%) had objective responses by IRC assessment with 95% CI of (47.6, 65.6) in the applicant's results. The complete response rate was 5.6% (7 patients); partial response rate was 51.2% (64 patients). One patient in the WM had one MR. The ORR assessed by investigator was 57.6% with 95% CI of (48.4, 66.4) and CR was the same with 5.6%.*

- Bendamustine was approved for the iNHL indication with 74% ORR and with 13% CR. The median duration of response was 9.2 months.

The applicant’s results for best overall responses assessed by IRC are summarized in Table 8.

Table 8 : Applicant’s Best Overall Responses by IRC assessment

	ITT Population (N=125)
Best Response	
Complete Response (CR)	7 (5.6)
Partial response (PR)	63 (50.4)
MR for subjects with WM	1 (0.8)
PD (progressive Disease(PD))	10 (8.0)
Stable Disease (SD)	42 (33.6)
Not Evaluable (NE)	2 (1.6)

Reviewer’s comment:

This reviewer examined the concordance between the IRC assessment and investigators assessment of applicant’s best overall responses. The results are as follow;

Best Overall Responses Difference between IRC and Investigators

Best ORR by investigator	Best ORR by IRC						
	CR	PR	MR	PD	SD	NE	Total
CR	6	1	0	0	0	0	7
PR	1	53	0	1	9	0	64
MR	0	0	1	0	0	0	1
PD	0	0	0	8	2	1	11
SD	0	9	0	1	31	0	41
NE	0	0	0	0	0	1	1
Total	7	63	1	10	42	2	125

The exact concordance rate between investigators and IRC was 80%, (100 out of 125 patients). Fifty nine patients (47.2%) observed the same CR or PR between the IRC and investigators assessments based on 125 ITT populations.

Secondary Endpoint Results

The secondary endpoints were duration of response (DOR), lymph node response rate, changes in tumor size, time to response (TTR), progression-free survival (PFS), and overall survival (OS).

The results for FDA’s duration of response are summarized in Table 9.

Table 9 : FDA Results for Duration of Response by IRC and Investigator assessments (ITT population)

	IRC Assessment (N=125)	Investigators Assessment (N=125)
No. of ORR, n (%)	68 (54.4)	69 (55.2)
No. of Events, n (%)	23 (33.8)	23 (33.3)
PD	20 (29.4)	21 (30.4)
Death	3 (4.4)	2 (2.9)
Duration of ORR (Months)		
Median	12.5	14.7
95% CI	(6.5, NA)	(7.3, NA)

NA: Not Applicable

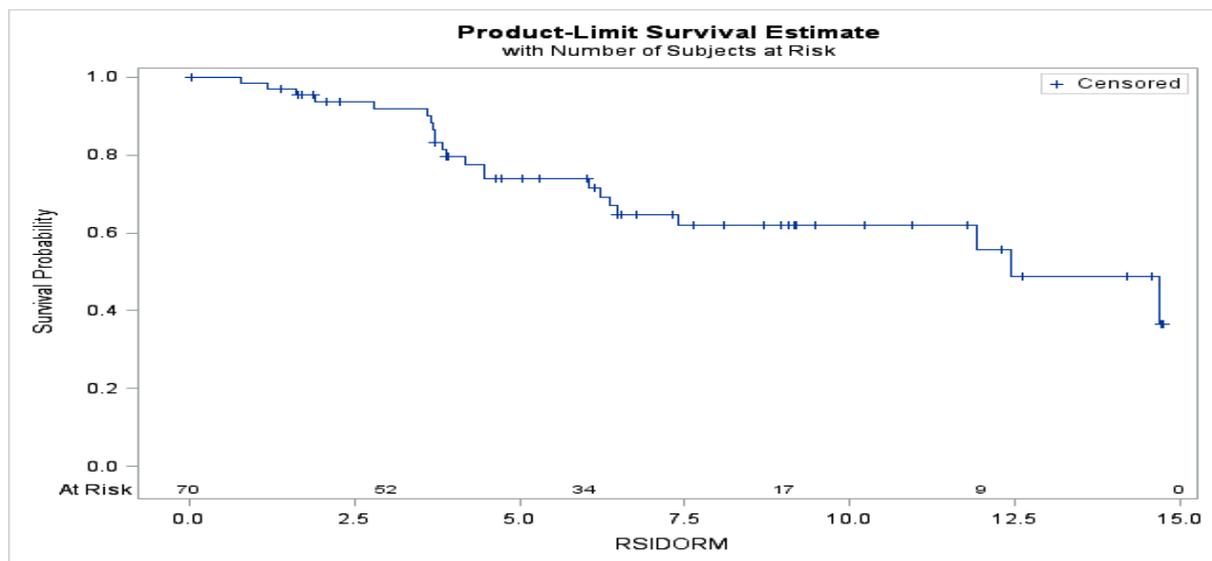
Among 68 observed OR patients by IRC assessment, 33.8% of them had events of progressive disease or death. The median durations of ORR assessed by IRC and by investigators were 12.5 and 14.7 months, respectively. The median duration of complete response assessed by IRC was not available.

Reviewer's comment:

The applicant's results are largely consistent with FDA's. The results are as follows; Among the applicant's results for 71 patients with OR by IRC assessment, 23 patients (32.4%) had progressive disease or death. The applicant's median duration of OR assessed by IRC was 12.5 months with 95% CI of (7.4, NA). The applicant's median duration assessed by investigators was 14.7 months with 95% CI of (7.3, NA).

Figure 1 shows the Kaplan-Meier curve for duration of objective responses based on FDA results.

Figure 1 : Kaplan-Meier Curve for Duration of Objective Responses Based on FDA Results



Reviewer's comment:

This reviewer noted that duration of OR for 5 patients was less than 1 month and for 53% of subjects was less than 6 months among 68 observed OR patients. The duration of responses among 68 patients are summarized below.

Months	≤ 1	$>1-\leq 3$	$>3-\leq 6$	$>6-\leq 9$	$>9-\leq 12$	>12
No. Patients (%)	5 (7.4%)	13 (19.1%)	18 (26.5%)	17 (25.0%)	6 (8.8%)	9 (13.2%)

Five patients' duration of responses (7.4%) were less than 1 month, cumulatively, 52.9 % patients' duration of responses were less than 6 months and cumulatively, 86.8% patients' duration of response were less than one year. Among 68 responding patients, 51.5% patients had duration of OR between 3 months and 9 months.

The applicant's results for lymph node response are summarized in Table 10.

Table 10: Applicant's Lymph node Responses

	IRC Assessment (N=125)	Investigators Assessment (N=125)
Baseline SPD (Sum of Area) Mean (SD), cm ²	41.1 (40.7)	62.2 (107.4)
Reduction from Baseline		
No. of $\geq 50\%$ SPD reduction, n (%)	67 (53.6)	71 (56.8)
95% CI	44.5, 62.3	47.6, 65.6
No. of any SPD reduction, n (%)	110 (88.0)	107 (85.6)
95% CI	81.0, 93.1	78.2, 91.2

Among 125 subjects, 110 subjects (88.0%) had improvement in lymphadenopathy and 67 subjects (53.6%) achieved a $\geq 50\%$ decrease from baseline in the SPD of index lesions by IRC assessment. Per investigator assessment, 107 subjects (85.6%) had improvement in lymphadenopathy and 71 subjects (56.8%) achieved a $\geq 50\%$ decrease from baseline in the SPD of index lesions.

The FDA's results for time to response are summarized in Table 11.

Table 11: FDA Analysis Results for Time to Response

	IRC Assessment (N=125)	Investigators Assessment (N=125)
No. of ORR, n (%)	68 (54.4)	69 (55.2)
Time to response (months)		
Mean (SD)	3 (1.7)	2.8 (1.9)
95% CI	2.6, 3.4	2.4, 3.2
Median (Min, Max)	1.9 (1.6, 8.3)	1.9 (1.6, 13.6)

The median time to response was 1.9 months for both IRC and investigators assessments.

Reviewer's comment:

The applicant's results were same as FDA results.

The results for applicant's progression free survival are summarized in Table 12.

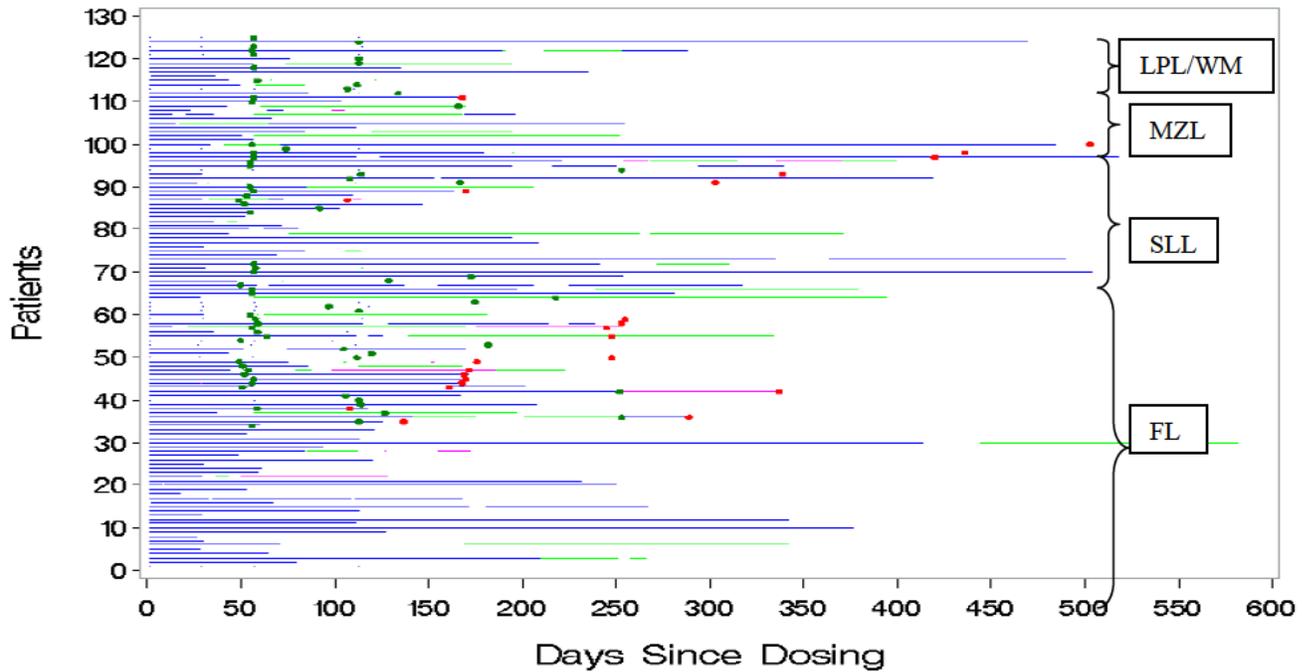
Table 12: Applicant's Results for Progression Free Survival

	IRC Assessment (N=125)	Investigators Assessment (N=125)
No. of Events, n (%)	57 (45.6)	56 (44.8)
PD	49 (39.2)	48 (38.4)
Death	8 (6.4)	8 (6.4)
Duration of PFS (Months)		
Median (95% CI)	11.0 (8.1, 13.8)	10.8 (8.3, 16.5)

Among 125 ITT patients, 57 patients (45.6%) had disease progression (by IRC assessment) (39.2%) or death (6.4%). Fifty six patients (44.8%) had disease progression or death by investigator assessments. The median PFS was 11 months for both IRC and Investigators assessment.

Reviewer's comment: Time to event endpoint results are not interpretable in single arm studies.

Figure 2 : Patient’s Time to response and duration of response by disease categories



Reviewer’s comment:

A description of Figure 2 is as follows;

All 125 patients’ drug exposure, time to response, and duration of response are presented by disease categories. Patient 1 to 72 are FL, patient 73 to 100 are SLL, patient 101 to 115 are MZL and patient 116 to 125 are LPL/WM.

A blue line represents 150 mg BID, the light green line represents 100 mg BID and the red line represents 75 mg BID. Approximately, 20% patients continued to be exposed to the drug after 6 months and approximately 10% patients were exposed to the drug for over 1 year.

A green dot represents time of response, and the red dot represents time of progression or death. The responses within 60 days were 56%, within 120 days were 83%, and within 180 days were 93%.

The applicant’s results for long-term follow-up overall survival are summarized in Table 13.

Table 13: Results of Long-Term Follow-up Overall Survival

	ITT Population (N=125)
No. of Events, n (%)	28 (22.4)
Duration of OS (Months)	
Median	20.3
95% CI	16.4, NA

There were a total of 28 deaths (22.4%) during the study long-term follow-up and the median duration of OS was 20.3 months with 95% CI of (16.4, NA).

Reviewer's comments:

There were 11 deaths (8.8%) within 30 days of the end of study date. As this is a single arm study, the results of progression-free survival and overall survival analyses are not interpretable in single arm studies. These results are exploratory analyses.

Conclusion for Efficacy Endpoints;

The FDA's efficacy results were largely consistent to the applicant's. The primary and secondary efficacy endpoints results showed reasonably acceptable results.

3.3 Evaluation of Safety

For a detailed summary of the evaluation of safety, refer to the reviews by Dr. Barry Miller and Dr. Donna Przepiorka.

3.4 Benefit-Risk Assessment

Treatment with Idelalisib 150 mg BID resulted in ORR assessed by IRC of 54.4%, but the observed CR rate was only 5.6%. The median duration of ORR was 12.5 months; time to OR was 1.9 months. Five patients' durations of OR were less than 1 month, cumulatively, 51.4% of patients' duration of OR were less than equal to 6 months. The lymph node response demonstrated the improvement of a $\geq 50\%$ decrease in SPD in 53.6% patients measured by index lesions by IRC assessment.

For the long-term follow-up for overall survival, 22% of patients had died and the median duration of long-term follow-up was 20.3 months.

Please refer to clinical reviews for a comprehensive assessment of Benefit-Risk.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The results from subgroup analyses should be interpreted with caution due to limited sample size.

4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses for age group (<65 years versus ≥65 years), gender, race, and region of the primary endpoint of ORR are summarized in Table 14.

Table 14: Subgroup Analyses of ORR: Age group, Gender, Race and Region

	N	ORR	
		n (%)	95% CI
Age			
<65	69	37 (53.6)	41.2, 65.7
≥65	56	31 (55.4)	41.5, 68.7
Gender			
Female	45	27 (60.0)	44.3, 74.3
Male	80	41 (51.3)	39.8, 62.6
Race			
White	110	59 (53.6)	43.9, 63.2
Other	14	8 (57.1)	28.9, 82.3
Missing	1	1	
Country			
US	83	46 (55.4)	44.1, 66.3
Non-US	42	22 (52.4)	36.4, 68.0

The primary endpoint of ORR was not different between Age <65 and Age ≥ 65 and between White and Others. The ORR was slightly higher for Female and for the US patients.

4.2 Other Special/Subgroup Populations

FDA's ORR analyses results are summarized by disease characteristics and prior therapy in Table 15.

Table 15: Subgroup Analyses ORR: Disease Characteristics and Prior Therapy

	N (%)	ORR	
		n (%)	95% CI
Disease subcategory			
FL	72 (57.6)	39 (54.2)	42.0, 66.0
SLL	28 (22.4)	15 (53.6)	33.9, 72.5
MZL	15 (12.0)	7 (46.7)	21.3, 73.4
LPL/WM	10 (8.0)	7 (70.0)	34.8, 93.3
ECOG			
0	56 (44.8)	31 (55.4)	41.5, 68.7
≥ 1	51 (40.8)	29 (56.9)	42.3, 70.7
Missing	18 (14.4)	8 (44.4)	21.5, 69.2
Prior Anthracycline			
Yes	80 (64.0)	41 (51.3)	39.8, 62.6
No	45 (36.0)	27 (60.0)	44.3, 74.3
Prior Purine Analog			
Yes	42 (33.6)	22 (52.4)	36.4, 68.0
No	83 (66.4)	46 (55.4)	44.1, 66.3
Prior Bendamustine			
Yes	81 (64.8)	45 (55.6)	44.1, 66.6
No	44 (35.3)	23 (52.3)	36.7, 67.5
Refractory to Bendamustine			
Yes	61 (48.8)	35 (57.4)	44.1, 70.0
No	20 (16.0)	10 (50.0)	27.2, 72.8
Prior therapy			
<4	52 (41.6)	25 (48.1)	34.0, 62.4
≥4	73 (58.4)	43 (58.9)	46.8, 70.3
Refractory to Rituximab			
≤2	101 (80.8)	52 (51.5)	41.3, 61.6
>2	24 (19.2)	16 (66.7)	44.7, 84.4
Refractory to Alkylating-agent			
<2	74 (59.2)	38 (51.4)	39.4, 63.2
≥2	51 (40.8)	30 (58.8)	44.2, 72.4
ACST Transplant			
Yes	14 (11.2)	10 (71.4)	41.9, 91.6
No	111 (88.8)	58 (52.3)	42.6, 61.8
Tumor diameter			
<7cm	92 (73.6)	50 (54.4)	43.6, 64.8
≥7cm	33 (26.4)	18 (54.6)	36.4, 71.9

Among iNHL patients enrolled, patients with FL, SLL, MZL, and LPL/WM were 57.6%, 22.4%, 12.0%, and 8%, respectively. The ORRs for FL and SLL were 54.2% and 53.6%, respectively,

and the ORRs were similar with the overall iNHL ORR. The ORR was best for LPL/WM (70%), but it was worst for MZL (46.7%). The sample size of each disease categories except FL was small. There was no pre-planned sample size calculation in order to rule out the certain lower percentage of responses in the subgroups.

The primary endpoint cannot be reliably estimated for the two subgroups, MZL and LPL/WM, which enrolled very few patients. [REDACTED] (b) (4)

[REDACTED] FL and SLL subgroup analyses for gender, gender, race and age group (<65 years versus \geq 65 years) of the primary endpoint of ORR are summarized in Table 16.

Reviewer's comment:

Two patients in the SLL who did not meet the SLL disease category were deleted by clinical reviewer. The total number of patients in the SLL was 26 patients instead of 28 patients.

Table 16: Subgroup Analyses for FL and SLL: Age, Gender, Race and Region

	N	ORR	
		n (%)	95% CI
FL	72 (57.6)	39 (54.2)	42.0, 66.0
Age			
<65	46 (63.9)	23 (50.0)	34.9, 65.1
≥65	26 (36.1)	16 (61.5)	40.6, 79.8
Gender			
Female	33 (45.8)	19 (57.6)	39.2, 74.5
Male	39 (54.2)	20 (51.3)	34.8, 67.6
Race			
White	64 (88.9)	34 (53.1)	40.2, 65.7
Other	7 (9.7)	4 (57.1)	18.4, 90.1
Missing	1 (1.4)	1 (100)	
Region			
US	44 (61.1)	22 (50.0)	34.6, 65.4
Non-US	28 (36.9)	17 (60.7)	40.6, 78.5
SLL	26 (20.8)	15 (57.7)	36.9, 76.7
Age			
<65	10 (38.5)	6 (60.0)	26.2, 87.8
≥65	16 (61.5)	9 (56.3)	29.9, 80.3
Race			
Female	7 (26.9)	6 (85.7)	42.1, 99.6
Male	19 (73.1)	9 (47.4)	24.5, 71.1
Race			
White	21 (80.8)	12 (57.1)	34.0, 78.2
Other	5 (19.2)	3 (60.0)	14.7, 94.7
Region			
US	20 (76.9)	14 (70.0)	45.7, 88.1
Non-US	6 (23.1)	1 (16.7)	0.4, 64.1

These subgroup analyses should be considered with caution due to limited sample size. For FL, the primary endpoint of ORR was slightly higher for Age ≥65, Female, Other, and Non-US. For SLL, ORR was slightly higher for Female and US. There was no difference between White and Other and between Age ≥ 65 and Age <65.

FL subgroup analyses results by prior therapy are summarized in Table 17.

Table 17: FL subgroup Analyses ORR: Disease Characteristics and Prior Therapy

	N (%)	ORR	
		n (%)	95% CI
FL	72 (57.6)	39 (54.2)	42.0, 66.0
ECOG			
0	35 (48.6)	20 (57.1)	39.4, 73.7
≥ 1	27 (37.5)	14 (51.9)	32.0, 71.3
Missing	10 (13.9)	5 (50.0)	18.7, 81.3
Prior Anthracycline			
Yes	51 (70.8)	27 (52.9)	38.5, 67.1
No	21 (29.2)	12 (57.1)	34.0, 78.2
Prior Purine Analog			
Yes	17 (33.6)	8 (47.1)	23.0, 72.2
No	55 (66.4)	31 (56.4)	42.3, 69.7
Prior Bendamustine			
Yes	50 (69.4)	27 (54.0)	39.3, 68.2
No	22 (30.6)	12 (54.6)	32.2, 75.6
Refractory to Bendamustine			
Yes	32 (44.4)	18 (56.3)	37.7, 73.6
No	18 (25.0)	9 (50.0)	26.0, 74.0
Prior therapy			
<4	30 (41.7)	14 (46.7)	28.3, 65.7
≥4	42 (58.3)	25 (59.5)	43.3, 74.4
Refractory to Rituximab			
≤2	59 (81.9)	30 (50.9)	37.5, 64.1
>2	13 (18.1)	9 (69.2)	38.6, 90.9
Refractory to Alkylating-agent			
<2	49 (68.1)	26 (53.1)	38.3, 67.5
≥2	23 (31.9)	10 (43.5)	34.5, 76.8
ACST Transplant			
Yes	12 (16.7)	9 (75.0)	42.8, 94.5
No	60 (83.3)	30 (50.0)	36.8, 63.2
Tumor diameter			
<7cm	56 (77.8)	31 (55.4)	41.5, 68.7
≥7cm	16 (22.2)	8 (50.0)	24.7, 75.4

FL subgroup analyses results by prior therapy were consistent to the results of overall iNHL except ECOG, Refractory to Alkylating-agent, and tumor diameter. The ORR was slightly higher for ECOG 0, Refractory to Alkylating-agent <2 and Tumor diameter < 7cm. SLL subgroup analyses for disease characteristic and prior therapy were omitted because there were only 26 patients in the SLL.

The results of duration assessed by IRC of OR for FL and SLL are summarized in Table 18.

Table 18: Duration of OR assessed by IRC for FL and SLL

	FL(N=72)	SLL (N=26)
No. of ORR, n (%)	39 (54.2)	15 (57.7)
No. of Events, n (%)	15 (38.5)	7 (46.7)
Duration of ORR (Months)		
Median (95% CI)	NA (4.5, NA)	11.9 (3.7, 14.7)
Range	(0.8, 14.8+)	(1.9, 14.7+)

The median OR duration for FL was not reached with 95 % CI of (4.5, NA). The median OR duration for SLL was 11.9 months with 95% CI of (3.7, 14.7).

Reviewer's comment:

The clinical reviewer defined the confirmed ORR, CR, or PR as patients with ORR, CR, or PR at least 2 consecutive assessments and duration of response greater than 2 months. Among FL and SLL patients, patients who had confirmed CR or PR are summarized in Table 19.

Table 19: Confirmed ORR, CR and PR for at least consecutively 2 months

Disease Categories	FL (N=72)	SLL (N=26)	Total (N=98)
ORR	33 (45.8%)	12 (46.2%)	45 (45.9%)
CR	6 (8.3%)	0	6 (6.1%)
PR	27 (37.5%)	12 (46.2%)	39 (39.8%)

Reviewer's comments:

Thirty three patients among 72 FL patients (45.8%) had at least two consecutively assessed responses and a minimum duration of response ≥ 2 months and 12 patients among 26 SLL patients (45.9%). The patients with CR for consecutive 2 months were 6 patients (8.3%) among FL and no patient among SLL. Patient ID GS-US-1101-09-111-09031 had PR at week 8, but became CR at week 16 and had progressive disease at week 24. This patient was counted as PR.

The duration of response and range for 45 patients who had consecutively OR for at least 2 months are summarized in Table 20.

Table 20: Duration and Range of FL and SLL for confirmed OR for at least consecutively 2 months

Disease Categories	PD	Median (95% CI)	Range
All confirmed 45 response	16 (34.8%)	12.5 (6.5, NA)	(3.7, 14.8+)
33 FL confirmed response	10 (30.3%)	NA (6.2, NA)	(3.7, 14.8+)
12 SLL confirmed response	6 (50.0%)	11.9 (3.7, 14.7)	(3.7, 14.7+)

PD: progression disease or death

Reviewer's comment:

The median duration of all 45 confirmed responses was 11.9 months and it was the same with overall responses. The median durations of confirmed response for FL and SLL were also same with the overall iNHL response.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

GS-1101-09 was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

(b) (4) Among iNHL patients, patients with FL, SLL, MZL, and LPL/WM were 57.6%, 22.4%, 12.0%, and 8%, respectively. The ORRs for FL and SLL were 54.2% and 53.6% respectively, and the ORRs were similar with the overall response rate of iNHL. The subgroup analyses for ORR seem consistent across disease subgroups. However, these subgroup analyses were post-hoc analyses. There was no pre-planned sample size calculation in order to rule out certain lower percentage responses for the disease category subgroups. The results should be interpreted with caution.

5.2 Collective Evidence

The FDA analysis of primary endpoint of ORR assessed by IRC was 54.4% (68 patients out of 125 ITT patients) (95% CI: 45.3, 63.3). The FDA's objective response rate results based on the investigators' assessments (55.2%) was similar.

Both applicant and FDA analysis of complete response rate was 5.6% (7 patients) assessed by both IRC and investigators.

The FDA analysis of median duration of ORR assessed by IRC was 12.5 months with 95% CI of (6.5, NA) and the median duration of ORR assessed by investigators was 14.7 months with 95% CI of (7.3, NA). The median duration of ORR was the same between the FDA and the applicant.

For the applicant reported lymph node response analysis, 110 subjects (88.0%) had improvement in lymphadenopathy and 67 subjects (53.6%) achieved a $\geq 50\%$ decrease from baseline in the SPD of index lesions by IRC assessment. Per investigator assessment, 107 patients (85.6%) had improvement in lymphadenopathy and 71 subjects (56.8%) achieved a $\geq 50\%$ decrease from baseline in the SPD of index lesions.

The FDA analysis of median time to response by IRC was 1.9 months with 95% CI of (1.6, 8.3) and the median time to response assessed by investigators was also 1.9 months with 95% CI of (1.6, 13.6). The applicant's time to response results were same as FDA results.

For the applicant's PFS analysis, 57 patients (45.6%) had either progressive disease assessed by IRC or death. The median PFS was 11 months with 95% CI of (8.1, 13.8).

For the applicant's OS results, there were 11 deaths (8.8%) within 30 days of the end of study date and the median duration of OS was not reached. There were a total of 28 deaths (22.4%) during the study long-term follow-up and the median duration of OS was 20.3 months with 95% CI of (16.4, NA).

Among 125 iNHL patients, patients with FL, SLL, MZL, and LPL/WM were 72 (57.6%), 28 (22.4%), 15 (12.0%), and 10 (8.0%), respectively. FDA excluded 2 patients in the SLL whom did not meet SLL disease category. The ORRs for FL and SLL were 54.2% and 57.7%, respectively. The ORR was best for LPL/WM (70%), but was worst for MZL (46.7%). However, the sample size of the MZL and LPL/WM was very small. These disease categories were post-hoc analyses.

The median OR duration for FL was not reached with 95 % CI of (4.5, NA). The median OR duration for SLL was 11.9 months with 95% CI of (3.7, 14.7).

5.3 Conclusions and Recommendations

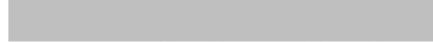
The observed primary endpoint of objective response rate (ORR) assessed by IRC was 54.4%, 68 patients out of 125 treated patients had response (intent-to-treat (ITT)), with 95% CI (46.8, 64.9). However, the complete response rate was 5.6% (7 patients) and partial response rate was 48.8% (61 patients). The median duration of objective response rate assessed by IRC was 12.5 months with a lower bound of 95% CI of 6.5 months.

Among 125 iNHL patients, patients with follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM), and marginal zone lymphoma (MZL) were 72 (57.6%), 28 (22.4%), 15 (12.0%), and 10 (8.0%), respectively. FDA excluded 2 SLL patients due to unmet SLL disease category, the number of SLL patient was 26 patients. The ORRs for FL and SLL were 54.2% and 57.7%, respectively. The median ORR duration for FL was not available with a lower bound of 95% CI of 4.5 months. The median ORR duration for SLL was 11.9 months with 95% CI of (3.7, 14.7).

The ORRs for FL and SLL were consistent to the overall iNHL. However, there were no pre-planned sample size calculations in order to rule out certain lower percentage of responses in the subgroup disease categories.

Based on the observed objective response rates and durations of median objective response rate of study GS-1101-09, it may be reasonably likely to predict that Idelalisib has clinical benefit in patients with previously treated FL and SLL, refractory to both rituximab and alkylating agent containing therapy.

5.4 Labeling Recommendations

 (b) (4)
 We therefore recommend that Idelalisib is indicated for the treatment of patients with relapsed FL and SLL.

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/s/

KYUNG Y LEE
05/09/2014

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05/09/2014

RAJESHWARI SRIDHARA
05/09/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205858

Applicant:

Stamp Date: 9/12/2013

Gilead Sciences, Inc.

Drug Name:

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 NDA205858

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Kyung Yul Lee, Ph.D.

Reviewing Statistician Date

Lei Nie, Ph.D.

Supervisor/Team Leader Date

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/s/

KYUNG Y LEE
10/18/2013

LEI NIE
10/18/2013