CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125486Orig1s000

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

BLA/Serial Number #:	BLA 125486 / 00
Supplement #:	Original Biologics License Application
Drug Name:	Gazyva (Obinutuzumab/GA101)
Indication(s):	In combination with chlorambucil as first-line treatment for patients with chronic lymphocytic leukemia
Applicant:	Genentech, Inc.
Date(s):	Submission date: 22 April 2013
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Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
Concurring Reviewers:	Lei Nie, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Hyon-Zu Lee, Pharm.D. (Primary reviewer for efficacy)
	Barry Miller, R.N., M.S. (Primary reviewer for safety)
	Virginia Kwitkowski, R.N., M.S. (Medical team leader)
Project Manager:	Beatrice Kallungal

Keywords: CLL, closed-test procedure, stratified log-rank test, group sequential design

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1 EXECUTIVE SUMMARY

This is an initial Biologic Licensing Application (BLA) seeking an indication for obinutuzumab in combination with chlorambucil in the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL).

The pivotal trial supporting this application is an ongoing Phase III, open-label, three-arm randomized, parallel-group study of obinutuzumab + chlorambucil (GClb) vs. rituximab + chlorambucil (RClb) vs. chlorambucil (Clb) alone in previously untreated CLL patients. This trial includes two stages, with Stage 1 further divided into Stage 1a and Stage 1b. The primary objective for Stage 1a is to show that GClb is superior to Clb for an initial application. Then the primary objective for Stage 1b is to show that RClb is superior to Clb. As results from Stage 1were promising, the trial proceeded as planned to recruit more patients and continued onto Stage 2, where GClb will be compared to RClb (b) (4). To control for the Type I error, the study first performed a global closed testing for any difference in the primary endpoint among the three study arms before proceeding to the pairwise comparisons in Stage 1. The Type I error was allocated to one interim analysis and one final analysis in Stage 2 according to the Lan-DeMets alpha spending function for group sequential designs.

This BLA is based on data from 356 patients randomized in Stage 1a of the pivotal trial (GClb 238, Clb 118). Superiority of GClb over Clb was demonstrated for the addition of obinutuzumab to chlorambucil based on the primary endpoint progression-free survival as assessed by an independent radiology committee (IRC-assessed PFS): hazard ratio [95% confidence interval] 0.16 [0.11 – 0.24]; stratified log-rank test p-value < 0.0001; improvement in median 11.9 months (GClb 23.0 months, Clb 11.1 months). The PFS results by investigators were similar to the results by IRC. Subgroup analyses and additional sensitivity analyses for PFS did not reveal major issues to the interpretation of the primary analysis. Secondary response outcomes and event-free survival also supported the benefit of adding obinutuzumab to chlorambucil. Overall survival data at the time of data cut-off was not mature enough to obtain a reliable estimate with 13 deaths and 9 deaths reported for the GClb and Clb arm, respectively.

This reviewer recommends this application be approved for the proposed indication. (b) (4) the pivotal trial did not have a multiple testing plan for the secondary endpoints.

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2 INTRODUCTION

2.1 Overview

Product and Proposed Indication
Obinutuzumab is a humanized anti-CD20 monoclonal antibody. This initial Biologic Licensing Application (BLA) is intended for the following indication:
"Obinutuzumab in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)"

Clinical Studies
This BLA includes one pivotal randomized Phase III study having obinutuzumab in combination with chlorambucil versus chlorambucil as the treatment in previously untreated CLL patients with comorbidities. It also includes supporting Phase I/II studies of obinutuzumab for patients with relapsed/refractory non-Hodgkin's lymphoma or chronic lymphocytic leukemia. The supporting studies will not be discussed in this review, because their study patient populations are different from the one that is intended for the proposed indication. Details on the pivotal study are provided in the statistical evaluation section of this review.

Regulatory Interactions
For the pivotal study, the Applicant had a meeting with the Agency in 2009 focused on the overall study design (including the patient selection and dosing regimens), and another meeting in 2012 focused on the statistical analysis plan. The Applicant filed a Breakthrough Therapy Designation request following the pre-BLA meeting held on 22 February 2013. The Agency received this BLA on 22 April 2013, and granted Breakthrough Therapy designation for the proposed indication to the associated IND 104,405 on 9 May 2013.

2.2 Data Sources

Material reviewed for this application: protocol, statistical analysis plan, study report, and submitted datasets for the pivotal study BO21004 (also known as CLL11).

Reviewed data were provided electronically with the standard analysis data formats. SAS programs used to create key efficacy and safety outputs for the pivotal study were submitted in this application. The electronic path of Study BO21004 datasets is:
\\cbsap58\eCTD_Submissions\STN125486\0000\m5\datasets\bo21004.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from the pivotal study BO21004 were provided electronically with standard formats. Documentations on datasets and programming were included with sufficient details for this reviewer to reproduce the applicant's key efficacy results. However, this reviewer was not able

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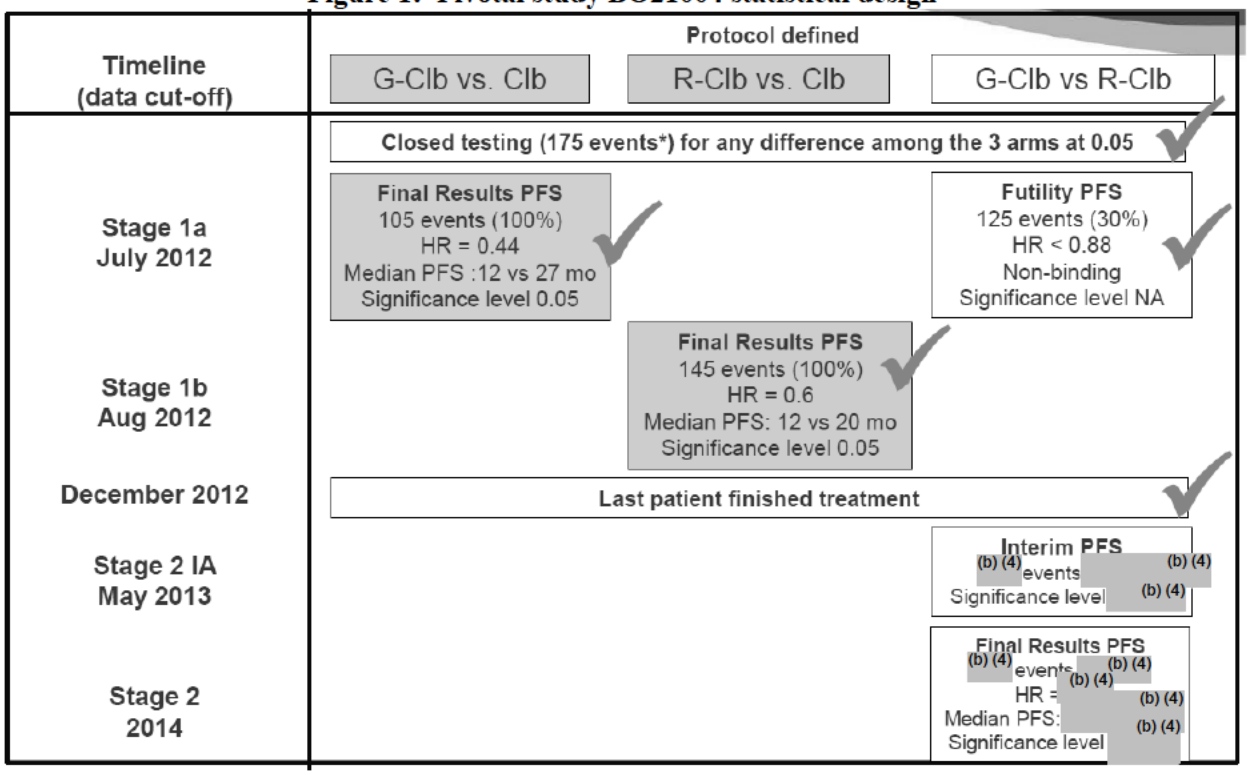
to verify the comorbidity status at baseline, an important baseline characteristic to this patient population, because of the SAS format catalog for medical conditions at baseline was not included in the initial submission. This format catalog was provided to the Agency on 25 June 2013 following an information request.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The pivotal study supporting this application is Study BO21004 (also known as CLL11). Study BO21004 is an ongoing Phase III, open-label, three-arm randomized, parallel-group study of obinutuzumab + chlorambucil (GClb) vs. rituximab + chlorambucil (RClb) vs. chlorambucil (Clb) alone in previously untreated CLL patients. This study is planned to enroll a total of 780 patients for testing the benefit of obinutuzumab based on progression-free survival (PFS). Study BO21004 includes 2 stages: Stage 1 is planned to randomize 590 patients into 3 study arms at 2:2:1 ratio (GClb 236 patients, RClb 236 patients, Clb 118 patients) in order to address 2 objectives: (1) to test superiority of GClb over Clb for an initial application; (2) to test superiority of RClb over Clb and non-futility of GClb against RClb for continuing the study onto Stage 2. Stage 2 is to randomize additional 180 patients to the GClb and RClb arms at 1:1 ratio for a total of 331 patients in each arm to test the superiority of GClb over RClb. Randomization for both stages of the study is stratified by Binet stage (A, B, C) at baseline and region (Asia and Oceania, Europe 1, Europe 2, North and Central America and Caribbean, South America and South Atlantic Islands). Figure 1 shows Study BO21004 statistical design in terms of protocol-specified hypotheses, timing of analyses, and type I error/alpha allocation.

Figure 1: Pivotal study BO21004 statistical design



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The protocol-defined primary efficacy endpoint for Study BO21004 is investigator-assessed PFS; however, the protocol indicates that PFS based on Independent Review Committee (IRC) assessments will be the basis of regulatory decisions in the United States. PFS is defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause.

The secondary efficacy endpoints for Study BO21004 include the following:

- End of treatment response rate: percentage of patients with complete response (CR), incomplete complete response (CRi), nodular partial response (nPR), or partial response (PR) at the end of treatment response assessment (the first assessment that occurred more than 56 days after the end of treatment)
- Best overall response rate: percentage of patients with CR, CRi, nPR, or PR as the best overall response recorded from 56 days after end of treatment onwards
- Duration of response: time from the date of response (either CR or PR) to the date of progressive disease or death due to any cause
- Molecular remission rate: percentage of patients with a minimum residual disease negative result at the end of treatment assessment
- Event-free survival: time from randomization to disease progression/relapse, death, or start of a new anti-leukemic therapy
- Disease-free survival: time from the date of complete response to the date of progressive disease or death due to any cause
- Time to new anti-leukemic therapy: time from randomization to first intake of re-treatment or new anti-leukemic therapy
- Overall survival: time from randomization to death due to any cause

3.2.2 Statistical Methodologies

The primary efficacy analysis population for Study BO21004 is the intent-to-treat (ITT) population of all randomized patients. However, patients who do not reach the end of treatment assessment will not be considered in the response endpoints.

Primary analysis for time-to-event endpoints will include treatment comparison using a two-sided stratified (by Binet stage) log-rank test and estimation of median times with 95% confidence intervals using Kaplan-Meier survival methodology. Percentages outcomes will be compared between treatment arms using a chi-square test with continuity correction.

To control for the type I error rate or alpha at 0.05, Study BO21004 will first perform a global closed testing for any difference in PFS among the 3 study arms before proceeding to the pairwise comparisons in Stage 1. If the study continues to Stage 2, the overall alpha of 0.05 will be allocated to one interim analysis and the final analysis according to the Lan-DeMets alpha spending function for group sequential designs.

No adjustment for multiplicity will be made for secondary endpoints.

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Reviewer Comments:

- *Multiplicity adjustment for secondary endpoints could not be made because the alpha from meeting Stage 1 objectives has been reserved for the continuing Stage 2 analyses.*
- *Randomization was stratified by Binet stage and region. However, due to the small number of patients from some regions, the primary analyses are stratified by Binet stage only.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 1 shows patient disposition for Study BO21004 Stage 1a patients. As of the data cutoff date (11 July 2012), Study BO21004 randomized a total of 781 patients on a 2:2:1 (GClb: RClb: Clb) basis between the three treatment arms and on a 1:1 (GClb: RClb) basis between the two treatment arms. This review focuses on the Stage 1a analysis which includes a total of 356 patients; 118 patients randomized to the Clb arm and 238 patients randomized to the GClb arm.

The first comprehensive response assessment was performed at the Month 3 follow-up visit, scheduled to be at least 56 days from the last dose of treatment. At the time of data cutoff, the majority of patients in each treatment arm had reached the Month 3 follow-up visit (90% and 89% in the Clb and GClb arm, respective), but not all of them had an assessment. A patient entered the follow-up period when the patient had a follow-up assessment. A higher proportion of patients in the GClb arm (82%) had entered follow-up period compared to the Clb arm (71%). Twenty-two patients (19%) who were randomized to Clb crossed over to GClb treatment.

The overall median observation time (from randomization to the last available assessment) was 14.2 months; 13.6 months (range: 0.2 to 26.8 months) for patients in the Clb arm and 14.5 months (range: 0.1 to 26.7 months) for patients in the GClb arm.

Table 1: Disposition of Stage 1a Patients (BO21004, ITT Population)

Study Subjects (As of 11 July 2012)	**Clb Arm n (%)**	**GClb Arm n (%)**
Randomized	118 (100%)	238 (100%)
Received study drug	116 (98%)	236 (99%)
Withdrawn from trial treatment	40 (34%)	48 (20%)
Primary reason for treatment withdrawn:		
Disease progression	8 (7%)	2 (1%)
Lack of therapeutic response	5 (4%)	1 (<1%)
Death	6 (5%)	3 (1%)
Adverse event	16 (14%)	32 (13%)
Other[1]	5 (4%)	10 (4%)
Reached Month 3 follow-up visit	106 (90%)	212 (89%)
Crossed-over[2]	22 (19%)	Not applicable
Started follow-up period	84 (71%)	195 (82%)
Completed[3] follow-up period	41 (49%)	26 (13%)

Clb = chlorambucil; GClb = obinutuzumab + chlorambucil
[1] Other includes consent withdrawal, other protocol violation, treatment refusal, selection criteria violation
[2] Patients with a progressive disease during Clb treatment or within 6 months of follow-up
[3] Percentages are calculated based on the number of patients entering the follow-up period

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Table 2 gives a summary on demographics and baseline characteristics for patients enrolled in Study BO21004 Stage 1a Clb and GClb arms. In general, patients in the two study arms were not dramatically different with respect to demographic and baseline factors. All but 1 patient were enrolled outside of the United States.

Table 2 Demographics and Baseline Characteristics (BO21004 Stage 1a, ITT Population)

Factor	Clb (N = 118)	GClb (N = 238)	Total (N = 356)
Demographics			
Age (years)			
<65 / >=65	26 / 92 (22% / 78%)	42 / 196 (18% / 82%)	68 / 288 (19% / 81%)
<75 / >=75	74 / 44 (63% / 37%)	131 / 107 (55% / 45%)	205 / 151 (58% / 42%)
mean (SD), median, min-max	70.7 (8.7), 72, 43−87	72.0 (8.6), 74, 39−88	71.6 (8.7), 73, 39−88
Sex			
Female / Male	43 / 75 (36% / 64%)	98 / 140 (41% / 59%)	141 / 215 (40% / 60%)
Race			
White / Other	108 / 10 (92% / 8%)	229 / 9 (96% / 4%)	337 / 19 (95% / 5%)
Region*			
Asia / Europe1 / Europe2 / America1 / America2	8 / 74 / 29 / 6[#] / 1 (7 / 63 / 25/ 5 / 1 %)	16 / 148 / 57 / 13 / 4 (7 / 62 / 24 / 5 / 2 %)	24 / 222 / 86 / 19 / 5 (7 / 62 / 24 / 5 / 1 %)
Baseline Characteristics			
Binet stage			
A / B / C	24 / 50 / 44 (20 / 42 / 37 %)	55 / 98 / 85 (23 / 41 / 36 %)	79 / 148 / 129 (22 / 42 / 36 %)
Total CIRS score			
<=6 / >6	26 / 92 (22% / 78%)	59 / 179 (25% / 75%)	85 / 271 (24% / 76%)
Calculated creatinine clearance			
<70 / >=70 ml/min	71 / 46 (60% / 39%)	161 / 77 (68% / 32%)	232 / 123 (65% / 35%)
Beta2-microglobulin			
<3.5 / >=3.5 mg/L	70 / 45 (59% / 38%)	158 / 73 (66% / 31%)	228 / 118 (64% / 33%)
IGVH mutational status			
Mutated / Un-mutated	36 / 58 (31% / 49%)	76 / 129 (32% / 54%)	112 / 187 (31% / 53%)
Hierarchical model			
+12 / 17p- / 11q- / 13q- /other / no abnormality	16/10/14/32/9/15 (14/8/12/27/8/13 %)	33/16/33/58/15/48 (14/7/14/24/6/20 %)	49/26/47/90/24/63 (14/7/13/25/7/18 %)
Time diagnosis to randomization			
<=12 / 13-24 / >24 months	33 / 14 / 71 (28 / 12 / 60 %)	59 / 45 /133 (25 / 19 / 56 %)	92 / 59 / 204 (26 / 17 / 57 %)
FCγ receptor IIa at baseline			
131 HH / 131 HR / 131RR	36 / 50 / 17 (31 / 42 / 14 %)	60 / 105 / 42 (25 / 44 / 18 %)	96 / 155 / 59 (27 / 44 / 17 %)
Circulating lymphocyte count			
<25 / >=25×10^9 cells/L	18 / 98 (15% / 83%)	58 / 179 (24% / 75%)	76 / 277 (21% / 78%)

Clb = chlorambucil; GClb = obinutuzumab + chlorambucil; SD = standard deviation

* Five geographic regions: Asia and Oceania; Europe Group 1; Europe Group 2; North and Central America and Caribbean; South America and South Atlantic Islands

[#] including one patient enrolled in the United States

Reviewer Comment: *PFS data from the 3 study arms used to perform the global closed testing were included in this BLA submission. No other data in the RClb arm were submitted.*

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3.2.4 Efficacy Results

3.2.4.1 The Primary Endpoint – Progression Free Survival

Study BO21004 began its first analysis with a global closed testing for any difference in PFS among the 3 study arms before proceeding to the pairwise comparisons in Stage 1. Data from the 3 study arms used to perform this global testing are included in this BLA submission. This reviewer has verified the global closed testing for IRC-assessed PFS with a p-value of <0.0001 rejecting the null hypothesis of no differences between the study arms in PFS.

The final Stage 1a PFS results, as shown in Table 3, are very positive. Both the IRC-assessed and investigator-determined PFS gave a highly significant hazard ratio and twice in length of median PFS for GClb versus Clb. The IRC-assessed PFS is the agreed-upon primary efficacy endpoint for regulatory decisions in the United States.

Table 3 IRC-Assessed and Investigator-Determined PFS (BO21004 Stage 1a, ITT Population)

	IRC		*Investigator*	
	Clb (N = 118)	GClb (N = 238)	Clb (N = 118)	GClb (N = 238)
Patients with event	66 (55.9%)	52 (21.8%)	71 (60.2%)	52 (21.8%)
Patients without event (censored)	52 (44.1%)	186 (78.2%)	47 (39.8%)	186 (78.2%)
Time to event (months)				
Median	11.1	23.0	10.9	23.0
95% CI for median	(10.6, 11.3)	(20.1, 23.2)	(9.8, 11.2)	(20.0, 23.2)
p-value (log-rank test, stratified*)	< 0.0001		< 0.0001	
Hazard ratio for GClb over Clb (stratified*)	0.16		0.14	
95% CI	(0.11, 0.24)		(0.09, 0.21)	
p-value	< 0.0001		< 0.0001	
1 year duration				
Patients remaining at risk	21	111	18	117
Event free rate	36%	83%	27%	84%
95% CI for rate	(25%, 47%)	(77%, 89%)	(17%, 37%)	(79%, 90%)

IRC = Independent Radiology Committee; CI = confidence interval; Clb = Chlorambucil; GClb = GA101 + Clb

* Stratified by Binet stage at baseline. The analysis was not stratified by region due to the small number of patients from some regions.

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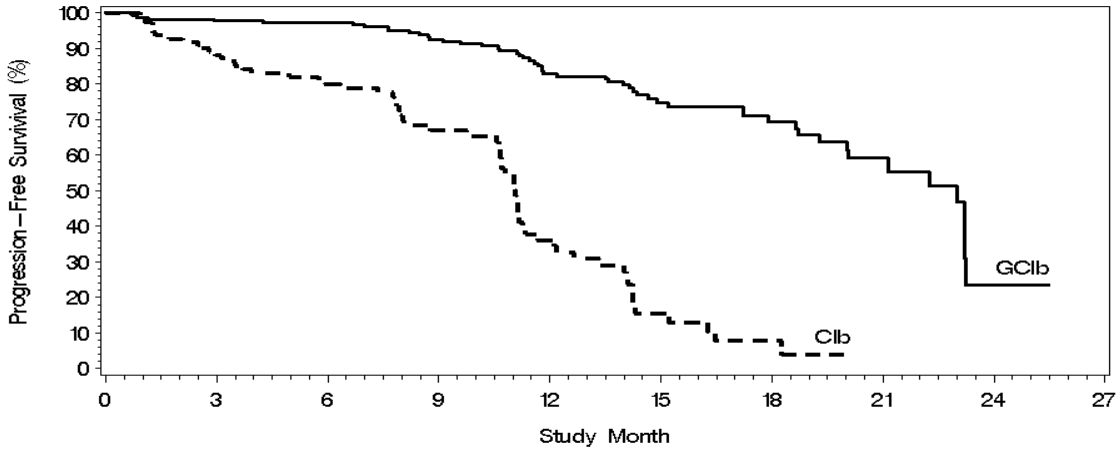
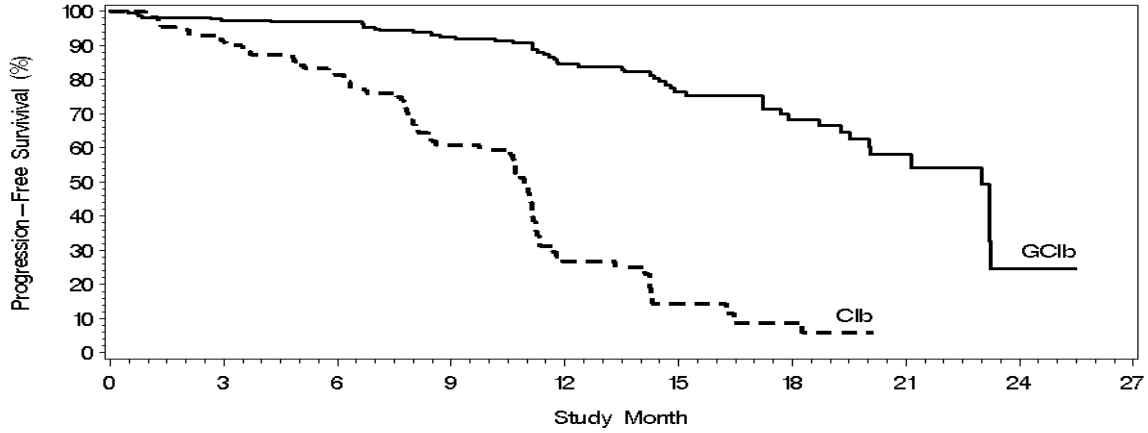


Clb	118	91	76	46	21	6	2	0	0	0
GClb	238	208	201	146	111	69	39	16	2	0

Figure 2: IRC-Assessed Progression-Free Survival (BO21004 Stage 1a, ITT Population)



Clb	118	99	82	47	18	5	3	0	0	0
GClb	238	213	207	152	117	75	40	15	2	0

Figure 3: Investigator-Determined Progression-Free Survival (BO21004 Stage 1a, ITT Pop)

3.2.4.2 The Secondary Endpoints

Stage 1a secondary efficacy endpoints include response and time-to-event outcomes. As shown in Table 4 and Table 5, benefit of adding obinutuzumab to chlorambucil was observed in the secondary response outcomes and event-free survival. However, it is premature to obtain a reliable estimate for overall survival based on current data. The Kaplan-Meier survival curves up to the data cut-off are shown in Figure 4. It is important to know the p-values presented in

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Table 4 and Table 5 did not adjust for multiplicity. Thus these secondary endpoint results were not confirmatory.

Table 4 Secondary Response Endpoints (BO21004 Stage 1a)

	Clb N = 118	**GClb N = 238**
End of treatment response		
Patients included in analysis	106 (100%)	212 (100%)
Responders: CR/CRi/PR/nPR, total (total %)	0/0/30/2, 32 (30.2%)	36/11/90/23, 160 (75.5%)
95% CI for response rates*	(21.7%, 39.9%)	(69.1%, 81.1%)
Difference in response rates	45.3%	
95% CI for difference in rates	(34.3%, 56.3%)	
p-value** for the difference (Chi-square test)	<0.0001	
Missing (no response assessment)[1]	24 (22.6%)	34 (16.0%)
Month 3 follow-up visit not reached[3]	12	26
Best overall response		
Patients included in analysis	106 (100%)	212 (100%)
Responders: CR/CRi/PR/nPR (total %)	0/1/31/2, 34 (32.1%)	52/7/88/14, 161 (75.9%)
95% CI for response rates*	(23.3%, 41.8%)	(69.6%, 81.5%)
Difference in response rates	43.9%	
95% CI for difference in rates	(32.8%, 55.0%)	
p-value** for the difference (Chi-square test)	<0.0001	
Missing (no response assessment)[1]	24 (22.6%)	34 (16.0%)
Month 3 follow-up visit not reached[3]	12	26
Duration of response		
Events / Responders (%)	20 / 34 (58.8%)	31 / 161 (19.3%)
Median# in months (95% CI)	3.5 (3.0, 6.4)	15.2 (12.5, 15.6)
Molecular remission at end of treatment		
Patients included in analysis	80 (100%)	142 (100%)
Minimum Residual Disease (MRD) negative	0 (0%)	28 (19.7%)
95% CI for MRD negative*	(0.0%, 4.5%)	(13.5%, 27.2%)
Difference in MRD negative rates	19.7%	
95% CI for difference in rates	(12.5%, 26.9%)	
p-value** for the difference (Chi-square test)	<0.0001	
Missing[2]	26	70
Month 3 follow-up visit not reached[3]	12	26

Clb = chlorambucil; GClb = obinutuzumab + chlorambucil; CR = complete response; CRi = complete response with incomplete marrow recovery; PR = partial response; nPR = nodular partial response; CI = confidence interval

* CI calculated based on Pearson-Clopper method for one-sample binomial

Kaplan-Meier estimate

** Nominal p-value

[1] Patients who had reached the M3 follow-up visit but had a missing assessment are considered as non-responders.

[2] Patients with a missing blood sample or bone marrow and had not experienced a progressive disease or death. MRD status could not be determined in these patients. These patients were not included in this analysis.

[3] Patients who had not reached Month 3 follow-up visit were not included in the analyses of response endpoints.

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Table 5 Secondary Time-to-Event Endpoints (BO21004 Stage 1a, ITT Population)

	Clb N = 118	GClb N = 238
Event free survival		
Patients who had an event	79 (66.9%)	64 (26.9%)
Median[#] in months (95% CI)	10.6	23.0
Hazard ratio[##] (95% CI)	0.18 (0.13, 0.26)	
p-value[###]	<0.0001	
Time to new anti-leukemic therapy		
Patients who started a new therapy	41 (34.7%)	29 (12.2%)
Median[#] in months (95% CI)	14.8	-
Hazard ratio[##] (95% CI)	0.26 (0.16, 0.42)	
p-value[###]	<0.0001	
Overall survival		
Patients who died	9 (7.6%)	13 (5.5%)
Median[#] in months (95% CI)	-	-
Hazard ratio[##] (95% CI)	0.68 (0.29, 1.60)	
p-value[###]	0.384	

Clb = chlorambucil; GClb = obinutuzumab + chlorambucil; CI = confidence interval
[#] Kaplan-Meier estimate; [##] From Cox model for GClb versus Clb, stratified by Binet stage at baseline; [###] From log-rank test for GClb versus Clb, stratified by Binet stage at baseline

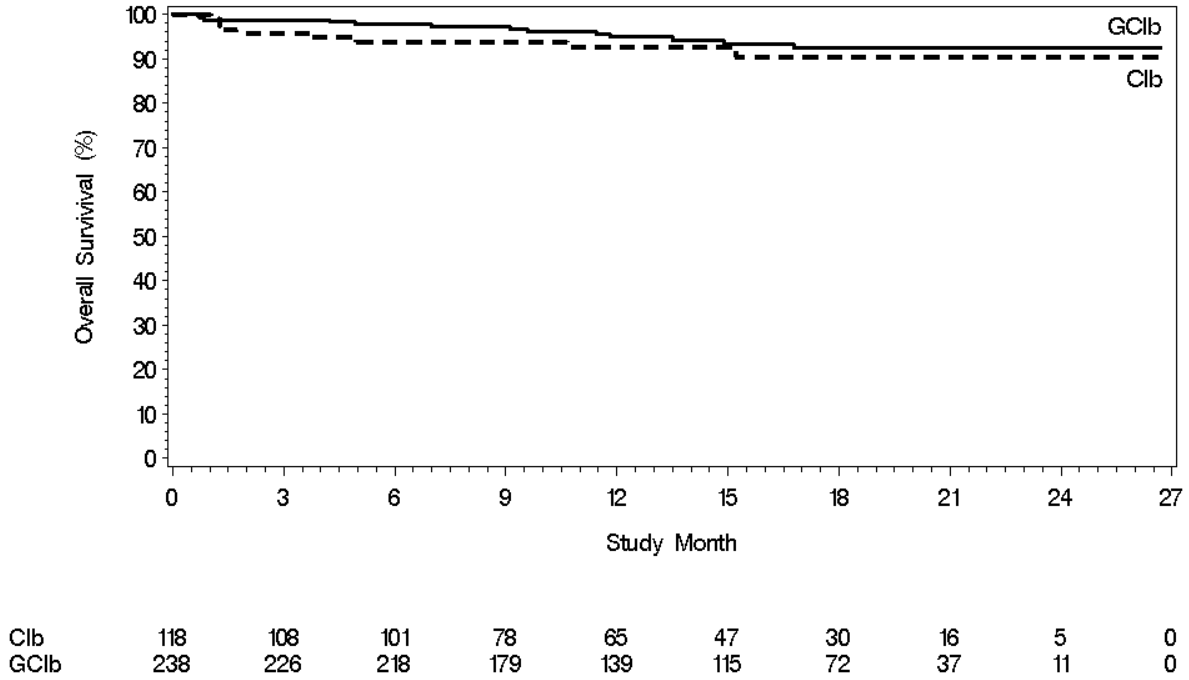

Figure 4: Overall Survival (BO21004 Stage 1a, ITT Population)

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Reviewer Comments:

1. *The comparisons between GClb and Clb arms in secondary endpoints are not confirmatory, because there was no multiplicity adjustment plan for secondary endpoints in Study BO21004. Multiplicity adjustment for secondary endpoints could not be made because the type I error rate or alpha from meeting Stage 1 objectives has been reserved for the continuing Stage 2 analyses.*
2. *Patients who did not reach the Month 3 follow-up visit were excluded from the calculation of response rates. In addition, patients whose MRD status could not be determined due to lack of a blood and/or bone marrow sample at the end of treatment visit were excluded from the calculation of molecular remission rate. Justifications for these exclusions were provided in the protocol and were considered reasonable by the medical reviewer.*
3. *The overall survival analysis included 22 Clb arm patients who crossed over to receive GClb upon their disease progression. At the time of data cut-off, none of these patients had died.*
4. *The secondary endpoint disease-free survival is not presented here, because there were no complete responders in the Clb arm.*

3.2.4.3 Statistical Evaluations for the Primary Endpoint

There were 6 protocol-defined sensitivity analyses for PFS, including: considering missing response assessments as events; censoring for new-leukemic treatment; counting early treatment withdrawal as an event; censoring for late death cases; using protocol-defined number of events; analyzing PFS in the per-protocol population. Results from these sensitivity analyses results were comparable to the primary analysis result, with the hazard ratio ranged from 0.12 to 0.26 for GClb versus Clb.

To investigate the impact from missing response assessments, this reviewer conducted 2 additional sensitivity analyses. The first analysis censored death or progression after more than one missed assessment. The second analysis followed a worst case scenario treating any lost to follow-ups (missing at least one tumor assessment prior to data cut-off) in the GClb arm as events, but as censored in the Clb arm. Results from these two additional sensitivity analyses are comparable to the primary analysis result as well, with a hazard ratio of GClb versus Clb in IRC-assessed PFS to be 0.15 and 0.30 for the first analysis and the second analysis, respectively.

Subgroup analyses shown below suggest that PFS result is fairly consistent across subgroups defined by demographics and baseline factors.

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Table 6 IRC-Assessed PFS by Subgroup (BO21004 Stage 1a, ITT Population)

Factor	Group	N	Hazard Ratio	95% CI
Demographics				
Age (years)	< 65	68	0.06	(0.02, 0.20)
	>= 65	288	0.18	(0.12, 0.28)
	< 75	205	0.12	(0.07, 0.22)
	>= 75	151	0.20	(0.11, 0.35)
Sex	Female	141	0.13	(0.07, 0.26)
	Male	215	0.17	(0.10, 0.28)
Race	White	337	0.16	(0.11, 0.25)
	Other	19	0.00	(-, -)
Region	Asia and Oceania	24	0.20	(0.04, 0.93)
	Europe Group 1	222	0.15	(0.09, 0.25)
	Europe Group 2	86	0.20	(0.09, 0.44)
	Central America	19	0.00	(-, -)
	South America	5	0.00	(-, -)
Baseline Characteristics				
Binet stage	A	79	0.08	(0.03, 0.22)
	B	148	0.17	(0.10, 0.30)
	C	129	0.21	(0.11, 0.42)
Total CIRS score	<= 6	85	0.18	(0.08, 0.42)
	> 6	271	0.14	(0.09, 0.22)
Calculated creatinine clearance	< 70 ml/min	232	0.20	(0.13, 0.32)
	>= 70 ml/min	123	0.07	(0.03, 0.16)
Beta2-microglobulin	< 3.5 mg/L	228	0.14	(0.08, 0.23)
	>= 3.5 mg/L	118	0.18	(0.09, 0.35)
IGVH mutational status	Mutated	112	0.07	(0.02, 0.18)
	Un-mutated	187	0.21	(0.13, 0.35)
Hierarchical model	+12	49	0.17	(0.05, 0.59)
	17p-	26	0.47	(0.16, 1.38)
	11q-	47	0.11	(0.04, 0.36)
	13q-	90	0.18	(0.08, 0.40)
	Other	24	0.20	(0.06, 0.67)
	No abnormality	63	0.16	(0.06, 0.46)
Time from diagnosis to randomization	<= 12 months	92	0.12	(0.05, 0.28)
	13-24 months	59	0.17	(0.06, 0.44)
	> 24 months	204	0.15	(0.09, 0.26)
FCγ receptor IIa at baseline	131 HH	96	0.13	(0.06, 0.29)
	131 HR	155	0.14	(0.07, 0.28)
	131 RR	59	0.24	(0.10, 0.53)
Circulating lymphocyte count	< 25×10^9 cells/L	76	0.19	(0.07, 0.47)
	≥ 25×10^9 cells/L	277	0.15	(0.10, 0.24)

There is one potential issue with the PFS results. The agreement between the investigators and IRC in the 1-year progression-free survival rate was much better for the GClb arm than was for the control arm. The comparison between the investigators and IRC in Table 7 suggests a very good overall agreement in event determination between the investigators and the IRC. However, with the PFS time shorter in the Clb arm, the majority of the discrepancies in the Clb arm were in the first year and therefore the bigger difference in 1-year PFS rate for the Clb arm. In addition to this tabulation, this reviewer also checked individual patients' response assessment comments.

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No systematic reasons were identified to suggest that the discrepancies were caused by an investigator bias.

Table 7 Concordance between IRC and Investigators in PFS Events (BO21004 Stage 1a)

	Clb (N = 118)			GClb (N = 238)		
IRC assessment	PD	Death	No event	PD	Death	No event
INV assessment						
PD	53	1	9	35	1	6
Death	0	8		0	10	
No event	4		43	6		180

3.3 Evaluation of Safety

Safety was evaluated in 240 GClb treated and 116 Clb treated patients from Study BO21004. Almost all the patients experienced at least one adverse event (AE) during their treatment (≥1 AE in 93% of the GClb treated and 100% Clb treated patients). Twenty percent (20%) of the GClb treated and 34% of the Clb treated patients discontinued treatment due to adverse events. The adverse events that GClb treated patients had a higher incidence compared to the Clb treated patients were related to infusion reactions.

Please refer to the medical safety review for more detailed safety results and clinical interpretation.

3.4 Benefit-Risk Assessment

Based on the efficacy and safety evaluations from the pivotal study, the benefit-risk appears to be positive for obinutuzumab in combination with chlorambucil in the treatment of previously untreated CLL.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to Table 6 for PFS results by demographics.

4.2 Other Special/Subgroup Populations

Please refer to Table 6 for PFS results by baseline characteristics and prognostic factors.

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5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No major statistical issues were identified during the statistical evaluations.

This application is based on data from 356 patients randomized in Stage 1a of the pivotal trial comparing obinutuzumab/GA101 + chlorambucil (GClb, 238 patients) to chlorambucil alone (Clb, 118 patients). Superiority was demonstrated for the addition of obinutuzumab to chlorambucil based on the primary endpoint progression-free survival as assessed by an independent radiology committee (IRC-assessed PFS): hazard ratio [95% confidence interval] 0.16 [0.11 – 0.24]; stratified log-rank test p-value < 0.0001; improvement in median 11.9 months (GClb 23.0 months, Clb 11.1 months). The progression-free survival results by investigators were similar to the results by IRC. Subgroup analyses and additional sensitivity analyses for PFS did not reveal major issues to the interpretation of the primary analysis. Secondary response outcomes and event-free survival also supported the benefit of adding obinutuzumab to chlorambucil. However, it is premature to obtain a reliable estimate for overall survival based on current data.

This reviewer recommends this application be approved for the proposed indication. (b) (4) (b) (4) the pivotal trial did not have a multiple testing plan for the secondary endpoints.

5.2 Conclusions and Recommendations

The pivotal study has demonstrated benefit of adding obinutuzumab to chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia. This reviewer recommends this application be approved for the proposed indication.

5.3 Labeling Recommendations

(b) (4) the pivotal study did not have a multiple testing plan for the secondary endpoints.

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/s/

CHIA-WEN KO
08/29/2013

LEI NIE
08/29/2013

RAJESHWARI SRIDHARA
08/30/2013

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA	125486
CONSULT REQUESTED BY DTP	June 13, 2013
TRADE NAME	Gazyva (conditionally approved)
ESTABLISHED NAME	Obinutuzumab
DOSAGE FORM	Liquid Single Use Vial
STRENGTHS	1000mg/40mL (25 mg/mL)
ROUTE OF ADMINISTRATION	Intravenous Infusion
INDICATION	For the treatment of patients with previously untreated chronic lymphocytic leukemia
SPONSOR	Genentech, Inc.
REVIEW FINISHED	Aug 29, 2013
STATISTICAL REVIEWER	Xiaoyu Dong, Ph.D.
PROJECT MANAGER	Beatrice Kallungal

Xiaoyu Dong, Mathematical Statistician, PhD, CDER/OTS/OB/DB VI

Concur:

Yi Tsong, Ph.D, Deputy Director, CDER/OTS/OB/DB VI

Distribution: BLA 125486
CDER/OTS/OB/DB VI/ Yi Tsong, Ph.D.
CDER/OTS/OB/DB VI/ Lillian Patrician, Ph.D.
CDER/OPS/OBP/DMA/ Chikako Torigoe, Ph.D.
CDER/DHP / Beatrice Kallungal

Reference ID: 3365451

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Reference ID: 3365451

1 INTRODUCTION

The sponsor conducted the qualification of the scale down model (b) (4)) to evaluate the equivalency between the small scale model and the manufacturing scale model (b) (4) bioreactor). The purpose of the qualification study is to qualify the scale-down model's ability to predict the performance at the manufacturing scale. (b) (4)

We received the consultation request from OBP/DMA to evaluate the qualification of the scale-down model. The statistics reviewer's reviewed "Qualification of Scale-Down Models" and its "Attachment: Justification of Practically Significant Difference Values". The Comments are summarized in Section II.

2 CONLUSIONS AND COMMENTS

In summary, the sponsor's conclusion that the scale-down models are suitable for the intended use is not supported by the data. The main statistical issues and questions for the qualification study are summarized below. (b) (4)

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Reference ID: 3365451

(b) (4)

(b) (4)

(b) (4)

In summary, the sponsor's conclusion that the scale-down models are suitable for the intended use *is not supported by the data.*

(b) (4)

Reference ID: 3365451

(b) (4)

Reference ID: 3365451

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

BLA	125486
CONSULT REQUESTED BY DTP	June 13, 2013
TRADE NAME	Gazyva (conditionally approved)
ESTABLISHED NAME	Obinutuzumab
DOSAGE FORM	Liquid Single Use Vial
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STATISTICAL REVIEWER	Xiaoyu Dong, Ph.D.
PROJECT MANAGER	Beatrice Kallungal

Xiaoyu Dong, Mathematical Statistician, PhD, CDER/OTS/OB/DB VI

Concur:

Yi Tsong, Ph.D, Deputy Director, CDER/OTS/OB/DB VI

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CDER/OTS/OB/DB VI/ Yi Tsong, Ph.D.
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CDER/OPS/OBP/DMA/ Chikako Torigoe, Ph.D.
CDER/DHP / Beatrice Kallungal

Reference ID: 3365451

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Reference ID: 3365451

1 INTRODUCTION

For process characterization and validation study (PC/PV), the sponsor applied multiple linear regression model to evaluate the impact of process parameters (input) on the critical quality attributes (CQA). This is a two-round procedure. In the first round, main effects and two-parameter interactions are evaluated. Those terms with statistical significance (p-value < 0.05) are kept to the next round. In the second round, response surface designs were used in which the quadratic terms were included in the model and the critical process parameters were tested at the center of and also at the edge of the operating range. The purpose of the second round study is to ensure that the CQAs will meet the acceptance criteria when the process parameters change with the operating range. The sponsor conducted the PC/PV studies for the cell culture process to identify the critical process parameters (CPPs) and the design space.

In the consultation request we received from OBP/DMA, (b) (4)

(b) (4)

We reviewed the above materials, and summarized our comments in the next section.

2 STATISTICAL COMMENTS

The statistical reviewer has the following comments regarding the sponsor's design of experiment.

Reference ID: 3365451

2.1 Comments on Design of Experiments (Page 1 – 10)

- Comments on Statistical Modeling: In general, the sponsor's multiple linear regression model in first and second rounds are acceptable. (b) (4)

- Comments on Identification of Critical Process Parameters:
  - The numerator of Impact Ratio computed from the scale-down model may underestimate the actual variation from the full scale data. The numerator represents the variation in CQA when a process parameter is moved from the target value to the edge of MAR, and the denominator represents the how much CQA variability is allowed. From the qualification study, the scale-down model shows less variability than the manufacturing scale data. From some attributes, variation from scale-down model is much smaller than the full scale data. Thus, the actual value of Impact Ratio at the manufacturing scale may be higher.

- (b) (4)

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(b) (4)

2.7 Comments on Justification of Specification (Page 13-16):

The reviewer has the following comments regarding to the sponsor's Criterion 3: Is the Process Model Sufficiently Predictive?

If the scale down model is consistent with the manufacturing scale model, and the multiple regression model provides a good description of the process, the model still may not be able to provide a reliable prediction. A quantitative measurement of prediction ability in linear regression model is Q^2. A high value of Q^2 may imply a good prediction from the model. As we noticed from the round 2 studies, some models have a low value of Q^2. Thus, the prediction at the worst-case setting from those models may not be reliable.

In addition, it is not clear to the reviewer the calculation of the prediction interval for CQA affected by more than one unit operations. (b) (4)

(b) (4)

Reference ID: 3365451

(b) (4)

Reference ID: 3365451

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/s/

XIAOYU DONG
08/29/2013

YI TSONG
08/29/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125486 **Applicant:** Genentech, Inc. **Stamp Date:** 04/22/2013

Drug Name: Obinutuzumab **NDA/BLA Type:** Original Application

Proposed Indication: *Obinutuzumab in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL)*

On **initial** overview of the NDA/BLA application for RTF: There are no filling issues - all necessary documents are available to allow statistical review to begin.

	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			This application is supported by data from Stage 1a of the pivotal trial BO21004 comparing obinutuzumab in combination with chlorambucil (GClb) versus chlorambucil (Clb) alone as the first-line treatment of CLL. The final Stage 1a analysis was based on PFS events in the Stage 1 population including 118 patients randomized to the Clb arm and 238 randomized patients in the GClb arm. The Agency has previously reviewed trial BO21004

Reference ID: 3314451

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

				protocol and statistical analysis plan prior to this BLA submission.
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			The pivotal trial BO21004 has 4 protocol specified analyses of the primary efficacy endpoint PFS – Stage 1a analysis, when 118 patients are randomized to the Clb arm and 175 PFS from the 3 study arms have occurred; Stage 1b analysis, when (b) (4) PFS events have occurred in the Clb and the RClb (rituximab plus chlorambucil) arms; Stage 2 interim analysis, when (b) (4) PFS events have occurred in the GClb and RClb arms; Stage 2 final analysis, when (b) (4) PFS events have occurred in the GClb and RClb arms. This application is supported by data from the Stage 1a analysis.
Appropriate references for novel statistical methodology (if present) are included.			X	Analyses did not involve novel statistical methodology
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			For patients without documented disease progression or death (for whatever reason including dropouts), PFS will be censored at the date of the last response assessment, or at the date of randomization if no response assessments were performed after the baseline visit. Patients with no response assessment will be considered non-responders in the analysis of treatment response rates.

Chia-Wen Ko 05/23/2013

Reviewing Statistician Date

Mark Rothmann 05/23/2013

Supervisor/Team Leader Date

Reference ID: 3314451

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/s/

CHIA-WEN KO
05/24/2013

MARK D ROTHMANN
05/28/2013