CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

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 – TEAM LEADER'S MEMO

NDA/Serial Number:	22-249
Drug Name:	Bendamustine (Treanda)
Indication(s):	patients with (Binet Stage B/C) B-CLL requiring therapy
Applicant:	Cephalon
Date(s):	Submission date: September 20, 2007 PDUFA due date: March 20, 2008
Review Priority:	Priority (pilot for GRMP)
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Primary Statistical Reviewer:	Shenghui Tang, Ph.D.
Secondary Reviewer:	Rajeshwari Sridhara, Ph.D., Team Leader/Deputy Division Director
Concurring Reviewer:	Aloka Chakravarty, Ph.D., Division Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Qin Ryan, M.D., Ph.D., Virginia Kwitkowski,, M.S., RN., CRNP Amna Ibrahim, M.D. (CDTL)
Project Manager:	Ms. Dorothy Pease

Keywords: Co-primary endpoints, objective response rate, progression-free survival

Conclusion and Recommendation

This is Team Leader's memo of the New Drug Application (NDA) submission seeking approval for bendamustine (Treanda) as the first line treatment of chronic lymphocytic leukemia (CLL) based on one randomized study comparing to chlorambucil in previously untreated adults with symptomatic Binet stage B or stage C CLL requiring treatment. I concur with the primary reviewer, Dr. Tang's conclusion that the data submitted supports the claim that bendamustine has demonstrated superior overall response rate (ORR) and progression-free survival (PFS) compared to chlorambucil (ORR of 59% vs. 26% and PFS HR = 0.52, p-value < 0.0001). Please refer to the primary review by Dr. Tang for the details of the study and the results.

Progression-free survival was assessed by a panel of three independent expert hematologic oncologists and also objectively calculated using an algorithm based on NCI working group criteria. According to the sponsor, in performing the review the members of the independent panel were allowed to exercise clinical judgment in determining response and did not include bone marrow evaluations as required by the NCI working group criteria. The FDA reviewers were able to verify the calculated response rates and PFS, but could not verify the same as determined by the independent panel due the subjective nature of the independent evaluation. Therefore, it is recommended that the calculated response rates and PFS estimates be included in the product label.

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/s/

Rajeshwari Sridhara
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Project Manager:	Ms. Dorothy Pease
Keywords:	Objective response rate, Duration of response, PFS

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1 Executive Summary

1.1 Conclusions and Recommendations

The sponsor submitted this application to evaluate the efficacy of Treanda (Bendamustine) compared with chlorambucil in the initial treatment of patients with chronic lymphocytic leukemia (CLL) in Binet stage B or Binet stage C requiring treatment. The applicant is seeking approval based on the co-primary efficacy endpoints-overall response rate (ORR) and progression-free survival (PFS). ORR was the proportion of patients in each treatment group with a best response of CR, nPR, or PR. Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first. The primary analyses were based on the Independent Committee for Response Assessment (ICRA) adjudicated responses and adjudicated event time points. This application was based primarily on data from an open-label, randomized, phase 3 study (02CLLIII). Patients were randomly assigned (with stratification by Binet stage and study center) to either the bendamustine or chlorambucil treatment group at a ratio of 1: 1.

A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries. Per the sponsor's statistical analysis plan, in order to account for the multiplicity of endpoints, superiority of bendamustine on PFS would not be claimed unless the 2-sided p-value for ORR and PFS were both less than or equal to 0.016. The sponsor reported that the proportion of patients with ORR (determined by ICRA) was 62% in the bendamustine treatment group compared with 33% in the chlorambucil treatment group ($p<0.0001$). The primary PFS analysis showed that the bendamustine treatment was superior to chlorambucil treatment (median 21 vs. 9 months, hazard ratio (HR) 0.23, $p<0.0001$). Based on the data submitted by the sponsor these results were confirmed by this reviewer and the data support the efficacy claim.

Whether the endpoints and the sizes of the effects on these two endpoints in this phase III study are adequate for approval is a clinical decision.

1.2 Brief Overview of Clinical Studies

Study 02CLLIII was a phase 3, randomized, open-label, multicenter study to evaluate the clinical efficacy and safety of bendamustine compared with chlorambucil in the treatment of previously untreated adults with symptomatic Binet stage B or stage C CLL requiring treatment. A 5-stage adaptive standard group sequential procedure was applied with a maximum of 4 planned interim analyses. The number of patients to be enrolled was assumed to be approximately 350 patients. This statistical design allowed closing study enrollment as soon as

the required level of significance was reached. Patients were randomized and prospectively stratified by study center and Binet stage (Binet B or Binet C). The recruitment period for the study was approximately 4 years and the follow-up period ends 1 year after the last enrolled patient completes treatment.

The data presented in this submission were those for the patients with data that were included in the third interim analysis. Following the third interim analysis the Independent Data Monitoring Committee (IDMC) made a recommendation that enrollment be stopped and the final analysis performed. The first patient was enrolled on November 5, 2002. The data were cleaned for the final analysis with a cut-off date of 26 March 2006.

1.3 Statistical Issues and Findings

Study 02CLLIII was designed to evaluate the efficacy of Treanda (Bendamustine) compared with chlorambucil in the initial treatment of patients with chronic lymphocytic leukemia (CLL) in Binet stage B or Binet stage C requiring treatment. The applicant is seeking approval based on the co-primary efficacy endpoints-overall response rate (ORR) and progression-free survival (PFS).

Statistical Issues:

1. This study was planned as a 5-stage adaptive standard group sequential design with a Pocock-type boundary and a rule for adaptively recalculating the sample size in the next stage. According to the protocol and statistical analysis plan, both primary endpoints, overall response rate (ORR) and progression-free survival (PFS), were analyzed at each interim analysis. In order to account for the multiplicity of endpoints, superiority of bendamustine on PFS would not be claimed unless the 2-sided p-value for ORR and PFS are both less than or equal to 0.016.

2. Because 3 interim analyses were performed, patients in this study could fall into the one of the following 3 segments: 1st interim analysis (n=87), 2nd interim analysis (n=77), or 3rd interim analysis (n=137). Table 1 shows that the final p-values for ORR and PFS from the combined results of all 3 segments were less than 0.0001.

Table 1. Interim Analyses for ORR and PFS

	Segment 1	Segment 2	Segment 3	Combined P-Value
Sample Size	87	77	137	
P-value for ORR[1]	0.0007	0.0043	0.0305	<0.0001
P-Value for PFS[2]	<0.0001	<0.0001	0.0295	<0.0001

1: 2-sided Fisher's Exact Test; 2: 2-sided log-rank test

This reviewer also calculated the unadjusted p-values for ORR and PFS. Both unadjusted p-values for ORR and PFS were also less than 0.0001.

The hazard ratio obtained for the combined ratio is 0.23 with a 95% confidence interval of 1.34 to 0.39 which was adjusted for repeated testing. Both point estimate and confidence interval were based on estimates within each study segment that were then combined across the segments. The unadjusted hazard ratio for PFS was 0.22 with a 95% confidence interval of 0.14 to 0.33.

3. Initial observations within the dataset received from Ribosepharm led to further quality control (QC) review of study center 1 in Bulgaria. During the QC process, a number of centers were reviewed in addition to study centers 1 and 2 in Bulgaria. The findings at center 1 in Bulgaria indicated that the center had not followed all the procedures in accordance with the protocol, ie, the data collected could not always be substantiated in the patient's medical charts or source data available for review. For center 2 in Bulgaria, the documents supporting the informed consent process were not in accordance with GCP. In order to ensure the consistency of the findings between these 2 centers and the other centers in the study, the sponsor also provided the analyses of the primary endpoint analyses with both centers 1 and 2 excluded from the analyses. A total of 54 patients were excluded (28 from center 1 and 26 from center 2). The analyses on ORR and PFS with Centers 1 & 2 Excluded showed the results were similar to those seen in the total population.

4. The log-rank test showed that there was no difference between two distributions of time to assessment, except the 1st assessment. The median difference in the 1st assessment was less than a week. With PFS medians of 21 months in the bendamustine arm and 9 months in the chlorambucil arm, these small differences in time to assessment is unlikely to influence the final outcome of the study (Table 11).

5. The investigator and the ICRA assessment showed an agreement in 258 (86%) patients; 38% of patients scored as progressors by both, and 48% of patients censored by both. In 14.3% of patients the results were discordant (Table 12).

Findings:

A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries. The sponsor reported that the proportion of patients with ORR was 62% in the bendamustine treatment group compared with 33% in the chlorambucil treatment group ($p<0.0001$) as determined by the ICRA. The primary PFS analysis showed that the bendamustine treatment was superior

to chlorambucil treatment (median 21 vs. 9 months, hazard ratio (HR) 0.23, p<0.0001). For patients in the ITT analysis set with ICRA responses of CR, PR, or nPR, the median duration of response was 16 months for the 95 responders in the bendamustine treatment group and 6 months for the 49 responders in the chlorambucil treatment group.

Table 2. Response Analysis (ITT Population)

	Bendamustine N=153	Chlorambucil N=148
Complete response (CR)	42 (27%)	3 (2%)
Nodular partial response (nPR)	15 (10%)	4 (3%)
Partial response (PR)	38 (25%)	42 (28%)
Unconfirmed response	9 (6%)	8 (5%)
Stable disease	22 (14%)	37 (25%)
Progressive disease	4 (3%)	26 (19%)
Not examined	23 (15%)	28 (19%)
Overall Response Rate (ORR) 95% CI	95 (62%) (54.4%, 69.8%)	49 (33%) (25.5%, 46.7%)
P-value for comparing ORR Fisher's exact test (adjusted)	P<0.0001	
P-value for comparing ORR Fisher's exact test (unadjusted)	P<0.0001	

Table 3. PFS Analysis in ITT Population

	Bendamustine N=153	Chlorambucil N=148
Patients with events	47 (31%)	66 (45%)
Median TTP in months (95% CI)	21.1 (17.7, 25.6)	9.4 (8.7, 11.7)
Adjusted P-value (log-rank test)	P<0.0001	
Unadjusted P-value (log-rank test)	P<0.0001	
Adjusted Hazard ratio (BEN/CLB) (95% CI)	0.23 (0.13, 0.39)	
Unadjusted Hazard ratio (CLB/BEN) (95% CI)	0.22 (0.14, 0.33)	

2 Introduction

2.1 Overview

The applicant has submitted this application to evaluate the efficacy of Treanda (Bendamustine) compared with chlorambucil in the initial treatment of patients with chronic lymphocytic leukemia (CLL) in Binet stage B or Binet stage C requiring treatment.

2.1.1 Background

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disorder that is characterized by a progressive accumulation of functionally incompetent lymphocytes of monoclonal origin. The disorder is considered under the current World Health Organization (WHO) classification to be identical to small lymphocytic lymphoma (SLL), representing a different stage of that disease. CLL is the most common form of leukemia in Western industrialized nations with an annual incidence of 3 to 3.5 cases per 100000. It is predominantly a disease of the elderly with a median age of diagnosis of 72 years. CLL is approximately twice as common in men as in women.

Two staging systems for CLL have been widely adopted. The Rai staging system is based on the progressive accumulation of malignant cells with physical signs of progression (eg, lymphadenopathy) and eventual compromise of bone marrow function. The Binet staging system is similar but places more emphasis on the number of involved sites. The Binet staging system is more commonly applied in Europe and was used in this study.

CLL typically follows an indolent course and the recommended clinical approach to patients with Binet stage A disease, with no specific risk factors or evidence of progression, is watchful waiting. Treatment is generally initiated for patients with symptomatic Binet stage B disease (3 or more enlarged nodal areas) or for those patients with stage C disease (disease-related anemia or thrombocytopenia). For patients under 65 years of age the therapeutic objective is to achieve long-lasting remissions, while in older patients the treatment is largely palliative with a goal of maintaining a high quality of life.

For these older patients with CLL, continuous or intermittent oral administration of chlorambucil, either alone or in combination with glucocorticoids, has been considered a principal treatment option (CLL Trialists' Collaborative Group) 999). This regimen has no impact on the natural history of CLL. However, alkylating agents such as chlorambucil are particularly suitable for the treatment of lymphocytosis in this indolent disease because they have cytotoxic effects on leukemic cells independently of cell division. In younger or healthier patients

fludarabine and fludarabine-based regimens have proven successful in achieving a higher proportion of durable responses than chlorambucil. However, this increased efficacy was achieved with a cost in the tolerability of the regimens, and the long-term benefits in overall survival remain to be determined.

Bendamustine is a cytotoxic compound with an alkylating nitrogen mustard group and a purine-like benzimidazole ring. Bendamustine appears to act primarily as an alkylating agent inducing extensive and durable deoxyribonucleic acid (DNA) breaks, which result in inhibition of DNA replication, repair, and transcription, and cell cycle arrest. The presence of the benzimidazole ring structure of bendamustine may explain differences between bendamustine and other alkylating agents, such as slower repair of damaged DNA following exposure, activity against multi drug resistant cells, and only partial cross-resistance with otheralkylating agents.

Bendamustine has been studied as a treatment for patients with CLL in a number of clinical studies, and is approved for the treatment of this disease in Germany. In a study of bendamustine in a mixed population of chemonaïve (previously untreated) and previously treated patients with CLL, Kath et al demonstrated a high rate of durable response with doses of bendamustine of 50 to 60 mg/m2, days 1 through 5 every 28 days, with a complete response (CR) rate of25% and an overall response rate of75% in the 12 previously untreated patients. A regimen of70 to 110 mg/m2 bendamustine on days 1 and 2 of a 3-week cycle was also shown to be efficacious in studies of patients with relapsed/refractory CLL.

Study 02CLLIII was a phase 3, randomized, open-label, multicenter study to evaluate the clinical efficacy and safety of bendamustine compared with chlorambucil in the treatment of previously untreated adults with symptomatic Binet stage B or stage C CLL requiring treatment. A 5-stage adaptive standard group sequential procedure was applied with a maximum of 4 planned interim analyses. The final number of patients to be enrolled could not be calculated apriori, but it was assumed to be approximately 350 patients. This statistical design allowed closing study enrollment as soon as the required level of significance was reached, but only at 1 of the prespecified interim analyses. Patients were randomized and prospectively stratified by study center and Binet stage (Binet B or Binet C). The recruitment period for the study was approximately 4 years and the follow-up period ends 1 year after the last enrolled patient completes treatment.

2.1.2 Statistical Issues

1. This study was planned as a 5-stage adaptive standard group sequential design with a Pocock-type boundary and a rule for adaptively recalculating the sample size in the next stage. According to the protocol and statistical analysis

plan, both primary endpoints, overall response rate (ORR) and progression-free survival (PFS), were analyzed at each interim analysis. In order to account for the multiplicity of endpoints, superiority of bendamustine on PFS would not be claimed unless the 2-sided p-value for ORR and PFS are both less than or equal to 0.016.

2. Because 3 interim analyses were performed, patients in this study could fall into the one of the following 3 segments: 1st interim analysis (n=87), 2nd interim analysis (n=77), or 3rd interim analysis (n=137). Table 1 shows that the final p-values for ORR and PFS from the combined results of all 3 segments were less than 0.0001.This reviewer also calculated the unadjusted p-values for ORR and PFS. Both unadjusted p-values for ORR and PFS were also less than 0.0001.

   The hazard ratio obtained for the combined ratio is 0.23 with a 95% confidence interval of 1.34 to 0.39 which was adjusted for repeated testing. Both point estimate and confidence interval were based on estimates within each study segment that were then combined across the segments. The unadjusted hazard ratio for PFS was 0.22 with a 95% confidence interval of 0.14 to 0.33.

3. Initial observations within the dataset received from Ribosepharm led to further quality control (QC) review of study center 1 in Bulgaria. During the QC process, a number of centers were reviewed in addition to study centers 1 and 2 in Bulgaria. The findings at center 1 in Bulgaria indicated that the center had not followed all the procedures in accordance with the protocol, ie, the data collected could not always be substantiated in the patient's medical charts or source data available for review. For center 2 in Bulgaria, the documents supporting the informed consent process were not in accordance with GCP. In order to ensure the consistency of the findings between these 2 centers and the other centers in the study, the sponsor also provided the analyses of the primary endpoint analyses with both centers 1 and 2 excluded from the analyses. A total of 54 patients were excluded (28 from center 1 and 26 from center 2). The analyses on ORR and PFS with Centers 1 & 2 Excluded showed the results were similar to those seen in the total population.

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5. The investigator and the ICRA assessment showed an agreement in 258 (86%) patients; 38% of patients scored as progressors by both, and 48% of patients censored by both. In 14.3% of patients the results were discordant (Table 12).

2.2 Data Sources

Data used for review is from the electronic submission received on September 20, 2007. The data is in the network path \\Cdsesub1\nonectd\N22249\N_000\2007-09-19.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries (non U.S.) as follows: Germany (126 patients at 22 centers), Bulgaria (117 patients at 8 centers), Italy (19 patients at 5 centers), France (16 patients at 2 centers), Spain (15 patients at 3 centers), Sweden (4 patients at 2 centers), Austria (3 patients at 2 centers), and the UK (1 patient). All randomized patients were evaluated for efficacy. The first patient was enrolled on November 5, 2002. The data were cleaned for the final analysis with a cut-off date of 26 March 2006.

3.1.1 Study Design

This is a phase 3, randomized, open-label, multicenter study to evaluate the clinical efficacy and safety of bendamustine compared with chlorambucil in the treatment of previously untreated adults with symptomatic Binet stage B or stage C CLL requiring treatment. A 5-stage adaptive standard group sequential procedure was applied with a maximum of 4 planned interim analyses. The final number of patients to be enrolled could not be calculated a priori, but it was assumed to be approximately 350 patients.

Patients were randomized and prospectively stratified by study center and Binet stage (Binet B or Binet C). Patients who met all inclusion and exclusion criteria were randomly assigned (1: 1) to receive either bendamustine at 100 mg/m2 administered by continuous intravenous (iv) infusion over a period of30 minutes on days 1 and 2 of each cycle or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on days 1 and 15 of each cycle (or as divided doses on days 1 and 2 and days 15 and 16 of each cycle). The recruitment period for the study was approximately 4 years and the follow-up period ended 1 year after the last enrolled patient completed treatment.

3.1.2 Study Objectives

The objective of this study was to demonstrate superior efficacy of bendamustine compared to chlorambucil in the initial treatment of patients with CLL in Binet stage B or Binet stage C requiring treatment.

The primary endpoints of this study were to compare overall response rate (ORR) and progression-free survival (PFS) between the bendamustine group and the chlorambucil group.

The secondary endpoints of the study were as follows:
. time to progression (TTP)
. duration of response
. overall survival (OS)
. infection rate
. quality of life
. toxicities

3.1.3 Efficacy Endpoints

The primary efficacy endpoints were overall response rate (ORR) and progression-free survival (PFS) assessed for the intent-to-treat (ITT) population using adjudicated responses and dates of progression from the ICRA.

Overall response rate (ORR) was defined as the proportion of patients in each treatment group with a best response of CR, nPR, or PR to treatment.

Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first. The primary analysis of progression-free survival was based on the ICRA adjudicated responses and adjudicated event time points.

ORR was to be determined using the NCI- WG criteria for response and these were detailed in the protocol as follows:

<u>Complete response/remission (CR)</u>

CLL response was considered a CR if all of the following criteria were met for at least 8 weeks:
- enlarged lymph nodes no longer detectable by palpation (x-ray or ultrasound were optional)
- absence of hepatomegaly or splenomegaly confirmed by palpation (computed
- tomography (CT) and ultrasound were optional)
- no disease symptoms (ie, B symptoms) present

- lymphocytes of 4.0xl 09/L or less
- neutrophils of 1.5xl09/L or more
- platelets greater than $100xl0^9$/L
- Hgb greater than 11 g/dL (without blood transfusion)
- Bone marrow biopsy (histology and cytology) was to be performed 8 weeks after meeting the above criteria. The bone marrow must have been at least normocellular for age with less than 30% lymphocytes.

Nodular partial response/remission (nPR)

Patients fulfilling all of the above criteria for CR with lymphocytes less than 30% in the bone marrow sample but still showing focal infiltration were assessed as having a response of nPR. These patients seem to have a shorter PFS than patients with confirmed CR and, therefore, were to be documented and analyzed separately.

Partial response/remission (PR)

CLL response was considered a PR if the following criteria were met for at least 8 weeks:
- at least a 50% decrease in peripheral blood lymphocyte counts from the pretreatment baseline value

and at least 1 of the following 2 criteria:
- at least a 50% reductiQn of enlarged lymph nodes (total of affected lymph nodes)
- a 50% reduction of hepatomegaly and/or splenomegaly (if enlarged at baseline)

and at least 1 of the following 3 criteria
- neutrophil count 1 .5x1 09/L or more or 50% improvement compared with the baseline value
- platelet count greater than 1 00x1 09/L or 50% improvement compared with the baseline value
- Hgb greater than 11 g/dL or 50% improvement compared with the baseline value (without a blood transfusion)

Progressive disease (PD)

A patient had PD if at least 1 of the following criteria was met:
- at least a 50% lymph node enlargement (from the nadir) (total of enlargement of at least 2 lymph nodes) (one of the enlarged lymph nodes was to have a diameter of at least 2 cm) on 2 consecutive occasions at least 2 weeks apart and/or new palpable lymph nodes
- at least a 50% increase (from baseline) in liver or spleen size, as determined by measurements under the respective costal arch; occurrence of definite hepatomegaly or splenomegaly that had not previously been detectable

- at least a 50% increase in absolute lymphocyte count (ALC) (from the nadir) to At least 5xio9/L
- transformation to a more aggressive histology (Richter or PLL with more than 55% pro lymphocytes)

Stable Disease (SD)

A patient had SD if CR, nPR, PR, and PD criteria were not met.

The ICRA were to measure the patient's response to treatment by response criteria outlined above, based on a review of clinical data listings provided by Ribosepharm. At the ICRA meeting on 24 and 25 August 2006, the ICRA adopted the following conventions:

- Disease progression was achieved if at least 1 parameter worsened by 50% compared to the best response during study conduct.
- For the evaluation of hepatomegaly and splenomegaly, results from palpation were used. Only ifno palpation data were available, were data from imaging techniques used for the response assessment.
- Calculations of the reduction in lymph node size took into account all enlarged nodes reported.
- Patients who had CR for all other parameters but had no bone marrow biopsy were considered PR. Patients with PR or CR but missing response confirmation due to the date of the data cut-off on 27 February 2006 were classified as "unconfirmed" and entered the analysis as nonresponders. Patients who had PR or CR but progressed prior to the first follow-up visit were considered nonresponders.
- Since no threshold for baseline ALC was given in the inclusion criteria the ICRA agreed to consider patients with a baseline ALC of less than 5x 109/L to be eligible. These patients may have had a diagnosis of SLL and this disease is now recognized as the same disease as CLL but at a different stage.

3.1.4 Sample Size Considerations

The previous studies suggested that the anticipated effects of bendamustine versus chlorambucil might be an ORR of approximately 60% versus 30% (initial primary endpoint) and a median PFS of approximately 20 months versus 14 months (second primary endpoint), respectively. Under these assumptions, the sample size required to provide 80% power with a 2-tailed test at α=0.05 was estimated at 42 patients per arm for the first primary endpoint of ORR, and at a total of 326 patients for the second primary endpoint of PFS. Both of these estimates were based on a fixed sample design with a single primary endpoint and no interim analyses. This study used a 5-stage adaptive standard group sequential design. The protocol provided for a maximum of 4 interim analyses and 1 final

efficacy analysis. When the proposed 5-stage adaptive standard group sequential was implemented, the actual number of patients in this study was 301.

3.1.5 Interim Analyses

The first interim efficacy analysis was to take place after 40 patients in each treatment group had received at last 5 cycles of treatment. At the time of the first interim analysis, although the prespecified stopping criteria and resultant p-value for efficacy had been reached, it was recommended that the study continue to obtain more safety data, and that the second interim analysis should be performed after data from approximately 80 additional patients had accrued. At the time of the second interim analysis, although the prespecified stopping criteria and resultant p-value for efficacy had again been reached, it was recommended that the study continue until a total of approximately 300 patients were enrolled in the study without any intervening interim analyses. During the conduct of the first 2 interim analyses, it became evident that the response evaluations were inconsistently managed by the individual investigators. Before the third interim analysis, to allow similar evaluations for all patients, an Independent Response Assessment Committee (ICRA) was established to assess the overall response for all patients included in the third interim analysis. The third interim analysis was performed after 305 patients had been enrolled. After review of data from the third interim analysis, the Independent Data Monitoring Committee (IDMC) recommended that patient recruitment be stopped and a final analysis performed based on available data. Enrollment was stopped by Ribosepharm on 21 November 2006 with a total of 319 patients enrolled. The decision of Ribosepharm was to perform the final analysis on the data that was supplied to the ICRA and IDMC for the third interim analysis; the additional patients and data would be part of a follow-up analysis when all patients completed follow-up. The database sent to Cephalon contained data on 305 patients; however, it was the understanding of Cephalon that the data were verified and cleaned only through 26 March 2006, although the database contained data beyond that date. Cephalon decided to analyze the cleaned data, and data from visit dates beyond 26 March 2006 were not included in this analysis, nor were data on adverse events, concomitant diseases, and concomitant medications with start dates beyond 26 March 2006. With the application of this cut-off date, the dataset used by Cephalon contains data on 302 patients.

3.1.6 Efficacy Analysis Methods

The overall response rate was analyzed with a Fisher's exact test stratified by Binet stage. The estimated overall response rate for each treatment group is presented with an unadjusted 95% CI. In order to estimate the difference in overall response rate between the 2 treatment groups, the estimator proposed by Lehmacher and Wassmer, stratified by Binet stage, was used. A 95% repeated CI

was constructed around this estimate of the difference in overall response rate based on Lehmacher and Wassmer.

PFS was analyzed with the log-rank test stratified by Binet stage. The overall hazard ratio of bendamustine versus chlorambucil and its unadjusted 95% CI were generated based on the log-rank statistic, stratified by Binet stage, and combined across study groups, following the approach proposed by Lehmacher and Wassmer.

Reviewer's Comments:

This study was planned as a 5-stage adaptive standard group sequential design with a Pocock-type boundary. The first interim analysis was performed after 40 patients in each group were followed up for at least 4 months (corresponding to 4 cycles). The sample size of the next sequence was recalculated after the interim analysis. According to the protocol and statistical analysis plan, both primary endpoints, overall response rate (ORR) and progression-free survival (PFS), were analyzed at each interim analysis. In order to account for the multiplicity of endpoints, superiority of bendamustine on PFS would not be claimed unless the 2-sided p-value for ORR and PFS are both less than or equal to 0.016, which is the cut-off point following Pocock's group sequential procedure with 5 stages.

3.1.7 Sponsor's Results and Statistical Reviewer's Findings/ Comments

A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries as follows: Germany (126 patients at 22 centers), Bulgaria (117 patients at 8 centers), Italy (19 patients at 5 centers), France (16 patients at 2 centers), Spain (15 patients at 3 centers), Sweden (4 patients at 2 centers), Austria (3 patients at 2 centers), and the UK (1 patient). There were no US patients entered on this study. All randomized patients were evaluated for efficacy.

3.1.7.1 Baseline Characteristics

Efficacy analyses were performed on data from the Intent-to-Treat Population. The Intent-to-Treat Population included 153 subjects in the bendamustine group and 148 subjects in the chorambucil group (Table 4).

Table 4. Demographics and Baseline Characteristics

Demographic information Variable/Statistic	Bendamustine (N=153)	Chlorambucil (N=148)	Total (N=301)
Age, (years)			
Mean	63.0	63.6	63.3
SD	7.68	8.62	8.15
Median	63.0	66.0	64.0
Min, max	45.0, 77.0	38.0, 78.0	38.0, 78.0
Age group			
<65 years	82 (54)	69 (47)	151 (50)
≥65 years	71 (46)	79 (53)	150 (50)
Sex, n (%)			
Men	97 (63)	90 (61)	187 (62)
Women	56 (37)	58 (39)	114 (38)
Race, n (%)			
White	153 (100)	147 (>99)	300 (>99)
Other[a]	0	1 (<1)	1 (<1)
Weight (kg)			
n	152	145	297
Mean	78.2	74.0	76.1
SD	15.06	13.26	14.35
Median	77.4	72.0	75.0
Min, max	50.0, 133.0	48.8, 118.0	48.8, 133.0
Height (cm)			
n	153	145	298
Mean	169.0	168.4	168.7
SD	8.60	9.04	8.80
Median	170.0	168.0	169.0
Min, max	147.0, 190.0	149.0, 189.0	147.0, 190.0

SOURCE: Summary 15.3.1, Listing 4.

[a] Race for patient 10516 in the chlorambucil treatment group was not specified.

Min=minimum; max=maximum; SD=standard deviation.

Disease specific characteristics Variable/Statistic	Bendamustine (N=153)	Chlorambucil (N=148)	Total (N=301)
Lymphadenopathy, n (%)			
Yes	121 (79)	122 (82)	243 (81)
No	32 (21)	26 (18)	58 (19)
Splenomegaly, n (%)			
Yes	117 (76)	118 (80)	235 (78)
No	34 (22)	27 (18)	61 (20)
Missing	2 (1)	3 (2)	5 (2)
Hepatomegaly, n (%)			
Yes	74 (48)	68 (46)	142 (47)
No	79 (52)	76 (51)	155 (51)
Missing	0	4 (3)	4 (1)
Hypercellular bone marrow, n (%)			
Yes	121 (79)	108 (73)	229 (76)
No	23 (15)	33 (22)	56 (19)
Missing	9 (6)	7 (5)	16 (5)
Constitutional symptoms, n (%)[a]			
Fever	15 (10)	27 (18)	42 (14)
Night sweats	73 (48)	74 (50)	147 (49)
Weight loss	42 (27)	38 (26)	80 (27)
Any (fever, night sweats, or weight loss)	78 (51)	78 (53)	156 (52)
None	74 (48)	67 (45)	141 (47)
Missing	1 (<1)	3 (2)	4 (1)
Lymphocyte count (10^9/L)			
n	150	140	290
Mean	65.7	65.1	65.4
SD	69.23	54.14	62.29
Median	42.4	53.2	47.3
Min, max	1.2, 462.8	0.8, 252.8	0.8, 462.8
Binet stage, n (%)			
B	109 (71)	102 (69)	211 (70)
C	44 (29)	46 (31)	90 (30)
Days since initial tumor diagnosis			
n	153	143	296
Mean	560.6	713.2	634.3
SD	963.73	997.67	981.59
Median	171.0	235.0	191.5
Min, max	3.0, 5629.0	2.0, 4463.0	2.0, 5629.0
Previous cancer treatments applied, n (%)			
Yes	0	0	0
No	153 (100)	147 (>99)	300 (>99)
Missing	0	1 (<1)	1 (<1)
Immunophenotype, n (%)[a]			
CD5	147 (96)	144 (97)	291 (97)
CD19	140 (92)	131 (89)	271 (90)
CD20	127 (83)	120 (81)	247 (82)
CD23	138 (90)	134 (91)	272 (90)
Coexpression of CD5, CD23, and either CD19 or CD20 or both	137 (90)	133 (90)	270 (90)
Unknown	3 (2)	2 (1)	5 (2)

Abbreviations and footnotes are provided on the last page of this table.

(continued)

Disease specific characteristics Variable/Statistic	Bendamustine (N=153)	Chlorambucil (N=148)	Total (N=301)
Transformed diagnosis, n (%)			
Yes	0	0	0
No	153 (100)	144 (97)	297 (99)
Missing	0	4 (3)	4 (1)
Coombs test			
Positive	13 (8)	8 (5)	21 (7)
Negative	115 (75)	112 (76)	227 (75)
Missing	25 (16)	28 (19)	53 (18)
Lactate dehydrogenase (U/L)			
n	149	139	288
Mean	370.2	388.4	379.0
SD	164.64	215.42	190.72
Median	345.0	350.0	346.5
Min, max	105.0, 1037.0	137.0, 1621.0	105.0, 1621.0

SOURCE: Summary 15.4.1, Listing 5.1, Listing 5.2, and Listing 5.3.
[a] Patients may be counted in more than 1 immunophenotype or constitutional symptom.
Min=minimum; max=maximum; SD=standard deviation.

Reviewer's Comments:

There were no apparent differences between two study arms with regard to demographic and baseline characteristics in the ITT population.

3.1.7.2 Primary Efficacy Analyses

The primary efficacy endpoints were overall response rate (ORR) and progression-free survival (PFS) assessed for the intent-to-treat (ITT) population using adjudicated responses and dates of progression from the ICRA.

Overall response rate (ORR) was defined as the proportion of patients in each treatment group with a best response of CR, nPR, or PR to treatment.

Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first. The primary analysis of progression-free survival was based on the ICRA adjudicated responses and adjudicated event time points.

Initial observations within the dataset received from Ribosepharm led to further quality control (QC) review of study center 1 in Bulgaria. During the QC process, a number of centers were reviewed by the sponsor in addition to study centers 1 and 2 in Bulgaria. The findings at center 1 in Bulgaria indicated that the center had not followed all the procedures in accordance with the protocol, ie, the data collected could not always be substantiated in the patient's medical charts or source data available for review. For center 2 in Bulgaria, the documents supporting the informed consent process were not in accordance with GCP. In

order to ensure the consistency of the findings between these 2 centers and the other centers in the study, the sponsor also provided the analyses of the primary endpoint analyses with both centers 1 and 2 excluded from the analyses. A total of 54 patients were excluded (28 from center 1 and 26 from center 2).

Overall response rate (ORR)

Results for the primary efficacy endpoint of ORR for all patients in the ITT analysis set using adjudicated responses from the ICRA showed statistically significant differences between treatment groups in favor of bendamustine treatment (2-sided p value <0.0001, which is lower than the required adjusted level of 0.016). The ORR for the 153 patients receiving bendamustine was 62% (CI: 54.40, 69.78) and for the 148 patients receiving chlorambucil was 33% (CI: 25.53, 40.69) (Table 5). Table 6 shows the calculated responses which were the result of an algorithmic application of the NCI-WG criteria.

Table 5. Response Analysis Based on ICRA Assessments (ITT Population)

	Bendamustine N=153	Chlorambucil N=148
Complete response (CR)	42 (27%)	3 (2%)
Nodular partial response (nPR)	15 (10%)	4 (3%)
Partial response (PR)	38 (25%)	42 (28%)
Unconfirmed response	9 (6%)	8 (5%)
Stable disease	22 (14%)	37 (25%)
Progressive disease	4 (3%)	26 (19%)
Not examined	23 (15%)	28 (19%)
Overall Response Rate (ORR) 95% CI	95 (62%) (54.4%, 69.8%)	49 (33%) (25.5%, 46.7%)
P-value for comparing ORR Fisher's exact test (adjusted)	P<0.0001	
P-value for comparing ORR Fisher's exact test (unadjusted)	P<0.0001	

Table 6. Response Analysis Based on Calculated Responses (ITT Population)

	Bendamustine N=153	Chlorambucil N=148
Complete response (CR)	13 (8%)	1 (<1%)
Nodular partial response (nPR)	4 (3%)	0 (0%)
Partial response (PR)	73 (48%)	37 (25%)
SD/PD/NE	63 (41%)	110 (74%)
Overall Response Rate (ORR) 95% CI	90 (59%) (51.0%, 66.6%)	38 (26%) (18.6%, 32.7%)
P-value for comparing ORR Fisher's exact test (adjusted)	P<0.0001	
P-value for comparing ORR Fisher's exact test (unadjusted)	P<0.0001	

Table 7. Response Analysis Based on ICRA Assessments (Centers 1 & 2 Excluded)

	Bendamustine N=126	Chlorambucil N=121
Complete response (CR)	30 (24%)	2 (2%)
Nodular partial response (nPR)	11 (9%)	4 (3%)
Partial response (PR)	34 (27%)	32 (26%)
Unconfirmed response	9 (7%)	7 (6%)
Stable disease	19 (15%)	31 (26%)
Progressive disease	3 (2%)	22 (18%)
Not examined	20 (16%)	23 (19%)
Overall Response Rate (ORR) 95% CI	75 (60%) (50.9%, 68.1%)	38 (31%) (23.1%, 39.7%)
P-value for comparing ORR Fisher's exact test (adjusted)	P<0.0001	
P-value for comparing ORR Fisher's exact test (unadjusted)	P<0.0001	

Progression-Free Survival Based on ICRA Assessments (Primary Analysis)

For patients in the ITT analysis set, median PFS based on the ICRA responses was 21 months in the bendamustine treatment group and 9 months in the chlorambucil treatment group; the difference between treatment groups in PFS was statistically significant in favor of bendamustine treatment ($p<0.0001$) with a hazard ratio of 0.23 (Table 8 and Figure 1). The PFS analysis based on calculated responses was shown in Table 9 and Figure 2.

Table 8. PFS Analysis Based on ICRA Assessments in ITT Population

	Bendamustine N=153	Chlorambucil N=148
Patients with events	47 (31%)	66 (45%)
Median in months (95% CI)	21.1 (17.7, 25.6)	9.4 (8.7, 11.7)
Adjusted P-value (log-rank test)	P<0.0001	
Unadjusted P-value (log-rank test)	P<0.0001	
Adjusted Hazard ratio (BEN/CLB) (95% CI)	0.23 (0.13, 0.39)	
Unadjusted Hazard ratio (BEN/CLB) (95% CI)	0.22 (0.14, 0.33)	

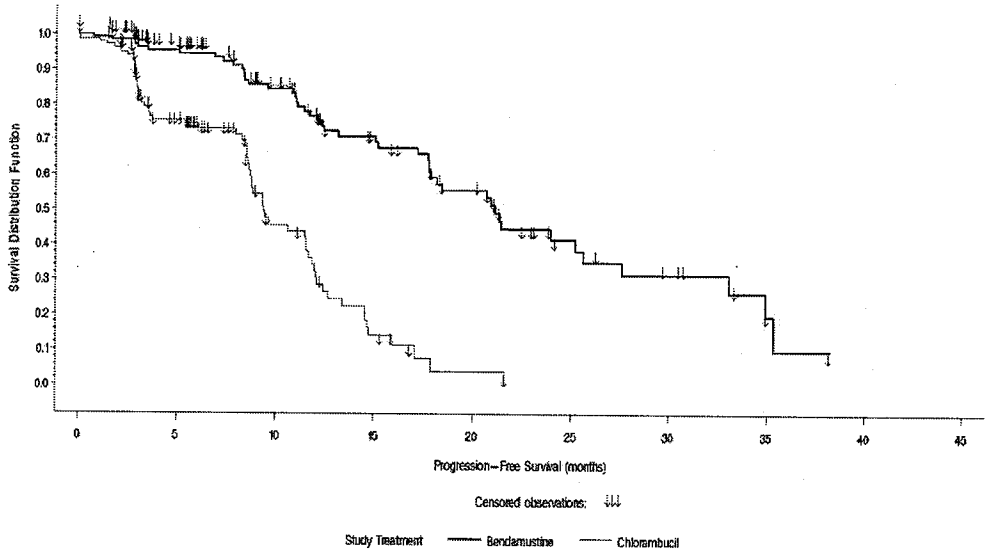

Figure 1: Progression-Free Survival Based on ICRA Assessments (ITT)
Source: Figure 4 of the sponsor's study report

Table 9. PFS Analysis Based on Calculated Responses in ITT Population

	Bendamustine N=153	Chlorambucil N=148
Patients with events	55 (36%)	83 (56%)
Median in months (95% CI)	17.6 (11.7, 23.5)	5.7 (5.6, 8.6)
Adjusted P-value (log-rank test)	P<0.0001	
Unadjusted P-value (log-rank test)	P<0.0001	
Adjusted Hazard ratio (BEN/CLB) (95% CI)	0.27 (0.17, 0.43)	
Unadjusted Hazard ratio (BEN/CLB) (95% CI)	0.52 (0.42, 0.62)	

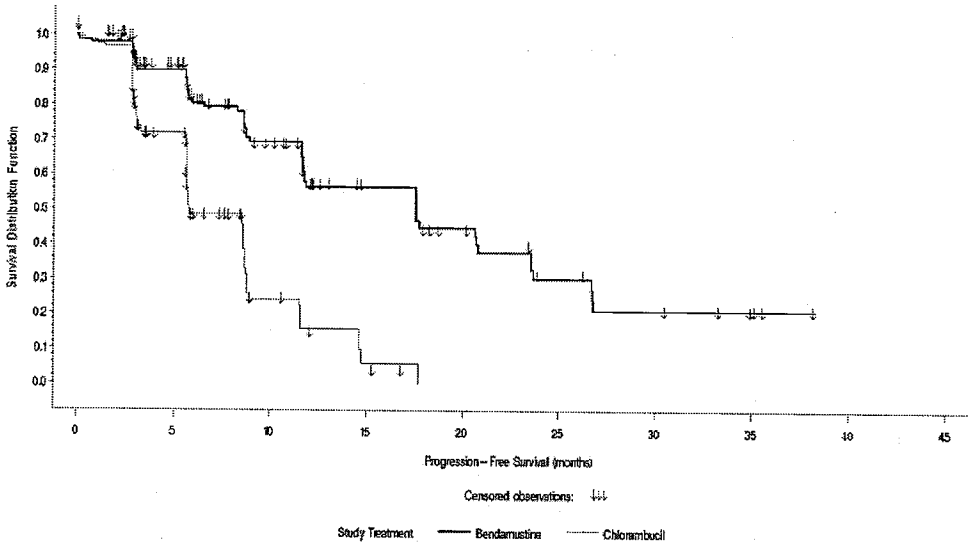

Figure 2: Progression-Free Survival Based on Calculated Responses (ITT)
Source: Figure 6 of the sponsor's study report

Table 10. PFS Analysis Based on ICRA Assessments (Centers 1 & 2 Excluded)

	Bendamustine N=126	Chlorambucil N=121
Patients with events	35 (28%)	54 (45%)
Median in months (95% CI)	21.1 (18.2, 33.0)	9.6 (8.8, 11.9)
Adjusted P-value (log-rank test)	P<0.0001	
Unadjusted P-value (log-rank test)	P<0.0001	
Adjusted Hazard ratio (CLB/BEN) (95% CI)	0.23 (0.13 , 0.42)	
Unadjusted Hazard ratio (CLB/BEN) (95% CI)	0.22 (0.13, 0.35)	

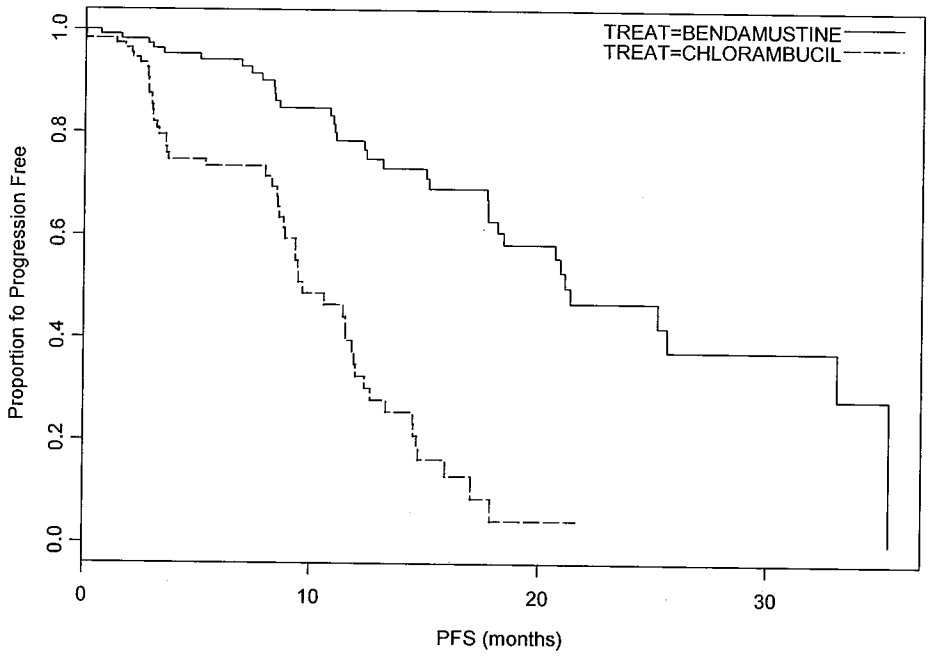

Figure 3: Progression-Free Survival Based on ICRA Assessments (Centers 1 & 2 Excluded)

Reviewer's Comments:

Because 3 interim analyses were performed, patients in this study could fall into the one of the following 3 segments: 1st interim analysis (n=87), 2nd interim analysis (n=77), or 3rd interim analysis (n=137). Table 1 shows that the final p-

values for ORR and PFS from the combined results of all 3 segments were less than 0.0001.This reviewer also calculated the unadjusted p-values for ORR and PFS. Both unadjusted p-values for ORR and PFS were also less than 0.0001.

The hazard ratio obtained for the combined ratio is 0.23 with a 95% confidence interval of 1.34 to 0.39 which was adjusted for repeated testing. Both point estimate and confidence interval were based on estimates within each study segment that were then combined across the segments. The unadjusted hazard ratio for PFS was 0.22 with a 95% confidence interval of 0.14 to 0.33.

The analyses on ORR and PFS with Centers 1 & 2 Excluded showed the results were similar to those seen in the total population (Tables 7 & 9, Figure 3).

In order to evaluate if the time of assessment influenced the PFS outcome, the following exploratory analyses were conducted.

Time from randomization to assessment was calculated. Log-rank test was used to test if cumulative percentages (survival curves) were equal. Results from the tests are presented in Table 11.

Table 11. Median (in Monthss) of Time to Assessment and Log-rank Test

Time from randomization to Assessment	**BEN N= 153**	**CLB N=148**	**Log-rank Test**
1st Assessment	3.0	2.9	0.009
2nd Assessment	5.7	5.6	0.561
3rd Assessment	8.9	8.8	0.957
4th Assessment	11.8	11.8	0.469
5th Assessment	15.1	15.0	0.975

The log-rank test showed that there was no difference between two distributions of time to assessment, except the 1st assessment. The median difference in the 1st assessment was less than a week. With PFS medians of 21 months in the bendamustine arm and 9 months in the chlorambucil arm, these small differences in time to assessment is unlikely to influence the final outcome of the study.

The investigator and the ICRA assessment showed an agreement in 258 (86%) patients; 38% of patients scored as progressors by both, and 48% of patients censored by both. In 143% of patients the results were discordant (Table 12).

Table 12. Comparison Between Independent Committee for Response Assessment and Investigator Assessment Responders (ITT)

	Number (%) of patients								
	Investigator response								
	Bendamustine (N=153)			Chlorambucil (N=148)			Total (N=301)		
ICRA response	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	83 (54)	12 (8)	95 (62)	30 (20)	19 (13)	49 (33)	113 (38)	31 (10)	144 (48)
No	7 (5)	51 (33)	58 (38)	5 (3)	94 (64)	99 (67)	12 (4)	145 (48)	157 (52)
Total	90 (59)	63 (41)	153 (100)	35 (24)	113 (76)	148 (100)	125 (42)	176 (58)	301 (100)

SOURCE: Summary 15.11, Listing 14.
ICRA=Independent Committee for Response Assessment.
NOTE: A responder is a patient with a best response of complete response (CR), nodular partial response (nPR), and partial response (PR). A patient with a missing response was assigned a responder value of no.

Source: Table 27 of the study report

3.1.7.3 Secondary Efficacy Analyses

The secondary efficacy variables included duration of response, survival and other clinical benefits. This review will focus on duration of response and survival.

Duration of Response (DR) The duration of response was the time from the ICRA date of response to progression or death. For patients in the ITT analysis set with ICRA responses of CR, PR, or nPR, the median duration of response was 16 months for the 95 responders in the bendamustine treatment group and 6 months for the 49 responders in the chlorambucil treatment group (Table 13).

Table 13. Duration of Response Analysis in ITT Population

	Bendamustine N=153	Chlorambucil N=148
Patients with response	95	49
Patients with progression	35 (37%)	31 (63%)
Median in months (95% CI)	15.9 (12.5, 23.9)	6.0 (5.4, 6.5)

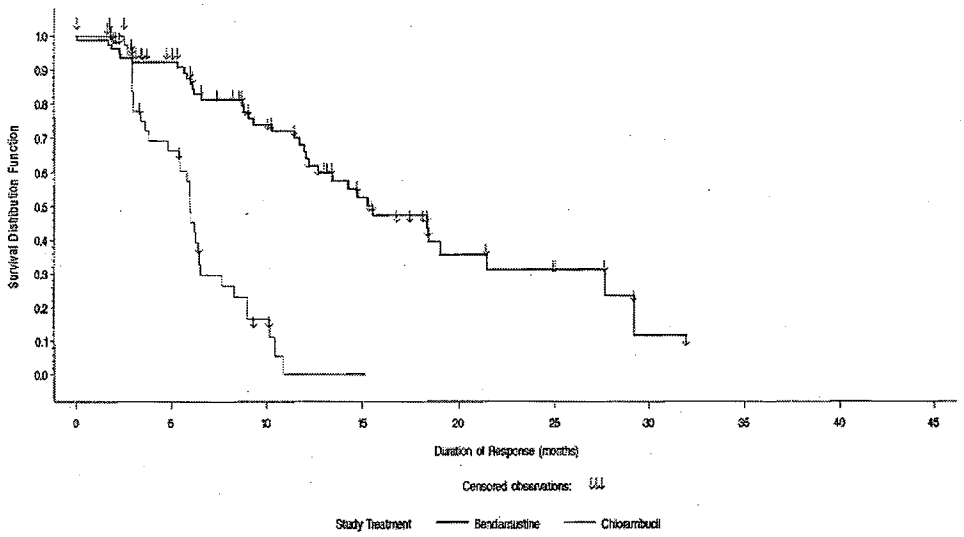

Figure 4 Duration of Response Based on Independent Committee for Response Assessment Responses by Treatment Group (Intent-to- Treat Analysis Set)

Table 14. Duration of Response Analysis (Centers 1 and 2 excluded)

	Bendamustine N=126	Chlorambucil N=121
Patients with response	75	37
Patients with progression	24 (32%)	25 (67%)
Median in months (95% CI)	19.0 (12.9, 29.1)	6.2 (5.4, 8.3)

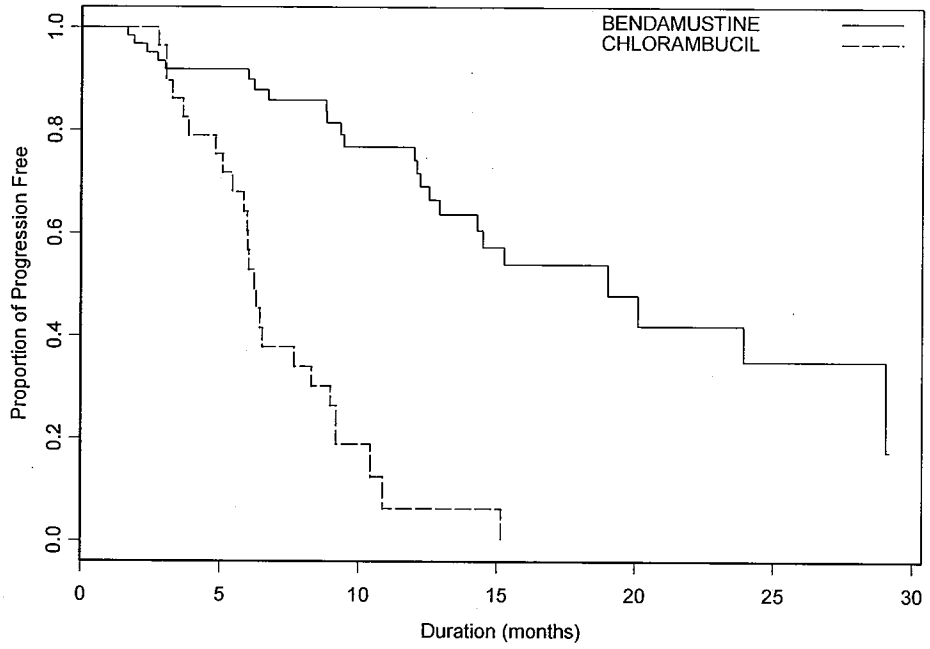

Figure 5. Duration of Response Based on Independent Committee for Response Assessment Responses by Treatment Group (Centers 1 and 2 excluded)

Overall Survival In the sponsor's original NDA submission, there were 17 deaths for each arm. Median survival was not reached in both arms. On 16 October 2007, the sponsor submitted an updated of survival data for study 02CLLIII. Of the 301 patients in the NDA, an additional 20 patients in study 02CLLIII died between 26 March 2006 and 31 May 2007. Seven of these patients were in the bendamustine treatment group and 13 were in the chlorambucil treatment group. Among these patients, per sponsor, there were 2 CLL-related deaths for bendamustine and 5 for chlorambucil (Table 15).

Table 15. Updated Survival Analysis in ITT Population

	Bendamustine N=153	Chlorambucil N=148
Patients with deaths	24 (16%)	30 (20%)
Median in months (95% CI)	40.7 (38.3, 51.7)	39.6 (34.2, 50.2)
P-value	0.9110	
Hazard Ratio (CLB/BEN) (95% CI)	0.967 (0.465, 2.009)	

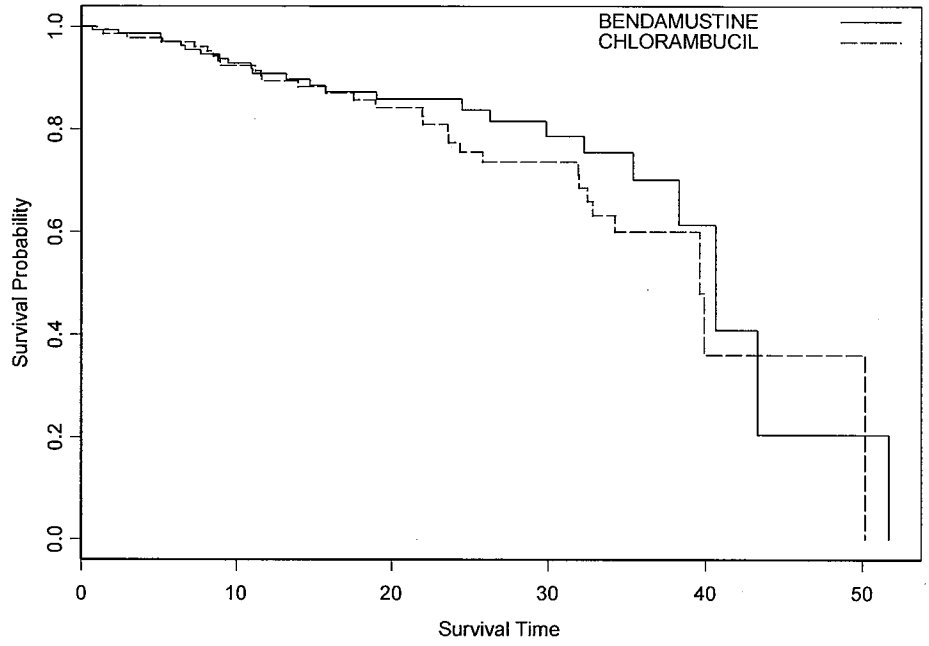

Figure 6. Overall Survival in the ITT Population

Reviewer's Comments:

There are very few death events. Therefore these results are preliminary and no conclusions can be drawn.

3.2 Evaluation of Safety

Please refer to Clinical Review of this application for safety evaluation.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

Among 301 patients in this study, 300 patients were Caucasians. This section will focus on ORR and PFS analyses by gender (male vs. female) and age (< 65 years vs. ≥ 65 years).

Table 16. ORR by Age and Gender

	Bendamustine N=153	Chlorambucil N=148	P-value[a] (Fisher's Exact Test)
Age			
<65 years	55/82 (67%)	24/69 (35%)	<0.0001
≥65 years	40/71 (56%)	25/79 (32%)	0.003
Gender			
Men	59/97 (61%)	30/90 (33%)	0.0002
Women	36/56 (64%)	19/58 (33%)	0.0013

[a]: not adjusted for multiple analyses.

Table 17. PFS Analyses by Age and Gender

	Bendamustine N=153	Chlorambucil N=148
Age <65		
Number of patients (ITT)	82	69
Number of events (%)	24 (29%)	33 (48%)
Median (months), 95% CI	21.4 (17.8, 33.0)	8.8 (8.5, 11.4)
Unstratified log-rank test[1]	P<0.0001	
Hazard ratio (95% CI)[2]	7.52 (3.89, 15.58)	
Age>=65		
Number of patients (ITT)	71	79
Number of events (%)	23 (32%)	33 (42%)
Median (months), 95% CI	20.7 (13.1, 27.6)	11.5 (8.6, 12.4)
Unstratified log-rank test[1]	P<0.0001	
Hazard ratio (95% CI)[2]	3.21 (1.80, 5.86)	
Female		
Number of patients (ITT)	56	58
Number of events (%)	20 (36%)	23 (40%)
Median (months), 95% CI	17.2 (11.4, 20.7)	8.8 (8.5, 14.6)
Unstratified log-rank test[1]	p=0.0014	
Hazard ratio (95% CI)[2]	2.77 (1.46, 5.38)	
Male		
Number of patients (ITT)	97	90
Number of events (%)	27 (28%)	43 (48%)
Median (months), 95% CI	25.2 (20.9, 34.9)	9.6 (8.7, 11.8)
Unstratified log-rank test[1]	P<0.0001	
Hazard ratio (95% CI)[2]	6.91 (3.84, 12.99)	

[1]: Not adjusted for multiple-comparison.
[2]: Hazard Ratio for progression in the BEN arm, as compared with the CLB arm.

Reviewer's Comments:

The subgroup analyses by age and gender showed that the bendamustine treatment group had consistently higher overall response rates than the chlorambucil treatment group. The bendamustine effect appears to be similar in gender and age subgroups.

5 Summary and Conclusions

Study 02CLLIII was designed to evaluate the efficacy of Treanda (Bendamustine) compared with chlorambucil in the initial treatment of patients with chronic lymphocytic leukemia (CLL) in Binet stage B or Binet stage C requiring treatment. The applicant is seeking approval based on the primary efficacy endpoints, overall response rate (ORR) and progression-free survival (PFS).

5.1 Statistical Issues and Collective Evidence

1. This study was planned as a 5-stage adaptive standard group sequential design with a Pocock-type boundary and a rule for adaptively recalculating the sample size in the next stage. According to the protocol and statistical analysis plan, both primary endpoints, overall response rate (ORR) and progression-free survival (PFS), were analyzed at each interim analysis. In order to account for the multiplicity of endpoints, superiority of bendamustine on PFS would not be claimed unless the 2-sided p-value for ORR and PFS are both less than or equal to 0.016.

2. Because 3 interim analyses were performed, patients in this study could fall into the one of the following 3 segments: 1st interim analysis (n=87), 2nd interim analysis (n=77), or 3rd interim analysis (n=137). Table 1 shows that the final p-values for ORR and PFS from the combined results of all 3 segments were less than 0.0001.This reviewer also calculated the unadjusted p-values for ORR and PFS. Both unadjusted p-values for ORR and PFS were also less than 0.0001.

   The hazard ratio obtained for the combined ratio is 0.23 with a 95% confidence interval of 1.34 to 0.39 which was adjusted for repeated testing. Both point estimate and confidence interval were based on estimates within each study segment that were then combined across the segments. The unadjusted hazard ratio for PFS was 0.22 with a 95% confidence interval of 0.14 to 0.33.

3. Initial observations within the dataset received from Ribosepharm led to further quality control (QC) review of study center 1 in Bulgaria. During the QC process, a number of centers were reviewed in addition to study centers 1

and 2 in Bulgaria. The findings at center 1 in Bulgaria indicated that the center had not followed all the procedures in accordance with the protocol, ie, the data collected could not always be substantiated in the patient's medical charts or source data available for review. For center 2 in Bulgaria, the documents supporting the informed consent process were not in accordance with GCP. In order to ensure the consistency of the findings between these 2 centers and the other centers in the study, the sponsor also provided the analyses of the primary endpoint analyses with both centers 1 and 2 excluded from the analyses. A total of 54 patients were excluded (28 from center 1 and 26 from center 2). The analyses on ORR and PFS with Centers 1 & 2 Excluded showed the results were similar to those seen in the total population.

4. The log-rank test showed that there was no difference between two distributions of time to assessment, except the 1st assessment. The median difference in the 1st assessment was less than a week. With PFS medians of 21 months in the bendamustine arm and 9 months in the chlorambucil arm, these small differences in time to assessment is unlikely to influence the final outcome of the study (Table 11).

5. The investigator and the ICRA assessment showed an agreement in 258 (86%) patients; 38% of patients scored as progressors by both, and 48% of patients censored by both. In 14.3% of patients the results were discordant (Table 12).

5.2 Conclusions and Recommendations

The sponsor submitted this application to evaluate the efficacy of Treanda (Bendamustine) compared with chlorambucil in the initial treatment of patients with chronic lymphocytic leukemia (CLL) in Binet stage B or Binet stage C requiring treatment. The applicant is seeking approval based on the primary efficacy endpoints, overall response rate (ORR) and progression-free survival (PFS). ORR was the proportion of patients in each treatment group with a best response of CR, nPR, or PR. Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first. The primary analyses were based on the Independent Committee for Response Assessment (ICRA) adjudicated responses and adjudicated event time points. This application was based primarily on data from a Phase III pivotal study (02CLLIII). This was an open-label, randomized, Phase 3 study. Patients were randomly assigned (with stratification by Binet stage and study center) to either the bendamustine or chlorambucil treatment group at a ratio of 1: 1

A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries. The sponsor reported that the proportion of

patients with ORR was 62% in the bendamustine treatment group compared with 33% in the chlorambucil treatment group ($p<0.0001$) as determined by the Independent Committee for Response Assessment (ICRA). The primary PFS analysis showed that the bendamustine treatment was superior to chlorambucil treatment (median 21 vs. 9 months, hazard ratio (HR) 0.23, $p<0.0001$). Based on the data submitted by the sponsor these results were confirmed by this reviewer and the data support the efficacy claim.

Whether the endpoints and the sizes of the effects on these two endpoints in this phase III study are adequate for approval is a clinical decision.

SIGNATURES/DISTRIBUTION LIST

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Date:

Concurring Reviewer: Rajeshwari Sridhara, Ph.D., Team Leader
Aloka Chakravarty, Ph.D., Director

Date:

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HFD-711/S. Tang
HFD-711/A. Chakravarty
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