CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type:	NDA
Submission Number:	22249
Submission Code:	000
Letter Date:	09/19/07
Stamp Date:	09/20/07
PDUFA Goal Date:	03/20/07
Reviewer Names:	Qin Ryan, MD, PhD (Efficacy) Virginia Kwitkowski, MS, RN, CRNP (Safety)
Date of Addendum:	03/18/08
Established Name:	bendamustine hydrochloride
(Proposed) Trade Name:	TRENDA ®
Therapeutic Class:	Alkylating agent
Applicant:	Cephalon
Priority Designation:	P
Formulation:	IV
Dosing Regimen:	100 mg/m2, Days 1 & 2, q28 days
Indication:	Treatment for CLL
Intended Population:	Chemotherapy naïve patients

Amendment Summary:

After the completion of the NDA review, the Applicant submitted additional information regarding the following:

1. Study 02CLLIII financial disclosures
2. Treatment dose modification information

This amendment is to include the reviewers' assessments of the new information. Amendments to Clinical Review sections 3.3, Financial Disclosure and 9.2 Labeling Recommendations are listed below.

After the initial review completion, an investigation for drug-induced liver injury was undertaken with the results prepared as an amendment to section 7.4.2 Laboratory Findings.

Efficacy Review Addendum

In section 3.3 Financial Disclosures in the original NDA review, it was stated that the financial disclosures could not be obtained for the following studies: 02CLLIII, 99CLL2E (BG), 99CLL2E (DE), 98B02, 20BEND1, 20BEN 03, 98B02W, 93BOP01, 94BP01, 96BMF02/1, 98B03, BE04, based on the initial NDA submission. However, upon FDA request, the applicant requested financial disclosures per the FDA recommended format through the original sponsor of study 02CLLIII. The collected disclosure information was submitted as an amendment to the NDA. Among the 45 principal investigators (PIs), 43 of them as well as the available sub-investigators from their sites submitted financial disclosures indicating no personal financial interest in the study drug. Of the 2 remaining PIs, one was deceased and one is on vacation. Based on the information provided in this NDA, there were 11 patients enrolled from the sites of the 2 PIs whose financial disclosures are not yet available. Excluding enrollments from the deceased PI, 6 patients (or 2% of the total enrollment of study 02CLLIII) were treated by an investigator who has not provided financial disclosure information. The applicant will continue to collect this information and submit it to the Agency as soon as the last one is available.

The available information does not suggest that the study results would be influenced by financial interest since no personal financial interest was reported by any of the investigators. Due to the small number of investigators for whom financial disclosure information is not available and the small number of patients enrolled by these investigators, it is unlikely that the information not available to date would influence FDA's interpretation of the study results.

Safety Review Addendum

The following text is added to Section 7.4.2, Laboratory Findings:

An exploration of the datasets submitted to the Cephalon NDA 22249 (Treanda for CLL) was undertaken to search for potential cases of Drug Induced Liver Injury (DILI) per the "Draft Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation". The clinical chemistry dataset was explored to identify any patients that met Hy's Law definition. Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.

2. Among subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum total bilirubin (TBL) to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

In the dataset exploration, no cases that met these criteria were found.

These results do not exclude the potential for DILI due to the small sample size, but no evidence for DILI was identified during this data exploration.

The following text is added to Section 9.2, Labeling Recommendations:

The original proposed product information label that was submitted by Cephalon [redacted] recommendations for dose reductions in the case of toxicities. FDA proposed the following language for the Dosage and Administration section [redacted]

[redacted]

Cephalon expressed concern that if these recommendations were followed verbatim, patients would be undertreated. Cephalon proposed the following text for the label:

- "Dose modifications for hematologic toxicity: consider a 50% dose reduction for Grade 3 or greater toxicity; if Grade 3 or greater toxicity recurs, consider a 75% dose reduction. (2.2)
- Dose modifications for non-hematologic toxicity: 50% dose reduction for clinically significant Grade 3 toxicity. (2.2)
- Dose re-escalation may be considered. (2.2)"

FDA asked Cephalon to provide an evaluation of how the dose reductions were handled in the 02CLLIII protocol to justify the above labeling recommendations.

Cephalon provided the following evaluation summary:

The main findings from this analysis were as follows:

1. The occurrence of Grade 2 and Grade 3/4 hematologic toxicities, as graded by the standard NCI-CTC, did not result in dose reduction for the majority of patient-cycles. Of the patient-cycles with Grade 2 and Grade 3/4 hematologic toxicity, 69% and 64% of the subsequent cycles were administered at >90% of the planned dose, respectively. Of the patient-cycles with Grade 2 and Grade 3/4 hematologic toxicity excluding leucopenia and lymphocytopenia (which are both related to disease), 58% and 53% of the subsequent cycles were administered at >90% of the planned dose, respectively.

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/s/

Virginia Kwitkowski
3/18/2008 05:02:59 PM
MEDICAL OFFICER
Signing as Acting Clinical Team Leader

Qin Ryan
3/18/2008 05:15:59 PM
MEDICAL OFFICER

2. The most common form of dose reduction was 50%, and the degree of dose reduction did not vary appreciably with the severity of the toxicity. Just over half the dose reductions were to 50% of the planned dose and approximately one third were to 25% of the planned dose (75% dose reduction). The remainder were to 75% of the planned dose (25% dose reduction).

3. Cheson/NCI-WG graded toxicity was only recorded in the hematology listing in the case of Grade 3/4 toxicity. Of the patient-cycles with Grade 3/4 hematologic toxicity, 53% of the subsequent cycles were administered at >90% of the planned dose. The extent of dose reduction was broadly as described for the NCI-CTC analysis, with just over half the dose reductions being 50% of the planned dose, and just over a third being 25% of the planned dose.

Applicant Recommendation

The following recommendation for dose modification is based on the findings from the analysis of the NCI-CTC graded toxicities since the Cheson/NCI-WG criteria are not used in routine clinical practice.

Dose modifications for hematologic toxicity: consider a 50% dose reduction for Grade 3 or greater toxicity; if = grade 3 toxicity recurs, consider a 75% dose reduction.

Given the findings of this evaluation, the Applicant's proposal for dose modification for hematologic toxicities for labeling is: "Dose modifications for hematologic toxicity: consider a 50% dose reduction for Grade 3 or greater toxicity; if > grade 3 toxicity recurs, consider a 75% dose reduction."

Discussions within the review team identified a lack of clarity about whether or not the 75% dose reduction should be taken from the original dose or the reduced dose. This led the team to decide that a clearer way to communicate these recommendations would be:

"Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician."

This plan should provide sufficient doses for efficacy without adversely effecting safety.

CLINICAL REVIEW

Application Type	NDA
Submission Number	22249
Submission Code	000
Letter Date	September 19, 2007
Stamp Date	September 20, 2007
PDUFA Goal Date	March 20, 2008
Reviewer Name	Qin Ryan, MD, PhD (efficacy) Virginia Kwitkowski, MS, RN, CRNP (safety)
Review Completion Date	February 26, 2008
Established Name	bendamustine
(Proposed) Trade Name	Treanda
Therapeutic Class	Alkylating agent
Applicant	Cephalon
Priority Designation	P
Formulation	IV
Dosing Regimen	100 mg/m^2, days 1 and 2, q28days
Indication	treatment for CLL
Intended Population	chemotherapy naïve patients

Table of Contents

TABLE OF TABLES

TABLE OF FIGURES

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The efficacy and safety reviewers recommend approval of Treanda for the following indication, if the applicant can provide adequate financial disclosure information.

"TREANDA (bendamustine hydrochloride) for Injection is ——— indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established."

1.2 Risk Benefit Analysis

The approval recommendation is based on the statistically significant improvement in response rate and progression free survival of Treanda compared to chlorambucil in a randomized study in CLL patients. The survival analysis was immature at the time of the study 02CLLIII final report; because only 11% death events occurred at the final analysis and 18.5% death had occurred at the 4 months follow up. The safety profile of Treanda is acceptable for the proposed indication.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations on Post Marketing Activities/Phase 4 Commitments

The following areas have been identified for post-marketing commitments (PMC). For final PMCs, please see the approval letter.

1. The applicant should continue to follow subject of study 02CLLIII for survival outcome.

2. Submit the completed report and data sets for the mass-balance evaluation. Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.

3. The potential for bendamustine to affect the QT interval needs to be investigated.

4. The influence of CYP1A2 inhibitors (fluvoxamine) on bendamustine pharmacokinetics needs to be evaluated in-vivo.

5. The influence of CYP1A2 inducers (smoking) on bendamustine pharmacokinetics needs to be evaluating in-vivo.

6. In-vitro p-glycoprotein screens need to be completed to determine if bendamustine is an inhibitor or substrate of p-glycoprotein.

7 [redacted]

1.5 Summary of Clinical Findings

1.5.1 Brief Overview of Clinical Program

The safety and efficacy of TREANDA were evaluated in a randomized, controlled, European multicenter, trial, Study 02CLLIII, compared TREANDA to chlorambucil as first line treatment for CLL patients. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment[1]. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

1.5.2 Efficacy

As detailed in section 5.3.1.5.3, the co-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, as per protocol plan. However, the ICRA efficacy assessments can not be verified fully. The applicant conducted an evidence-based efficacy analysis, termed "calculated assessment". This analysis employed data from the primary source documents and eCRFs, and assessment was based on NCI Working Group Criteria for CLL as prespecified in the original protocol.

The final co-primary analyses based on evidence-based assessment demonstrated an overall response rate of 59% for Treanda versus 26% for chlorambucil ($p < 0.0001$). The median progression free survival was 17.6 months for Treanda versus 5.7 months for chlorambucil, with a hazard ratio (Treanda/chlorambucil) of 0.27 (95% CI 0.17,0.43; $p < 0.0001$). The secondary endpoint analysis of median response duration based on the evidence-based assessment was 18.6 months for Treanda versus 6.5 months for chlorambucil. The survival analysis was immature at the time of the study 02CLLIII report, since there were only 11% death at the clinical cut-off date and 18.5% at 4 month follow up.

1.5.3 Safety

The randomized, multi-center comparative trial of bendamustine vs. chlorambucil in treatment-naïve patients with CLL (02CLLIII) provided the basis for the safety review of bendamustine in

the CLL indication. In this trial, 296 patients received treatment (153 who were randomized to bendamustine and 143 to chlorambucil).

In this study, patients in the bendamustine treatment arm had a higher incidence of adverse reactions (89%) than those in the chlorambucil treatment arm (79%). Adverse reactions (any grade) with a frequency greater than 15% in the bendamustine treatment arm were neutropenia (28%), pyrexia (24%), thrombocytopenia (23%), nausea (20%), anemia (19%), leukopenia (18%), and vomiting (16%).

The incidence of grade 3/4 adverse reactions was higher in the bendamustine arm at 58% compared to 31% in the chlorambucil arm. Grade 3/ 4 hematologic adverse reactions with a frequency greater than 10% in the bendamustine treatment group were neutropenia (24%), leukopenia (15%), and thrombocytopenia (13%). Grade 3/4 non-hematologic adverse reactions were reported by 52 (34%) patients in the bendamustine treatment group and 25 (17%) patients in the chlorambucil treatment group. Grade 3/ 4 non-hematologic adverse reactions with a frequency greater than 1% in the bendamustine treatment group were pyrexia (4%), pneumonia (3%), hypertension (3%), rash (3%), hypertensive crisis (2%), hyperuricemia (2%), and infection (2%).

Grade 3/4 adverse reactions by System Organ Class with a frequency $\geq$5% in the bendamustine group were blood and lymphatic system disorders (41%), infections and infestations (7%), general disorders and administrative site conditions (5%), vascular disorders (5%), and skin and subcutaneous disorders (5%).

Serious adverse events (SAEs) occurred with a higher frequency in the bendamustine arm with 27 (18%) patients experiencing 32 SAEs compared to 16 (11%) patients experiencing 20 SAEs. SAEs by Systems Organ Class in the bendamustine arm with a frequency greater than or equal to 1% were infections and infestations (5%), blood and lymphatic system disorders (3%), and immune system disorders (2%). SAEs by Preferred Term in the bendamustine arm with a frequency greater than or equal to 1% were pneumonia (2%), hypersensitivity (2%), anemia (1%), vomiting (1%), and tumor lysis syndrome (1%).

The number of deaths during the treatment period was the same in both the chlorambucil and bendamustine treatment arms (17 per group). Four deaths occurred within 30 days of the last dose of study drug; 1 in the bendamustine arm and 3 in the chlorambucil arm. Thirty of the 34 deaths occurred more than 30 days after the last dose of study drug. Seventy-one percent of all of the deaths that occurred in each arm of the study occurred more than 100 days after the last dose of study drug. Forty-one percent (7 per group) of patients who died during the study had an attribution of death from CLL placed by the investigator.

The safety issues identified in this safety review are myelosuppression, infections, tumor lysis syndrome, hypersensitivity reactions, hypertension, and cardiac toxicity. Overall, the common adverse reaction profile resembles that of other alkylating agents.

1.5.4 Dosing Regimen and Administration

TREANDA is intended for administration as an intravenous infusion over 30 minutes. The recommended dose is 100 mg/m2 administered intravenously on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

1.5.5 Drug-Drug Interactions

Data is not available, see section 1.4, post-marketing commitment.

1.5.6 Special Populations

1.5.6.1 Pregnancy

Pregnancy category D - TREANDA can cause fetal harm when administered to a pregnant woman.

1.5.6.2 Labor and Delivery

The safety of TREANDA during labor and delivery has not been established.

1.5.6.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions and tumorigenicity shown for bendamustine in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

1.5.6.4 Pediatric Use

The safety and effectiveness of TREANDA in pediatric patients has not been established.

1.5.6.5 Geriatric Use

Bendamustine exposure (as measured by AUC and C_{max}) has been studied in patients with **indolent non-Hodgkin's lymphoma (NHL), ages 31** through 84 years. The pharmacokinetics of bendamustine (AUC and C_{max}) were not significantly different between patients less than or greater than/equal to 65 years of age.

In the randomized CLL clinical study, 153 patients received TREANDA at the recommended dose. The overall response rate for patients younger than 65 years of age was 70% (n=82) for bendamustine and 30% (n = 69) for chlorambucil. The overall response for patients 65 years or older was 47% (n=71) and 22% (n = 79) for chlorambucil. The difference of median progression-free survival was 10 months for patients younger than 65 years of age (Bendamustine 19 months; Chlorambucil 9 months) and 4 months for patients 65 year or older (Bendamustine 12 months; Chlorambucil 8 months). The overall incidence of treatment-emergent adverse reactions was 87% in patients < 65 years and 92 % in patients ≥ 65 years. There were no clinically significant differences in the adverse reaction profile.

1.5.6.6 Renal Impairment

There is no information available regarding the renal excretion of bendamustine in humans. There are currently no clinical studies with bendamustine in patients with impaired renal function.

In a population pharmacokinetic analysis of bendamustine in NHL patients receiving 120 mg/m^2 there was no meaningful effect of renal impairment (CrCL 45 - 80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL <45 mL/min.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < [redacted] mL/min

1.5.6.7 Hepatic Impairment

There is no information available regarding the hepatic excretion of bendamustine in humans. There are currently no clinical studies with bendamustine in patients with impaired hepatic function.

In a population pharmacokinetic analysis of bendamustine in NHL patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin ≤ ULN, AST ≥ ULN to 2.5 x ULN, and/or ALP ≥ ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine.

These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5-10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment.

1.5.6.8 Effect of Gender

The pharmacokinetics of bendamustine were similar in male and female patients.

In the pivotal CLL clinical trial, the overall response rate (ORR) for men (n=97) and women (n=56) in the TREANDA group was 60% and 57%, respectively. The ORR for men (n=90) and women (n=58) in the chlorambucil group was 24% and 33%, respectively. In this study, the median progression-free survival for men was 19 months in the TREANDA treatment group and 6 months in the chlorambucil treatment group; for women, the median progression-free survival was 13 months in the TREANDA treatment group and 8 months in the chlorambucil treatment group. No clinically significant differences between genders were seen in the overall incidences of treatment-related adverse reactions in patients who reported at least one adverse reaction.

1.5.6.9 Effect of Race

In six Japanese subjects receiving 120 mg/m^2 bendamustine IV over 1-hour the AUC was on average 20% higher than non-Japanese subjects. Japanese subjects receiving bendamustine should be monitored frequently for increased toxicities.

The effect of race on the pharmacokinetics, safety, and/or efficacy of TREANDA has not been established.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Treanda
Proprietary Name: bendamustine

Applicant: Cephalon, Inc
41 Moores Road
PO Box 4011
Frazer, PA 19355

Drug Class: Alkylating antineoplastic agent

Original Proposed Indication: "TREANDA is ——— indicated for treatment of patients with chronic lymphocytic leukemia (CLL)."

At the request of the US FDA to clarify that there may be other first-line treatments in US, the applicant submitted the following revised indication:

TREANDA (bendamustine hydrochloride) for Injection is ——— indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.

Proposed Dosage and Administration: TREANDA is intended for administration as an intravenous infusion over 30 minutes. The recommended dose is 100 mg/m^2 administered intravenously on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

2.2 Tables of Currently Available Treatments for Proposed Indications

The first line antineoplastic therapies for patients with CLL are as below:

Table 2-1: Currently available first line treatments for proposed indication

Single Agent therapies	Rituximab
	chlorambucil with or without corticosteroids
	Fludarabine, 2-chlorodeoxyadenosine, or pentostatin
Combination therapies	Fludarabine plus rituximab (CALGB-9712 and CALGB-9011)
	Fludarabine plus cyclophosphamide plus rituximab.
	Fludarabine plus cyclophosphamide
	Pentostatin plus cyclophosphamide plus rituximab (MAYO-MC0183).
	CVP: cyclophosphamide plus vincristine plus prednisone.
	CHOP: cyclophosphamide plus doxorubicin plus vincristine plus prednisone.
	Fludarabine plus cyclophosphamide versus fludarabine.
	Fludarabine plus chlorambucil (CALGB-9011).
	cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)

Note: A meta-analysis of ten trials comparing combination chemotherapy (before the availability of rituximab) to chlorambucil alone showed no difference in OS at 5 years.

Commonly used first line regimens in United States include rituximab in combination with fludarabine, fludarabine plus cyclophosphamide plus rituximab, CVP and CHOP.

2.3 Availability of Proposed Active Ingredient in the United States

Bendamustine is not presently marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

2.4.1 General Class Toxicities

Alkylating agents can cause severe myelosuppression which can lead to life-threatening infections, bleeding, and complications of anemia. Gastrointestinal toxicity consisting of nausea, vomiting, stomatitis, and diarrhea is common with alkylating agents. Alkylating agents are considered carcinogenic, which can lead to secondary malignancies which are typically resistant to available therapies. Alkylating agents are likely to be mutagenic and teratogenic in humans.

Alkylating agents can produce human infertility. Intravenous alkylating agents can be vesicants or irritants when extravasated.

2.4.2 Specific Alkylating Agent Toxicities

Chlorambucil, has been associated with severe rash leading to erythema multiforme, toxic epidermal necrolysis (Stevens-Johnson Syndrome). Chlorambucil is also considered epileptogenic, particularly in children with nephrotic syndrome and in patients receiving high, pulse doses of chlorambucil.

Cyclophosphamide can induce hemorrhagic cystitis, sometimes leading to bladder cancer. Cases of acute cardiac toxicity have occurred in conjunction with cyclophosphamide treatment. These cases have included congestive heart failure and pericarditis. Severe hypersensitivity reactions have been associated with the use of cyclophosphamide and there appears to be possible cross-reactivity with other alkylating agents. Cyclophosphamide toxicity has been noted to be increased in adrenalectomized patients. This finding has led to recommendations to adjust the doses of both the corticosteroids and cyclophosphamide in adrenalectomized patients.

Cisplatin is associated with cumulative nephrotoxicity, neurotoxicity, anaphylactic hypersensitivity reactions, and ototoxicity.

Carmustine is associated with dose-related pulmonary toxicity, which can be delayed in onset for years, and hepatic toxicity.

Busulfan is associated with hepatotoxicity, neurotoxicity, pulmonary toxicity, and rash.

Dacarbazine has been associated with hepatic necrosis, and anaphylactic hypersensitivity reactions.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

July 2003 IND initiated.

September 02, 2004, an EOP2 meeting was held between the applicant and FDA to discuss clinical development plan in —— CLL. FDA agreed that a single randomized study might support registration and recommend use an independent response review committee for efficacy evaluation. In CLL setting, a pediatric waiver would be appropriate.

April 12, 2007, pre-NDA meeting, statistical analysis plan and multiple look issues, safety sample size and profile, PK and toxicology studies were discussed.

April 27, 2007, CMC pre-NDA teleconference (detail see CMC review).

2.6 Other Relevant Background Information

2.6.1 Development history

Treanda is an alkylating agent chemically related to nitrogen mustards. It is an antineoplastic agent that was developed as IMET 3393 in the early 1960s by Ozegowski and Krebs (1971) at the Central Institute for Microbiological and Experimental Therapy in Jena, Germany (formerly East Germany [German Democratic Republic]). Early clinical research identified the activity for the compound for plasmacytoma, chronic lymphocytic leukemia (CLL), lymphoma, and bronchial carcinoma (Anger et al 1975).

It is marketed in the German Democratic Republic since 1974, in Germany since 1993, and in Bulgaria since 2000. It is authorized for the **treatment of Hodgkin's disease, NHL, chronic** lymphocytic leukemia, multiple **myeloma (MM), and breast cancer. It's presently undergoing** reauthorization in Germany, because it was originally grandfathered at the time of the re-unification of Germany.

2.6.2 Marketing history

From 1971 through 1992, Jenapharm marketed bendamustine as CYTOSTASAN®. From 1993 to 2006, Ribosepharm GmbH marketed bendamustine as RIBOMUSTIN®. In October 2006, Mundipharma International Corp. Ltd. acquired development and marketing rights for bendamustine for all European Union countries.

In July 2005, bendamustine was formally re-approved by the German health authority, BfArM, for the treatment of patients with **indolent non-Hodgkin's lymphoma (NHL),** CLL, and multiple myeloma. Ribosepharm is also the sponsor of the European clinical studies described in this application, including the pivotal efficacy and safety study (study 02CLLIII) in previously untreated patients with CLL. Clinical development of bendamustine in the United States (US) began in June 2003 with the filing of an Investigational New Drug (IND) application by Salmedix, Inc., the initial licensee for North America. This program of clinical research focused on indolent NHL. In June 2005, Salmedix became a wholly owned subsidiary of Cephalon, Inc. and the IND application was transferred. Cephalon is currently completing a pivotal study of bendamustine (study SDX-105-03) in patients with indolent or transformed B-cell rituximab-refractory NHL. In addition, a clinical program has been initiated in Japan by Symbio Pharmaceuticals Co. Ltd., the licensee for Japan.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Study, 02CLLIII, has been submitted as the major study to support the approval of Treanda in patients with CLL. The applicant had conducted a quality control (QC) review of selected study centers where study 02CLLIII were conducted. Violations were found at Centers 1 and 2. The findings at center 1 indicated that the center had not followed all the procedures in accordance with the protocol, i.e., the data collected could not always be substantiated in the patients' medical charts or source data available for review. For center 2, 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 analyses of the primary endpoints and the overall safety analyses are presented both with centers 1 and 2 included and with them excluded from the analyses in the NDA submission.

As discussed with DSI, the following sites essential for approval have been identified for inspection, as listed below. The basis of the selection was the number of enrollment and response. The review team decided not to inspect the sites with problems identified by the applicant, but requested applicant to submit their inspection report.

Table 3. 1: Sites selected for scientific investigation

Site number	Investigator and affiliation	Number of patients enrolled
05		26
12		18
04		14
16		10

Source: Study 02CLLIII report

The DSI conducted inspection on applicant's central facility and above sites and concluded that all finding were acceptable, except there were some dosing violations. In one of the sites inspected, that of Dr. —— some patients on the bendamustine arm received about 90% of protocol defined dose and those on the chlorambucil arm received 110-120% of protocol defined dose. The cases identified as listed as below.

Chlorambucil Arm

Patient #	Calculated Dose	Dosage Given
11202	105 mg/cycle	120 mg/cycle
21203	113 mg/cycle	160 mg/cycle
21205	112 mg/cycle	128 mg/cycle
11207	108 mg/cycle	118 mg/cycle
11208	110 mg/cycle	128 mg/cycle
11209	96 mg/cycle	216 mg/cycle (Only one cycle)

Bendamustine Arm

Patient #	Calculated Dose	Dosage Given
11201	205 mg/day	190 mg/day
21201	221 mg/day	200 mg/day
21202	221 mg/day	190/200 for cycle one, then 210 mg/day for cycles 2-6

Reviewer: These dosing violations are not expected to increase the efficacy of bendamustine, since the testing arm dose was decreased and the control arm dose was increased.

3.2 Compliance with Good Clinical Practices

As per applicant, the clinical studies were conducted in accordance with the Good Clinical Practice (GCP):

Consolidated Guideline approved by the International Conference on Harmonisation (ICH), the Declaration of Helsinki, the German Medicinal Products Act (AMG), and applicable local laws.

In Germany pursuant to the AMG, the study protocol was submitted for review and approval to the Ethics Committee (EC) applicable to the principal investigator and to the local ECs applicable to the study centers. In Austria, Bulgaria, France, Italy, Spain, Sweden, and United Kingdom (UK), the ICH GCP regulations were followed with regard to the ECs.

Before the start of the studies, the German state authorities applicable to Ribosepharm GmbH and the investigators were notified of this study pursuant to section 67 paragraph 1 of the AMG. In Austria, Bulgaria, France, Italy, Spain, Sweden, and UK, the local authority was notified as required by local law.

3.3 Financial Disclosures

In accordance with 21 CFR 54.4, the applicant acknowledges the required financial disclosure requirements and certification. Studies, except for 3 studies providing PK data (SDX-105-01, SDX-105-02, and SDX-105-03), contained in this NDA supporting safety and efficacy of proposed CLL indication, including the pivotal trial Study 02CLLLIII were conducted by

another sponsor, Astellas, at clinical sites in Europe only; they were not conducted under an IND. The sponsor of these studies did not prospectively request financial disclosure information from any investigator.

The applicant of this NDA, Cephalon Inc., asked representatives from Astellas if it were possible to obtain information from the investigators in support of this application. Astellas responded that they would be unable to obtain the required information for the following studies: 02CLLIII, 99CLL2E (BG), 99CLL2E (DE), 98B02, 20BEND1, 20BEN 03, 98B02W, 93BOP01, 94BP01, 96BMF02/1, 98B03, BE04.

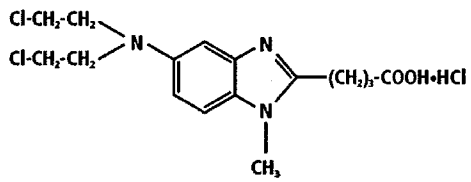
Reviewer: The personal interest and integrity of study investigators for above study can not be determined without financial disclosure. The financial disclosure of study investigators is required by FDA regulation. As per FDA request, the applicant is collecting financial disclosure from investigators of study 02CLLIII and will submit this information before the PDUFA day. The clinical reviewer will provide a follow up in an amendment to this review, when the financial disclosure is available.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Based on the FDA CMC review, TREANDA (bendamustine hydrochloride) for Injection is an alkylating agent. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$, and the molecular weight is 394.7. Bendamustine hydrochloride is a nitrogen mustard derivative and has the following structural formula:

Figure 1: Chemical structure of bendamustine



TREANDA® (bendamustine hydrochloride) for Injection is intended for intravenous infusion only after constitution with 20 mL of Sterile Water for Injection, USP and after further dilution with 0.9% Sodium Chloride Injection USP. It is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single use vial. Each vial contains 100 mg of bendamustine hydrochloride and 170 mg of mannitol, USP. The pH of the constituted solution is 2.5 - 3.5.

4.2 Clinical Microbiology

Based on the FDA clinical microbiology review, The drug product is [redacted]. No microbiology deficiency found.

4.3 Preclinical Pharmacology/Toxicology

The following conclusion was drawn from the FDA pharmacology/toxicology review of this NDA.

4.3.1 Carcinogenesis

Treanda was carcinogenic in mice. After intraperitoneal injections at 37.5 mg/m^2/day (12.5 mg/kg/day, the lowest dose tested) and 75 mg/m^2/day (25 mg/kg/day) for four days, , peritoneal sarcoma in female AB/jena mice were produced. Oral administration at 187.5 mg/m^2/day (62.5 mg/kg/day, the only dose tested) for four days induced mammary carcinoma and pulmonary adenoma.

4.3.2 Mutagenesis

Treanda is a mutagen and clastogen. In a reverse bacterial mutation assay (Ames assay), Treanda was shown to increase revertant frequency in the absence and presence of metabolic activation. Treanda was clastogenic in human lymphocytes *in vitro*, and in rat bone marrow cells *in vivo* (increase in micronucleated polychromatic erythrocytes) from 37.5 mg/m^2, the lowest dose tested.

4.4 Clinical Pharmacology

The following conclusion was drawn from the FDA clinical pharmacology review of this NDA.

4.4.1 Mechanism of Action

Bendamustine is a bifunctional nitrogen mustard derivative. Nitrogen mustard and its derivatives are alkylating agents which dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage can lead to cell death via several pathways. The exact mechanism of action of bendamustine remains unknown.

In both in vivo and in vitro tests, bendamustine showed cell cycle effects analogous to other alkylating agents. Bendamustine is active against both quiescent and dividing cells.

4.4.2 Pharmacodynamics

Based on the pharmacokinetic/pharmacodynamic profile of bendamustine, it is anticipated that a dose of 100 mg/m^2 infused over 30 minutes on Days 1 and 2 of each 28-day cycle for the treatment of CLL will produce adequate plasma concentrations to yield the desired pharmacological effect. Elevated plasma concentrations are believed to be important to the cytotoxic effect of bendamustine rather than prolonged exposure; thus, the cyclic dosing scheme using an infusion of this duration is considered to be appropriate for the treatment of CLL.

4.4.3 Pharmacokinetics

Absorption

Following a single IV dose of bendamustine hydrochloride in patients with NHL, the mean Cmax was 5606 ng/mL (coefficient of variation, CV = 43%) and mean AUC was 6636 ng hr/mL (CV 54%). Typically Cmax occurred at the end of the 1-hour infusion. The dose proportionality of bendamustine has not been studied.

Distribution

In vitro, the binding of bendamustine to human serum plasma proteins ranged from 94-96% and was concentration independent from 1-50 µg/mL. Data suggest that bendamustine is not likely to displace or to be displaced by highly protein-bound drugs. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 µg/mL indicating that bendamustine distributes freely in human red blood cells.
In humans, the mean volume of distribution (Vz) was approximately 208 L (Vss = 12.8).

Metabolism

In vitro data indicate that bendamustine is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. *In vitro,* studies indicate that two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these

metabolites in plasma are 1/10 and 1/100 that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to bendamustine.

In-vitro studies using human liver microsomes indicate that bendamustine dose not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4/5 enzymes in primary cultures of human hepatocytes.

Elimination

No mass balance study has been undertaken in humans. Preclinical radiolabeled bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces.

Bendamustine clearance in humans is approximately 700 mL/minute. The terminal elimination $t_{½}$ of the parent compound ranged from 0.8 to 13.5 hr (mean 5 hr) after a single dose of 120 mg/m^2 bendamustine IV over 1-hour. Little or no accumulation in plasma is expected for bendamustine administered on Days 1 and 2 of a 28-day cycle.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The clinical studies included in this NDA are summarized in the table below.

Table 5-1: Studies included in NDA 22249

Study ID	Support	Design	US/Canada sites	Regimen	Number of subjects
02CLLIII	efficacy and safety	Randomized study compare bendamustine to first line chlorambucil in B-CLL	None	100 mg/m^2 IV on D1&2 q28d vs. chlorambucil 0.8 mg/kg PO D1&15 q28 weeks.	301 (Bendamustine=153 Chlorambucil=148)
99CLL2E (BG)	Safety & PK	Single arm 2nd line B-CLL treatment (Bulgaria)	None	100, 110, and 120 mg/m^2 IV on two consecutive days q21 days. Up to 6 cycles.	15
99CLL2E (DE)	Safety & PK	Single arm 2nd line B-CLL treatment (Germany)	None	70, 80, 90, and 100mg/m^2 IV on 2 consecutive days every 21 days. Up to six 3-week cycles	16
SDX105-01	PK and safety	Single arm study in rituximab refractory NHL patients	yes	120 mg/m^2 IV D1&2 every 21d. Minimum of 6 cycles.	76
SDX105-02	safety	Single arm combination study in relapsed indolent or mantle cell NHL	yes	Rituximab 375 mg/m^2 at Day -7; Followed by Rituximab 375 mg/m^2 D1 plus Bendamustine 90 mg/m^2 Days 2&3; for four 28-day cycles.	66
SDX105-03	safety	Single arm study in Rituximab-Refractory Indolent NHL	yes	120 mg/m2 D1&2 q21d (minimum of 6 cycles). Dose reductions to 90 or 60 mg/m^2 would occur for toxicity	On going, 100 as of 07/31/07
20BEN03	safety	Phase 1 study in advanced solid tumors (Belgium)	No	120-180 mg/m^2 IV days 1 & 2 q21 days (dose escalation in 20 mg/m^2 increments. Minimum of 2 cycles.	15
98B02W	safety	Phase 1 study in advanced solid tumors (Germany)	No	60, 70, and 80 mg/m^2 IV weekly D1, 8, 15, 22, 29. (Up to 8 weeks of treatment).	12
98B03	Safety and PK	Phase 1 parallel group study in advanced solid tumors patients with renal or hepatic impairment (Germany)	No	120 mg/m^2 IV D1&2 of a 4-week cycle (dialysis patients received one dose every 4 weeks)	37
BE04	safety	Phase 1 study in cholangiocacinoma (Germany)	None	140 mg/m^2 C1D1 and 100 mg/m^2 D1&2 of later cycles lasting 21 days and 4 cycles.	6
98B02	Safety	Phase 1 study in advanced solid tumor (Germany)	None	100-180 mg/m^2 (dose escalating) IV Days 1 and 8 q28 days. Minimum of 2 cycles.	18
20BEN D1	Safety	Phase 1 study in advanced solid tumors (Belgium)	None	160-280 mg/m^2 IV q21 days (dose escalation in 20mg/m^2 increments). Minimum of 2 cycles.	26
93BOP01	safety	Single center randomized study in Advanced Centroblastic / Centrocytic Lymphomas and Lymphoplasmacytoid	None	A: Bendamustine 60 mg/m^2 IV D1-5 plus vincristine 2mg IV D1 plus prednisone 100 mg/m^2 D1-5 B: Cyclophosphamide 400 mg/m^2 IV D1-5 plus	BOP=84 COP=83

Study ID	Support	Design	US/Canada sites	Regimen	Number of subjects
		Immunocytomas Germany)		vincristine 2mg IV D1 plus prednisone 100 mg/m^2 D1-5 Cycle=21d; up to 8 cycles	
96BMF02/1	safety	Multicenter randomized study for first line breast cancer therapy		A: Bendamustine 120 mg/m^2 IV D1&8 plus methotrexate and 5-FU B: CMF	BMF=169 CMF=185

5.2 Review Strategy

This NDA clinical review was primarily based on the efficacy and safety data of the study 02CLLIII, which are relevant to the proposed indication. Other 13 studies were also reviewed as support to the study 02CLLIII safety data. The electronic submission, with the CSRs, and other relevant portions of the study 02CLLIII were reviewed and analyzed. The key review materials and activities were outlined as below:
The electronic submission of the NDA;
Relevant published literature;
Relevant submissions in response to medical officer's questions;
Sponsor presentation slides to FDA on Oct 1, 2007;
Major efficacy and safety analyses reproduced or audited using the SAS datasets data.

5.3 Discussion of Individual Studies

5.3.1 Study 02CLLIII Protocol

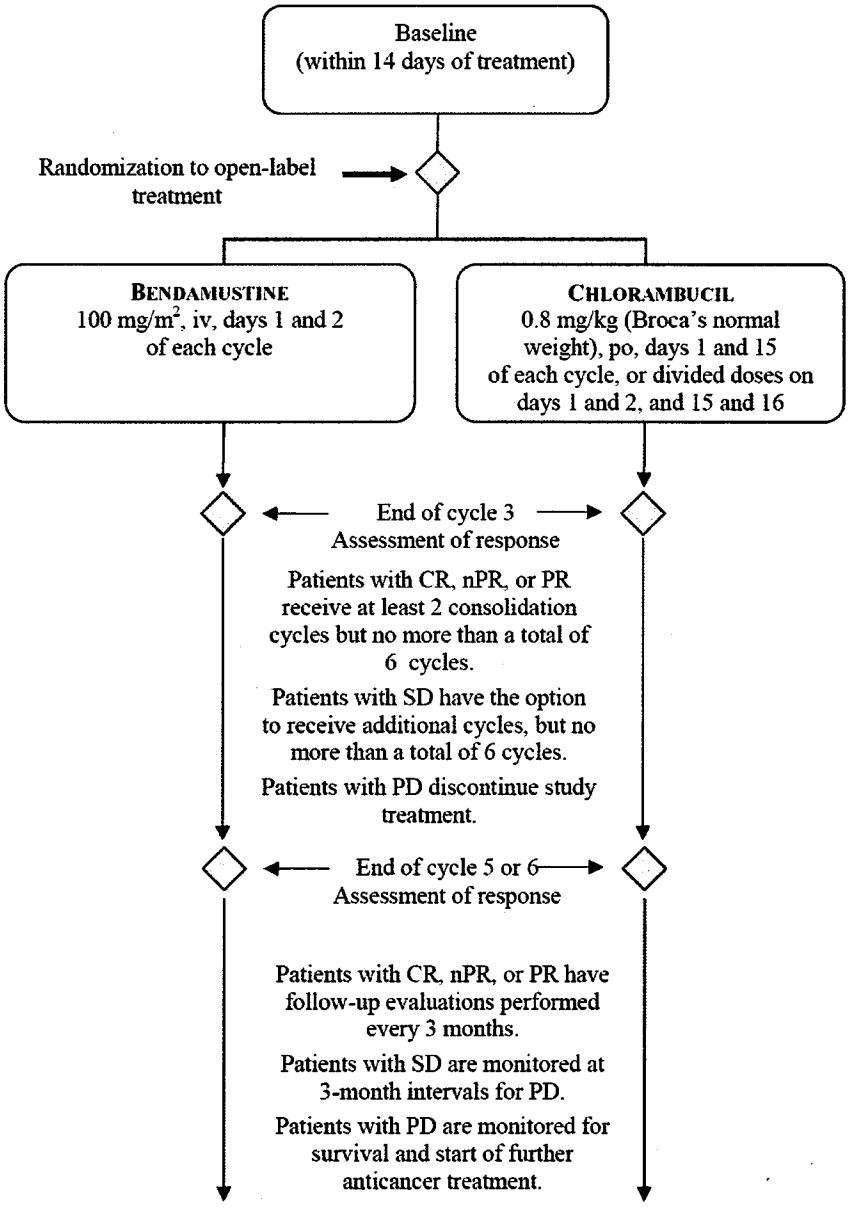
5.3.1.1 Study Title

Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) B-CLL Requiring Therapy

5.3.1.2 Study design

This was an open label, non-stratified, randomized study to evaluate the efficacy of bendamustine compare to chlorambucil as first line treatment in CLL patients staged Binet B or C. The co-primary endpoints of this study were ORR (CR + PR) and progression free survival. The secondary end points were time to progression, duration of remission, overall survival, infection rate, quality of life and toxicity. Prior to 3rd interim analysis, an independent committee of response assessment (ICRA) was formed to review overall response rate and date of progression blindly, as the basis of efficacy analyses. The study scheme is as shown below.

Figure 2 Study 02CLLIII Scheme



Source: NDA 22249 Study 02CLLIII report

Major Eligibility Criteria

Inclusion:

- The patient was a previously untreated, legally competent adult, 75 years of age or less, and capable of following study instructions.
- The patient gave written informed consent.

- The patient had a WHO Performance Status of 0, 1, or 2.
- The patient had a life expectancy of 3 months or more.
- The patient agreed to contraception for at least 6 months after treatment.
- The patient had confirmed chronic B-cell lymphocytic leukemia (coexpression of CD5, CD23, and either CD19 or CD20 or both).
- The patient had symptomatic Binet stage B or Binet stage C disease and meet need-to-treat criteria in B-cell chronic lymphocytic leukemia
- All patients met the need-to-treat criteria defined as at least 1 of the following:
    - hematopoietic insufficiency with non-hemolysis-induced hemoglobin (Hgb) of less than 10 g/dL
    - thrombocytopenia of less than $100x10^9$/L (equivalent to Binet stage C)
    - B symptoms defined as an unexplained weight loss of more than 10% in the last 6 months, and/or a persistent or recurrent fever of unknown origin of more than 38°C, and/or night sweats
    - rapidly progressive disease (such as rapid increase of lymph node size, rapid increase in lymphocyte count, rapid fall in Hgb or platelet count not due to autoimmune phenomena)
    - risk of organ complications from bulky lymphomas (ie, lymphadenopathy) (eg, vascular compression)

Exclusion:

- The patient received previous treatment with other cytotoxic drugs.
- The patient participated in another clinical study within 4 weeks prior to or during this study.
- The patient had mental disorders, drug or alcohol dependence, or any other disorder that suggested compliance problems or limited ability to cooperate in the study.
- The patient had a history of a second malignancy (except cured basal cell carcinoma or cured cervical cancer).
- The patient had a manifested immune hemolysis that could be treated with glucocorticoids alone.
- The patient had a manifested immune thrombocytopenia that could be treated with glucocorticoids alone.
- The patient had Richter's syndrome or transformation to prolymphocytic leukemia (PLL).
- The patient had hepatic dysfunction defined as bilirubin greater than 2.0 mg/dL or transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) greater than 3 times the upper limit of normal (ULN).
- The patient had renal dysfunction (creatinine clearance less than 30 mL/min, calculated).
- The patient had any of the following concomitant diseases:
    - overt heart failure
    - cardiomyopathy
    - myocardial infarction within the last 6 months

  - severe, uncontrollable diabetes mellitus
  - severe, uncontrollable hypertension
  - active infection that required a systemic antibiotic treatment
  - uncontrollable infection
  - clinically manifested cerebral dysfunction
- The patient had known human immunodeficiency virus (HIV) infection.
- The patient had major surgery within 30 days before the start of the study.
- The patient was pregnant or lactating. If the patient was a woman of childbearing potential, she must have been using adequate contraception (eg, abstinence, oral contraceptives, intrauterine devices, barrier method [diaphragm or condom] plus spermicide).
- The patient had hypersensitivity to any of the study drugs.

Patients were randomized 1:1 to either bendamustine or chlorambucil. Prior to randomization, patients were stratified by the following factors:

- Binet stage B or C
- Study center

The regimens are shown in table below.

Table 5-2: 02CLLIII study treatments

Arms	Regimen
bendamustine	100 mg/m^2 by iv infusion over a period of 30 minutes on days 1 and 2 during each 28-day cycle.
chlorambucil	0.8 mg/kg (Broca.s normal weight) orally on days 1 and 15 or, if necessary, divided doses on days 1 and 2 and on days 15 and 16 during each 28-day cycle

Source: Study 02CLLIII report and protocol

After completing three treatment cycles an interim tumor assessment was performed. Depending on the outcome patients were discontinued from the trial (PD), received a maximum of 3 additional treatment cycles (NC), or did receive another two treatment cycles for consolidation (PR, nPR, CR). At the end of the treatment phase a final tumor assessment was performed. Responding patients and patients with NC were followed for progression at 3 months intervals. Non-responders and relapsed patients were followed for survival at 3 months intervals.

In addition, the patient might be withdraw from the study for the following reasons:

- The patient had an adverse event(including an intercurrent disease) that precluded continued treatment with study drug or would have compromised the study results if the patient remained in the study.
- The patient was unlikely to be able to return to the clinic or hospital for study visits.
- The benefit/risk assessment for a patient was no longer acceptable.
- The patient took excluded medications during the study.
- There was poor patient cooperation.
- The patient became pregnant.

- The patient relocated or there were other logistic reasons that required withdrawal of the patient from the study.

In case of adverse reaction, dose justification was designed as below:

Table 5-3: Dose modification for study 02CLLIII

Hematology Toxicity		
Percentage decrease in hemoglobin or platelets compared with baseline	Absolute neutrophil count ($x10^9$/L)	Recommended dose adjustment (relative to last dose)
0-24 (grade 0-1)	> 1.5 (grade 0-1)	No reduction
25-49 (grade 2)	> 1.0 and <1.5 (grade 2)	50% dose reduction
50-74 (grade 3)	> 0.5 and <1.0 (grade 3)	75% dose reduction
>75 (grade 4)	<0.5 (grade 4)	Interruption of treatment until recovery to grade 1
Non-hematological toxicity		
Common Toxicity Criteria (CTC) grade		Total dose
0.2 (and grade 3 nausea/vomiting and alopecia)		100%
3 (except nausea/vomiting and alopecia)		50% dose reduction or withdrawn from study [a]
4		Withdrawn from study

a. The decision whether or not to stop treatment depended on the nature of the toxicity and on what the investigator decided was best for the patient.
Source: Study 02CLLIII protocol.

5.3.1.3 Study landmark and protocol amendments

The study landmarks and protocol amendments are summarized as below.

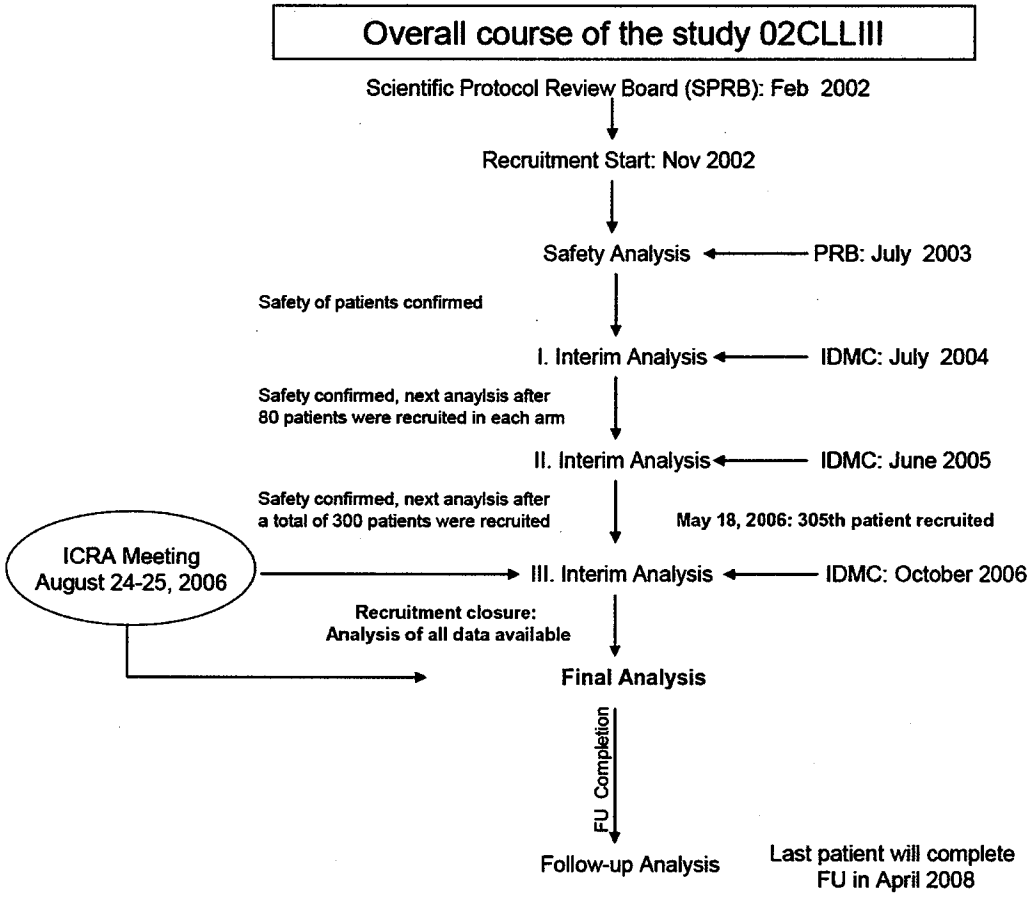
Table 5-4: Study landmark and amendments

Date	Landmark
05/10/2002	Original Protocol
08/27/2002 N = 0	Amendment 1, before study started. The timeframe for completing baseline evaluations in the study flow chart and in baseline study procedures was specified as within 14 days before the first cycle;. Blood and urine samples were to be collected within 8 days before the first cycle. The evaluation of **immunophenotype was changed from "coexpression of CD5 and at least 1 of CD19, CD20, CD23)" to "coexpression of CD5, CD19 and at least 1 of CD20 and CD23)".**
11/05/2002	**Study started and 1st patient enrolled**
05/02/2003 N = 57	Amendment 2, accepting baseline tumor evaluation from 14 days to 3 months prior to first cycle, exclusion of pregnancy and women with pregnancy potential, add nodular PR (nPR) to response evaluation.
04/16/2004 N = 135	Amendment 3, added all AEs will be classified by CTC 2.0 (before was CTC 1.0), proposed nPR sub-analysis, added first interim analysis to be performed after 40 patient of each arm has beeen followed for at least 5 months.
06/21/2005 N = 245	Amendment 4, add that CT or CXR used for follow up only if it was used for baseline disease documentation.
10/17/2006 N = 302	Amendment 5, For defining the roles and responsibilities of two expert committees (IDMC and ICRA), added **"During the conduct of the first two Interim Analyses it became evident that the** response evaluations are inconsistently managed by the individual investigators. To allow similar evaluations for all patients an Independent Response Assessment Committee (ICRA) was established. It was first implemented as a pilot project for the third Interim Analysis. Due to the positive experience the committee will be called for **further interim and the final analysis."**
05/18/2006	**End of the study as last patient enrolled**

Date	Landmark
02/02/2007	Change statistic plan by the applicant based on the deviations from examining actual data set (details see statistical review and section 10.1.1.1.6).
06/20/2007	Amendment 6, sponsor changed

Source: Study 02CLLIII report

Figure 3: Study landmark flow chart



Source: Study 02CLLIII report

5.3.1.4 Efficacy and safety evaluation

The efficacy and safety evaluation was scheduled as below.

Table 5-5: Efficacy and safety evaluation

Procedures and assessments	Baseline[a]	Weekly	Cycle 1	2	3	4	5	6[b]	Follow-up (every 3 months)[c]
Informed consent	X								
Inclusion and exclusion criteria	X								
History/past medical history and treatment	X								
Concomitant diseases and treatments	X		X	X	X	X	X	X	X[d]
Demographics	X								
Height	X								
Physical examination, weight, and BSA	X		X	X	X	X	X	X	X[e]
Blood pressure, pulse, and temperature	X		X	X	X	X	X	X	X
WHO Performance Status	X		X	X	X	X	X	X	X
Quality of life	X		X	X	X	X	X	X	
Hematology[f]	X	X[g]	X	X	X	X	X	X[g]	X
Biochemistry[h]	X	X[i]	X	X	X	X	X	X	X[j]
Urinalysis	X		X	X	X	X	X	X	
Baseline status (CTC), adverse events/toxicities	X		X	X	X	X	X	X	
Electrocardiogram	X							X	
Tumor Evaluation by:									
CT or CXR	X		X[k,l]	X[k,l]	X	X[k,l]	X[k]	X[m]	X
Abdominal ultrasonography	X		X[k,l]	X[k,l]	X	X[k,l]	X[k]	X[m]	X
Bone marrow biopsy (histology and cytology)	X		X[l]	X[l]	X[n]	X[n]	X[n]	X[n]	
Lymph node palpation/spleen and liver size evaluation	X		X[l]	X[l]	X	X[l]	X[l]	X	X
Immunophenotype	X[o]								
Serum immunoglobulins	X		X[l]	X[l]	X[o,p]	X[l]	X[l]	X[p]	X[p]
Disease symptoms (B symptoms)	X		X[l]	X[l]	X	X[l]	X[l]	X	X

a. Baseline procedures were to be performed within 14 days prior to the first cycle with the following exceptions: hematology, biochemistry, and urinalysis: were to be performed within 8 days prior to the first cycle, and CT or chest radiography, bone marrow biopsy and determination of immunophenotype were to be performed within 3 months prior to the first cycle.
b. Cycle 6 or upon completion of the treatment period.
c. Follow-up evaluations were performed only for patients with CR, nPR, or PR as specified in the protocol. Patients with SD were monitored for the date of progression. For all patients **with PD, only "alive", "dead", or "lost to follow-up"** and further anticancer treatment was documented every 3 months.
d. Concomitant antineoplastic (drug) treatment reported only during follow-up.
e. Body weight only.
f. **Hemoglobin, hematocrit, WBC with differential, platelets, Coombs' test (hematocrit and Coombs' test performed only at baseline and after cycle 6 or at closeout).**
g. Hemoglobin, WBC with differential, platelets only.
h. Potassium, creatinine, alkaline phosphatase, LDH, SGOT, SGPT, γ-GT, bilirubin, glucose, total protein, albumin, uric acid.
i. Creatinine, LDH, SGOT, SGPT, bilirubin, uric acid only.
j. LDH only.
k. CT or CTX and ultrasonography were performed only if enlarged lymph nodes were present on corresponding baseline test.
l. Tumor assessments to be performed only in the event of blood count normalization.
m. CT or CTX and ultrasonography were performed only if enlarged lymph nodes present on previous corresponding test.
n. Bone marrow biopsy was performed 8 weeks after hematologic and clinical CR was first observed.
o. Coexpression of CD5, CD23, and either CD19 or CD20 or both.
p. Optional after cycle 3.

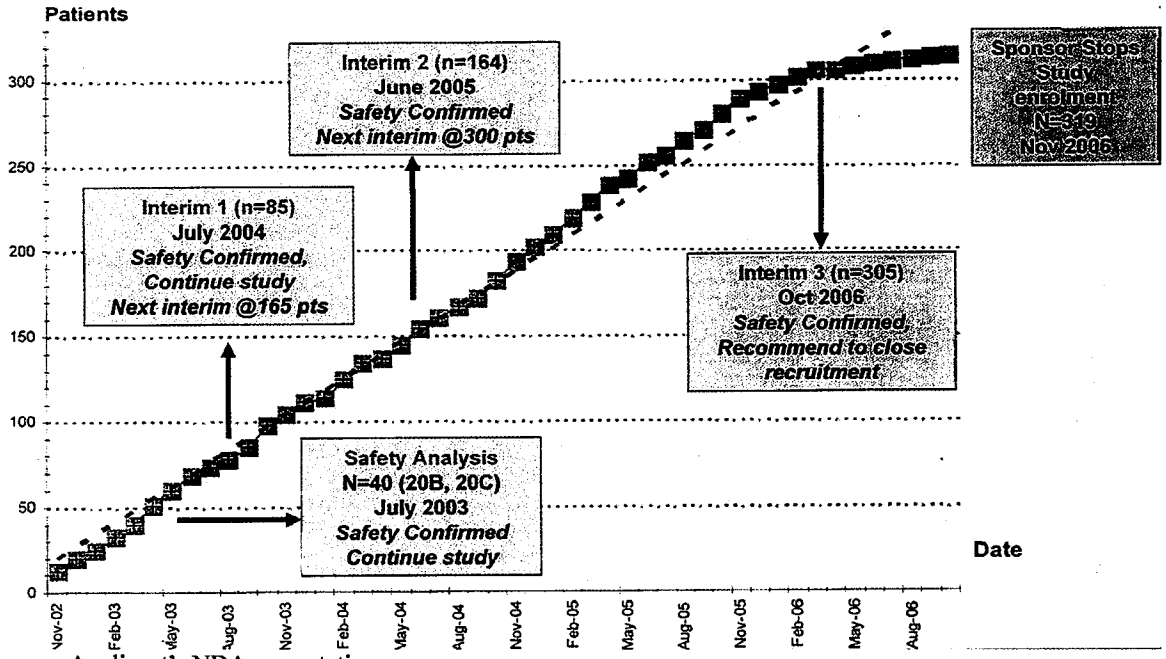
BSA=body surface area; CR=complete response; CT=computed tomography; CTC=common toxicity criteria; CXR=chest radiography; γ-GT=gamma-glutamyl transpeptidase; LDH=lactate dehydrogenase; nPR= nodular partial response; PD=progressive disease; PR=partial response; SD=stable disease; SGOT=serum glutamic oxaloacetate transaminase; SGPT=serum glutamic pyruvate transaminase; WBC=white blood cell; WHO=World Health Organization.

5.3.1.5 Statistics

5.3.1.5.1 Sample size estimation

The study was initially design to have a sample size of 80 with a efficacy analyses based sample size estimation design. The applicant depicted steps of sample estimation as below.

Figure 4: Steps of sample estimation during study 02CLLIII



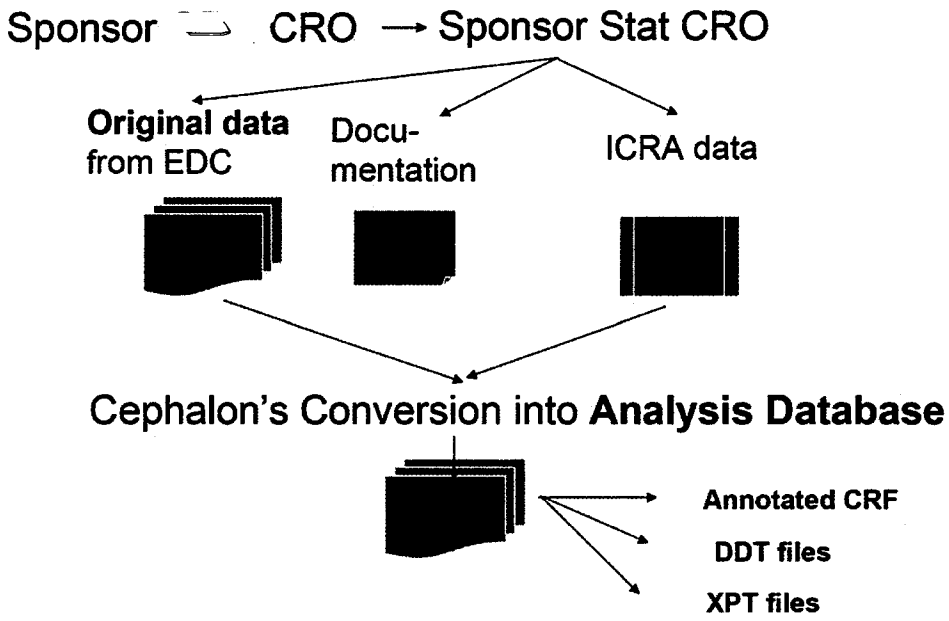
Source: Applicant's NDA presentation

Reviewer: This sample size estimation design and statistical analysis plan was discussed with FDA prior to the NDA submission. The agreetment on this design and plan was reached.

5.3.1.5.2 Data collection and conversion

Ribosepharm, whom applicant defined as study sponsor, conducted study 02CLLIII and obtained original results of the study. The applicant acquired results and assessed database, and then converted database and reanalyzed results. The applicant summarized their process as below.

Figure 5 Applicant's data reorganization



Source: Applicant dataset presentation, submission Oct 24, 2007.

Applicant identified following problems during the data evaluation and disclosed to FDA during the database illustration/presentation (Oct 16, 2007, EDR date Oct 24, 2007):

- no annotated CRF
- No censoring dates in the ICRA data
- Some key variables stored in different dataset (e.g. visit date)
- Dates may be partially imputed but this is not evident from the data
- Data contained record after the official data clean cut
- Long SAS variable names - Not possible to create transport files

During the data conversion, applicant implemented two quality control steps:

- Complete double programming of data conversions and electronic comparison of resulting datasets.
- Comparison of resulting data back to print-outs of eCRFs, for 60 patients.

In addition, applicant also conducted audits in 7 of the study sites for GCP compliance (see section 5.3.1.5.3 statistics, endpoints and measures, exploratory analyses for detail).

Reviewer: Due to the inherited problems of original data, both ICRA and investigator's efficacy assessments can not be verified fully. The applicant's quality control measures and site audits were reasonable approach in order to ascertain the data originality. In addition, applicant also reassessed co-primary endpoints (response and progression free survival) for all subjects in the study 02CLLIII. Both data conversion and reassessment by applicant provided more reliable information of the 02CLLIII study for the efficacy review of this NDA.

5.3.1.5.3 Statistics, endpoints and measures

The co-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, defined as Cheson criteria, 1999. The rules of response evaluation are summarized as below.

Table 5-6: Rule for response evaluation (part 1)

Parameter [Data source]	Complete response	Partial response	Progressive disease
(A) Peripheral lymphocyte count [Lymphocyte ABS from Listings 30.1 and 30.2]	Peripheral lymphocyte count of $4.0x10^9$/L or less	A decline of at least 50% in peripheral lymphocytes from pretreatment baseline value	≥50% increase in peripheral lymphocytes to at least $5.0x10^9$/L
(B) Hematology laboratory data [Neutrophils ABS, Platelets, and Hemoglobin from Listings 30.1 and 30.2, and Hematologic Supportive Care, Listing 42]	The following normal levels must be maintained for all 3 parameters: • neutrophils ≥$1.5x10^9$/L • platelets ≥$100x10^9$/L • hemoglobin ≥110g/L without transfusions	At least 1 of the following 3 criteria must be met: • neutrophils ≥$1.5x10^9$/L or ≥50% increase over baseline value • platelets ≥$100x10^9$/L or ≥50% increase over baseline value • hemoglobin ≥110 g/L or ≥50% increase over baseline value without transfusions	No criteria
(C) Spleen [Spleen Evaluation, Listing 9[a]]	The following option must be checked: THE SPLENOMEGALY IS NO LONGER PALPABLE	One of the following options must be checked: • REDUCTION IN THE SIZE OF SPLEEN ENLARGEMENT OF AT LEAST 50% • THE SPLENOMEGALY IS NO LONGER PALPABLE.	One of the following must be checked: • INCREASE IN THE SIZE OF SPLEEN ENLARGEMENT OF AT LEAST 50% • if enlarged=NO at baseline then need to observe enlarged=YES
(D) Liver [Liver Evaluation, Listing 10[a]]	The following option must be checked: THE HEPATOMEGALY IS NO LONGER PALPABLE	One of the following options must be checked: • REDUCTION IN THE SIZE OF LIVER ENLARGEMENT OF AT LEAST 50% • THE HEPATOMEGALY IS NO LONGER PALPABLE.	One of the following must be checked: • INCREASE IN THE SIZE OF LIVER ENLARGEMENT OF AT LEAST 50% • if enlarged=NO at baseline then need to observe enlarged=YES

Source: Study 02CLLIII report

Table 5-7: Rule for response evaluation (part 2)

(E) Lymph nodes [Evaluation of Indicator Lesions: 1st and 2nd dimensions and product, Listing 8]	All lesions measured at baseline must be measured at time point. There must be no lesion present whose longest diameter is greater than 1.5 cm. No new lesions must have occurred. Patients without lymphadenopathy at baseline and no post-baseline lymph node findings were also considered as exhibiting CR, provided the other criteria were met.	All lesions measured at baseline must be measured at a postbaseline time point. A decrease of at least 50% from baseline in the sum of the products of the diameters is needed. No new lesion must have occurred.	≥50% increase in the products of the diameters of at least 2 lesions and 1 of the lesions must be at least 2 cm in diameter, and/or the appearance of a new lesion.
(F) Bone marrow biopsy [Bone Marrow Evaluation: cellularity, lymphocytes as % of normal cells, lymphoid nodules, Listing 11]	A normal bone marrow is required which is defined as a bone marrow with Cellularity = NORMAL or HYPOCELLULAR, Lymphocytes % nucleated cells <30, Lymphoid nodules = ABSENT. If Lymphoid nodules = PRESENT but other criteria are met then CR is downgraded to nPR. The normal bone marrow needs to be at least 2 months (8 weeks or 56 days in protocol) from the date at which CR first recorded for parameters A to E and G.	No criteria	No criteria
(G) Constitutional. symptoms/transformation [Evaluation of Constitutional Symptoms: fever, night sweats, weight loss, transformation diagnosed, Listing 12]	A complete absence of constitutional symptoms must be observed. In practice this means "NO" for fever, night sweats and weight loss Missing data are interpreted to mean absence of the symptom as long as they are between two non-missing affirmations of absence of symptoms.	No criteria	Evidence of transformation to more aggressive phenotype, eg, Richter's syndrome or PLL, as indicated by transformation diagnosed = YES

Source: Study 02CLLIII report

Table 5-8: Rule for response evaluation (part 3)

Overall	***All*** improvements noted above in the different disease parameters must occur over a coincident period of at least 56 days, meaning that all of the criteria must have been observed simultaneously for at least 56 days. There must be no new anticancer treatment during this time.	A ***and*** B (at least one of the components of B), plus one of C, D, or E is observed simultaneously for a period of at least 56 days. There must be no new anticancer treatment during this time.	***Any*** of the above criteria are met. There is no requirement for a repeat observation after 2 weeks. If new chemotherapy is given, the patient is censored at last assessment before new chemotherapy.

[a] Spleen and liver measurements were not consistently recorded as the extent below the costal arch. Therefore, the "current status" field was used to assess improvement or worsening of splenomegaly and hepatomegaly.
ABS=absolute count; CR=complete response; nPR=nodular partial response; PLL=prolymphocytic leukemia; ALC=absolute lymphocyte count.
NOTE: For patients who did not experience progression based on the above criteria, the following date was determined to provide a censoring date: For all 4 dimensions (ALC, spleen, liver, lymph nodes), the last date of nonmissing postbaseline data was determined, and the first date chronologically served as the censoring date. If there were no postbaseline data for any of these 4 dimensions, the day of randomization was used as the censoring date.

Source: Study 02CLLIII report.

- Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first. The absence of an adjudicated progression date was interpreted as meaning that the patient did not progress. In this case, the data were censored at the last adequate assessment date. An assessment was considered adequate if it contained enough information for an outcome

assessment of CR, nPR, PR, SD, or PD. Deaths were incorporated as index events as outlined in the table below.

Table 5-9: Deriving a date of progression or censoring for PFS analysis (02CLLIII ITT)

Situation	Date of progression or censoring	Outcome
No baseline assessment or no post baseline assessment	Date of randomization	Censored
Progression documented between scheduled visits	Date of progression	Progressed
No progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for undocumented progression, toxicity, or other reason	Date of last visit with adequate assessment	Censored
Death before first progressive disease assessment	Date of death	Progressed
Death between adequate assessment visits, or after patient missed 1 visit	Date of death	Progressed
Death or progression after more than 1 missed visit	Date of last visit with adequate assessment	Censored

Source: 02CLLIII study report

In addition, in a modification to the Statistical Analysis Plan, new anticancer treatment was taken into account if given before or without progression, by censoring such patients at the last visit with an adequate assessment before the change in therapy. This was requested by FDA based on their review of the SAP (Letter from FDA, April 2007). Such new treatment was ignored in the analysis described in the Statistical Analysis Plan.

The statistical hypothesis to be tested for the second primary variable of progression-free survival was

Ho: hBEN(t) = hCLB(t) versus

Ha: hBEN(t) < hCLB(t)

where hBEN(t) and hCLB(t) are the hazards of progressing at time t.

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 in Lehmacher and Wassmer (1999).

Results from this procedure may have been invalid if the interval censoring affected each treatment group differently. Therefore, as an assumption check, the interval length was tested for differences between the treatment groups as follows: The time to 1st, 2nd, ., n^{th} assessment for disease progression was compared between treatments using the log-rank test.

Secondary efficacy endpoints for this study were time to progression (TTP), duration of response, overall survival (OS), and quality of life.

- Time to progression (TTP) was defined as the time from randomization to PD or death due to CLL. Patients were censored at the time of death if it was due to causes other than CLL.

- Duration of response was defined as the time from first observation of any response (CR, nPR, or PR) to PD or death due to any cause. This analysis included only patients with a best overall response of CR, nPR, or PR.

- Overall survival (OS) was defined as the time from randomization to death.

- Quality of life was assessed by the use of European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ) EORTC-C30 and EORTC QLQ-CLL25 completed by patients at baseline and at the end of each cycle.

Safety endpoints was assessed for the treated analysis set by evaluating the following:

- adverse events
- clinical laboratory test results (blood chemistry, hematology, and urinalysis)
- infections
- physical examination findings
- WHO Performance Status
- vital signs measurements (blood pressure, pulse, and temperature)
- electrocardiogram (ECG) findings
- study drug administration (ie, number of cycles treated and total dose of study drug received during the study)
- hematologic supportive care (eg, transfusions)
- concomitant medication usage

For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF. The investigator judged the clinical significance of any abnormalities, and abnormalities were described in detail.

Additional Exploratory Analyses

- Investigator response analysis: The best overall response was determined to be the best response that was recorded on 2 visits that were at least 56 days apart.

- Analysis excluding study centers 1 and 2: Based on initial observations within the dataset received from Ribosepharm, a quality control (QC) review of selected study centers were conducted. The findings at center 1 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 patients medical charts or source data available for review. For center

2, 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 analyses of the primary endpoints and the overall safety analyses are presented both with centers 1 and 2 included and with them excluded from the analyses in the NDA submission.

Sensitivity analyses:

- A: Progression-free survival based on scheduled visit dates. This analysis was to explore the effect of varying rules for censoring and assessment dates in determination of PFS. The analysis was based on ICRA adjudicated responses. This analysis corrected for potential bias in follow-up schedules for disease assessment by assigning the dates for censoring and events at the closest scheduled assessment date. For example, if PD was documented between scheduled visits, the primary analysis would use
- B: An analysis to explore robustness of effect using a calculated response rather than the ICRA adjudicated response was performed on the ITT analysis set of patients, based on the rule of response evaluation.

Subgroup Analyses:
The following subgroup analyses were to be performed for overall response rate and progression-free survival using the ITT patient populatiom and the ICRA response data:

- Sex
- Race
- Binet stage
- age (>65 versus <65)
- country

5.3.1.5.4 Independent Review

The study co-primary endpoints was originally designed to be assessed by independent response review committee (IRCA).

Reviewer: As per applicant, the ICRA assessments can not be verified. The applicant conducted **their own efficacy assessment, "calculated assessment". This assessment used a computer** programmed algorithm based on data from the primary source documents and eCRFs. This algorithm is based on NCI WG criteria for CLL and is evidence based, more reliable and verifiable assessment for the study 02CLLIII efficacy.

6 Review of Efficacy

6.1 Indication

TREANDA (bendamustine hydrochloride) for Injection is [redacted] indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.

6.1.1 Methods

As described in section 5.1 and 5.2, the efficacy review is based on the study 02CLLIII data.

6.1.2 Patient Baseline Characteristics and Demographics

As shown below, baseline characteristics and demographics of patients enrolled in study 02CLLIII were similar between the two arms.

Table 6-1: Study 02CL LIII patient baseline characteristics and demographics (ITT)

Demographic and Disease characters	Bendamustine (N= 153)	Chlorambucil (N = 148)
Age, mean (range)	63 (45-77)	66 (38-78)
Sex (M/F %)	63/37	61/39
Race (white %)	100	>99
Weight, mean (kg), (range)	78.2 (50.0-133.0)	74.0 (48.8, 118.0)
Height, mean (cm), (rang)	169.0 (147.0, 190.0)	168.4 (149.0, 189.0)
Lymphadenopathy, n (%)	121 (79)	122 (82)
Splenomegaly, n (%)	117 (76)	118 (80)
Hepatomegaly, n (%)	74 (48)	68 (46)
Hypercellular bone marrow, n (%)	121 (79)	108 (73)
Any constitutional symptoms, n (%) (fever, night sweats, or weight loss)	78 (51)	78 (53)
Lymphocyte count, mean (10^9/L), (range)	65.7 (12, 462.8)	65.1 (0.8, 252.8)
Binet Stage B/C n (%)	109 (71) / 44 (29)	102 (69) / 46 (31)
Immunophenotype, CD5, CD23, and either CD19 or CD20 or both, n (%)'	137 (90)	133 (90)
Lactate dehydrogenase, mean (U/L), (range)	370.2 (105, 1037)	388.4 (137, 1621)
Coombs test positive, n (%)	13 (8)	8 (5)
Hemoglobin (g/dl)	12.3	12.3
Platelet (10^9/L)	167.6	159.3
Neutrophil (10^9/L)	6.7	6.6
WHO performance status, n (%) 0	105 (69)	95 (64)
1	43 (28)	45 (30)
2	3 (2)	4 (3)
3/4	0	0
Missing	2 (1)	4 (3)

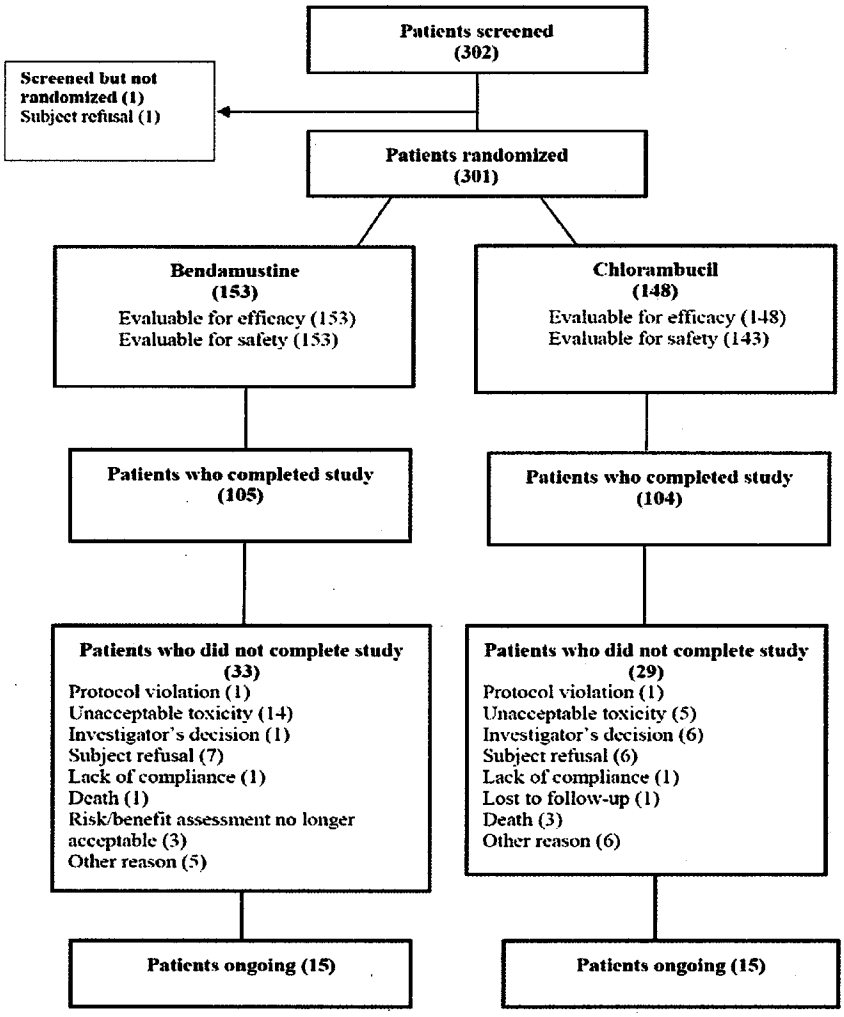
Source: Study 02CLLIII report.

6.1.3 Patient Disposition

Three hundred nineteen patients were enrolled in this study; the applicant's report only included 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 cut-off date for the final analysis was 26 March 2006. Applicant excluded data on visit dates beyond 26 March 2006, data for adverse reactions, concomitant diseases, concomitant medications with start dates beyond 26 March 2006 from analyses. Applicant also did not include 17 patients who enrolled after the cut-off date (Mar 26, 2006), resulting 302 patients of ITT population for the final analyses.

Of the 302 patients, 301 were randomly assigned to treatment (153 to bendamustine and 148 to chlorambucil) and 296 received at least 1 dose of study drug (153 received bendamustine and 143 received chlorambucil). The disposition of these 302 patients is summarized in the figure below.

Figure 6: Study 02CLLIII patient disposition (ITT, Mar 26, 2006 cut-off)



Source: Study 02CLLIII report.

Limited data are available on the 17 patients enrolled after the cut-off date of 26 March 2006. Of these 17 patients, 9 received bendamustine treatment and 8 received chlorambucil treatment. Two patients were still active in the study at the time of NDA submission, 1 in each treatment group. Of the other 8 patients on bendamustine treatment, 4 completed the study (1 CR, 2 PRs, and 1 SD) and 4 were withdrawn (1 due to unacceptable toxicity, 1 investigator decision, 1 subject refusal after adverse reactions during cycle 5], and 1 had a new malignancy of lung diagnosed during the study treatment. Of the other 7 patients on chlorambucil treatment, 6 completed the study (3 PRs, 2 SD, and 1 PD) and 1 was withdrawn after a 4-week delay due to a serious adverse reaction. After the 26 March 2006 cut-off date, there were 14 serious adverse reactions reported by 8 patients, 5 on bendamustine treatment and 3 on chlorambucil treatment. The 11 serious adverse reactions reported by the 5 patients receiving bendamustine were thoracic

pain, phlebitis, fever, cerebellar infarction, pneumonia, lung tumor, dyspnea, lung disorder, aortic arteriosclerosis, pleural effusion, and autoimmune thrombocytopenia. The 3 serious adverse reactions reported by the 3 patients receiving chlorambucil were focal liver lesion of unknown origin, retroperitoneal hematoma, and scabies.

6.1.4 Protocol deviation and violation

A total of 34 patients randomized to bendamustine treatment and 33 patients randomized to chlorambucil treatment were recorded as having violated at least 1 inclusion or exclusion criterion (a missing value was considered a violation). The major protocol deviations and violations are summarized as below.

Table 6-2: Major protocol deviations or violations

	Patients	
Criteria	Bendamustine	Chlorambucil
Treatment naive, legally competent adult patients < 75 years of age capable of following instructions (INC1)	1	2
Patient given informed consent (INC2)	0	1
WHO Performance Status 0-2 (INC3)	1	0
Confirmed chronic B-cell lymphocytic leukemia (coexpression of CD5, CD23 and either CD20 or CD19 or both (INC7)	8	3
Symptomatic Binet Stage B or Binet Stage C disease (INC8)	3	0
Need-to-treat (INC9)	0	1
Exclusion History of a second malignancy (except cured basal cell carcinoma or cured cervical cancer) (EXC4)	2	0
Hepatic dysfunction: bilirubin >2.0 mg/dL and/or transaminases >3xULN (EXC8)	1	2
Renal dysfunction (creatinine clearance <30 ml/min, calculated) (EXC9)	1	1
randomized but did not receive study drug	0	4

Source: Study 02CLLIII report.

The minor deviations were patients lack of documentation of negative pregnanacy test (men or women were older than 46 years), no pregnancy or no lactation (men or women more than 61 years old), considering the sex and age of the patients listed for these criteria, in actuality, there were no violations of these criteria.

Reviewer: About 10% patients had some major protocol deviations or violations. The most concerning deviations/violation among them were lack of phenotypic confirmation of CLL (8 for bendamustine arm and 3 for the control arm) and patients who were randomized but did not received study drug (4 for control arm, none in bendamustine arm). However, the total number of patients in which these two major violations occurred are small (less than 10%). These are unlikely to have an impact on the study results.

6.1.5 Analysis of Primary Endpoint(s)

Reviewer: As mentioned in section 5.3.1.5.3, the co-primary efficacy endpoints were overall response rate (ORR) and progression-free survival (PFS) using responses and dates of progression based on NCI-WG CLL criteria for CLL. These co-primary endpoints were later changed to response assessment as per the ICRA in protocol amendment #4. However, due to the issues with data availability and ownership change, the ICRA efficacy assessments can not be verified fully.

The co-primary endpoint analyses of Study 02CLLIII are shown in rest of the section 6.1.5.

6.1.5.1 Overall Response Rate

6.1.5.1.1 ICRA Overall Response Analysis

The overall response rate was analyzed by the applicant based on the assessment of ICRA, as summarized in the table.

Table 6-3:Overall response rate based on ICRA assessment (ITT)

ICRA Response	Bendamustine N=153 (%)	Chlorambucil N=148 (%)
Overall response rate	95 (62)	49 (33)
(95% CI)	(54.40, 69.78)	(25.53, 40.69)
p-value	<0.0001	
Complete response	42 (27)	3 (2)
Nodular partial response	15 (10)	4 (3)
Partial response	38 (25)	42 (28)
Unconfirmed response	9 (6)	8 (5)
Stable disease	22 (14)	37 (25)
Progressive disease	4 (3)	26 (18)
Not examined	23 (15)	28 (19)

Source: Study 02CLLIII report.

Reviewer: ICRA assessment cannot be verified, because applicant was not able to obtain details of elements on which the ICRA based their response assessments from previous sponsor who completed this study Also see section 6.1.5.1.4.

6.1.5.1.2 Investigator Overall Response Analysis

The applicant's analysis of overall response by investigators'' assessment is summarized as below.

Table 6-4: Investigator assessed overall response (ITT)

Investigator Response	Bendamustine N=153 (%)	Chlorambucil N=148 (%)
Overall response rate	90 (59)	35 (24)
(95% CI)	(51.03, 66.62)	(16.80, 30.90)
p-value	<0.0001	
Complete response	40 (26)	4 (3)
Nodular partial response	11 (7)	1 (<1)
Partial response	39 (25)	30 (20)
Unconfirmed response	24 (16)	23 (16)
Stable disease	19 (12)	53 (36)
Progressive disease	9 (6)	17 (11)
Not examined	11 (7)	20 (4)

Source: Study 02CLLIII report.

Reviewer: The details of elements on which investigators based their assessment are not available for FDA review, because applicant is not able to obtain this information from the previous sponsor who completed this study

6.1.5.1.3 Sensitivity Assessment of Overall Response by excluding centers 1 & 2

The applicant conducted a sensitivity analysis that exclude the subjects from centers 1 and 2, at which the applicant has identified study violations during their audits, to determined whether efficacy data from these sites has any impact to the overall response.

Table 6-5: Overall response rate based on ICRA (ITT excluding centers 1 & 2)

Investigator Response	Bendamustine N=263 (%)	Chlorambucil N=121 (%)
Overall response rate	75 (60)	38 (31)
(95% CI)	(50.95, 68.09)	(23.14, 39.67)
p-value	<0.0001	
Complete response	30 (24)	2 (2)
Nodular partial response	11 (9)	4 (3)
Partial response	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)

Source: Study 02CLLIII report.

Reviewer: The ORR analysis is still statistically significant after excluding sites 1and 2. The clinical and statistical reviewers verified applicants' sensitivity analysis and agree that the impact of sites 1 and 2 to the overall response is minimal.

Analyses on discordance between the ICRA and investigators' ORR assessment.

In addition, a concordance analysis between the ICRA and investigator were conducted and summarized as below.

Table 6-6: Overall response assessment comparison between ICRA and investigator (ITT)

ICRA	Investigator								
	Bendamustine (N=153)			Chlorambucil (N=148)			Total (N=301)		
	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: Study 02CLLIII report.

Reviewer: There were a total of 43 cases (19 of Bendamustine and 24 of Chlorambucil) of disagreement between the ICRA and investigator, although both response analyses are statistically significant. Overall response rate in either arm by ICRA assessment was better than the investigator assessment, which raises the question of whether all data was available for the ICRA review. The reviewers requested applicant to provide individual case narratives for these 43 cases and an analysis of reasons for discordance in response assessment between IRCA and investigators. Upon FDA request of clarification, the applicant responds as in section 6.1.5.1.4.

6.1.5.1.4 Calculated response assessment and analyses on discordance within the calculated, ICRA and investigators' ORR assessments

Per applicant: "The ICRA assessment was prospectively designated as the primary efficacy analysis for the 02CLLIII study. This assessment was based on an independent blinded review of the efficacy data by 3 experts in the treatment of chronic lymphocytic leukemia (CLL). Detailed minutes were not taken at the ICRA meeting and therefore, it is not possible to provide a specific reason for the discordance. Similarly, the investigators were not required to provide details of the reasons for their response assessments. Therefore, we do not have the reasons for the discordances nor can an analysis of those discordances in responses assessments be conducted." Therefore, the applicant conducted a post-hoc primary assessment of their own, "calculated assessment" (detailed in NDA22249 list 14), using available data from the legacy study 02CLLIII to ensure the adequacy and reliability of the primary analyses by ICRA assessment.

Calculated Response	Bendamustine N=153 (%)	Chlorambucil N=148 (%)	p-value
Complete response	13 (8)	1 (<1)	<0.0001
Nodular partial response	4 (3)	0	
Partial response	73 (48)	37 (25)	
Stable disease/Progressive disease/NE	63 (41)	110 (74)	
Overall response rate (95% CI)	90 (59) (51.03, 66.62)	38 (26) (18.64, 32.71)	

Source: Study 02CLLIII report.

The comparison of assessments by ICRA, investigator, and applicant calculation are summarized as below.

Table 6-7: Comparison of assessments by ICRA, investigator, and applicant calculation

Response/number (%) of patients	Bendamustine (N=153)			Chlorambucil (N=148)		
	ICRA	**Calculated**	Investigator	ICRA	**Calculated**	Investigator
Complete response	42 (27)	**13 (8)**	40 (26)	3 (2)	**1 (<1)**	4 (3)
Nodular partial response	15 (10)	**4 (3)**	11 (7)	4 (3)	**0**	1 (<1)
Partial response	38 (25)	**73 (48)**	39 (25)	42 (28)	**37 (25)**	30 (20)
Unconfirmed response	9 (6)	-	24 (16)	8 (5)	-	23 (16)
Stable disease	22 (14)	-	19 (12)	37 (25)	-	53 (36)
Progressive disease	4 (3)	-	9 (6)	26 (18)	-	17 (11)
Not examined	23 (15)	-	11 (7)	28 (19)	-	20 (14)
SD/PD/NE	-	**63 (41)a**	-	-	**110 (74)a**	-
Overall response	95 (62)	**90 (59)**	90 (59)	49 (33)	**38 (26)**	35 (24)

a The calculated response did not distinguish between SD, PD, and NE.
ICRA=Independent Committee for Response Assessment; SD=stable disease; PD=progressive disease; NE=not examined.
Source: 02CLLIII study report, summary 15.9.1, Summary 15.9.2, Summary 15.9.4, and Listing 14.

The concordance within ICRA, calculated and investigators assessments is summarized as below. There were 82% (246/301) of total concordance within 3 response assessment, 82% (126/153) for bendamustine arm and 81% (120/148) for chlorambucil arm. The cross sectional and three way comparisons are as shown below.

Table 6-8: The concordant analyses within tumor response assessment of ICRA, calculated and investigators.

Arm \ Response	ICRA	Calculated	Investigators	N (%)
Bendamustine (N=153)	No	No	No	**47 (31)**
	No	No	Yes	3 (2)
	No	Yes	No	4 (3)
	No	Yes	Yes	4 (3)
	Yes	No	No	9 (6)
	Yes	No	Yes	4 (3)
	Yes	Yes	No	3 (2)
	Yes	Yes	Yes	**79 (52)**
Chlorambucil (N=148)	No	No	No	**93 (63)**
	No	No	Yes	2 (1)
	No	Yes	No	1 (1)
	No	Yes	Yes	3 (2)
	Yes	No	No	12 (8)
	Yes	No	Yes	3 (2)
	Yes	Yes	No	7 (5)
	Yes	Yes	Yes	**27 (18)**

Source: Study 02CLLIII report, data set submitted on Jan 25, 2008 and Listing 14.
ICRA=Independent Committee for Response Assessment. Yes = response (CR, nPR or PR), No = no response (SD, PD, NE)
NOTE: A responder is a patient with a best response of complete response (CR), nodular partial response (nPR), or partial response (PR). A patient with a missing response was assigned a responder value of .No. The concordance within 3 analyses is bolded.

The concordance between the ICRA and calculated response assessment was 87% for both bendamustine arm and chlorambucil arm.

Table 6-9: Concordant rates between ICRA and calculated response assessments: response (CR, nPR, PR) versus none (unconfirmed response, SD, PD, NE)

Arm \ Response	ICRA	Calculated	N (%)
Bendamustine (N=153)	No	No	**50 (33)**
	No	Yes	8 (6)
	Yes	No	13 (9)
	Yes	Yes	**81 (54)**
Chlorambucil (N=148)	No	No	**95 (64)**
	No	Yes	4 (3)
	Yes	No	15 (10)
	Yes	Yes	**34 (23)**

Source: 02CLLIII study report.

Reviewer: Despite a high concordance rate, the CR rate in the ICRA assessment falls from 27% to 8% in the calculated assessment. Based on above analyses, the calculated overall response assessment, is the only assessment that can be verified, and is the most reliable analysis in interpretation of ORR result of the study 02CLLIII.

6.1.5.2 Progression Free Survival

6.1.5.2.1 ICRA Progression Free Survival Analysis (PFS)

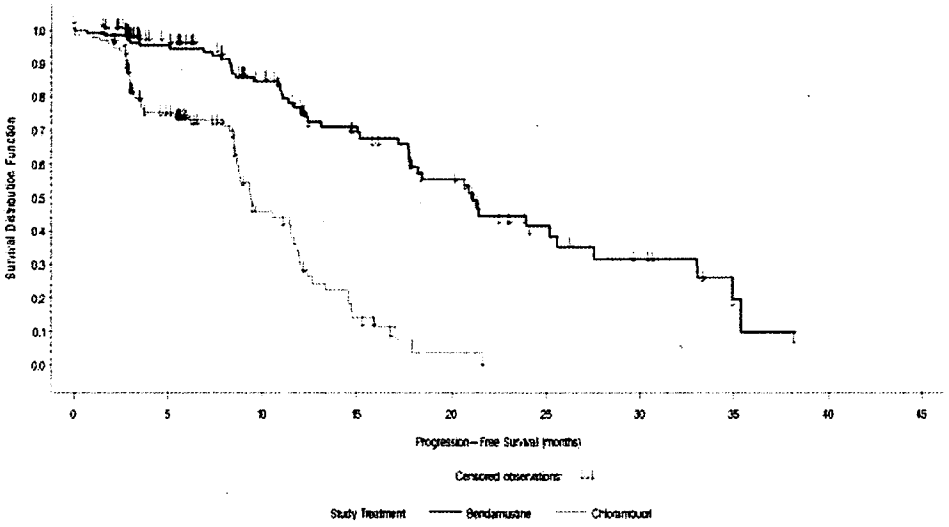
The PFS analysis based on independent assessment are as below.

Table 6-10: PFS based on ICRA assessment (ITT)

Progression-free survival	Bendamustine (N=153)	Chlorambucil (148)
Patients with events	47 (31)	66 (45)
Censored patients	106 (69)	82 (55)
Hazard ratio (CLB/BEN) (95% CI)	4.386 (2.581, 7.453)	
p-value	<0.0001	
Quartiles (95% CI), months		
25th percentile	12.3 (11.0, 17.7)	5.3 (3.0, 8.5)
50th percentile (median)	21.1 (17.7, 25.6)	9.4 (8.7, 11.7)
75th percentile	34.9 (25.2, n/a)	12.7 (11.7, 14.8)

Source: Study 02CLLIII report.

Figure 7: Progression free survival by ICRA assessment (ITT)



Source: Study 02CLLIII report.

Reviewer: Clinical and statistical reviewers verified result of this analysis based on the applicant provided data sets. The PFS was primarily driven by the events of disease progression (n = 81), less then 20% of PFS events were death (n = 22) at the clinical cut-off date. Since study 02CLLIII was conducted by a different sponsor, the detailed or supporting documentation of this assessment was not available to the applicant; therefore, the reviewer can not verify or confirm the reliability of the independent assessment.

6.1.5.2.2 Investigator Progression Free Survival Analysis

No investigator assessment for PFS analysis were conducted for study 02CLLIII.

6.1.5.2.3 Applicant Calculated Progression Free Survival Analysis

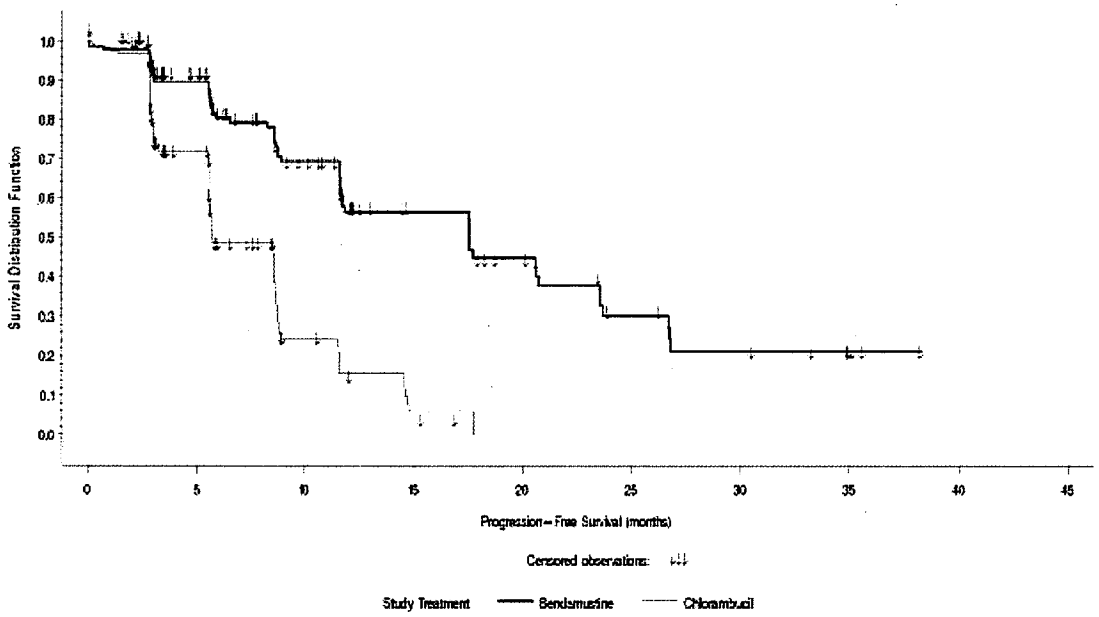
In order to confirm and verify the result of ICRA assessed PFS, the applicant conducted their own PFS assessment, calculated assessment, based on the converted data and primary source documents. The PFS analysis based on the calculated assessment are summarized as below.

Table 6-11: PFS analysis based on the calculated assessment (ITT)

Progression-free survival	Bendamustine (N=153)	Chlorambucil (148)
Patients with events	55 (36)	83 (56)
Censored patients	98 (64)	65 (44)
Hazard ratio (CLB/BEN) (95% CI)	3.722 (2.338, 5.926)	
p-value	<0.0001	
Quartiles (95% CI), months		
25th percentile	8.6 (5.9, 11.6)	3.0 (2.9, 5.6)
50th percentile (median)	17.6 (11.7, 23.5)	5.7 (5.6, 8.6)
75th percentile	26.8 (23.5, NAV)	11.5 (8.7, 14.6)

Source: Study 02CLLIII report.

Figure 8: Applicant estimated PFS analysis - Kaplan-Meier curve (ITT)



Source: Study 02CLLIII report.

Reviewer: The clinical and statistical reviewers verified this analysis and agreed with the result.

6.1.5.2.4 Sensitivity Assessment of Overall Response and PFS by excluding centers 1 & 2

The applicant conducted a sensitivity analysis that exclude the subjects from centers 1 and 2, at which the applicant has identified study violations during their audits, to determined whether efficacy data from these sites has any impact to the progression free survival.

Table 6-12: PFS based on ICRA (ITT Excluding Centers 1 and 2)

Progression-free survival	Bendamustine (N=126)	Chlorambucil (121)
Patients with events	35 (28)	54 (45)
Censored patients	91 (72)	67 (55)
Hazard ratio (CLB/BEN) (95% CI)	4.341 (2.408, 7.827)	
p-value	<0.0001	
Quartiles (95% CI), months		
25th percentile	12.4 (11.0, 18.2)	3.7 (3.0, 8.6)
50th percentile (median)	21.1 (18.2, 33.0)	9.6 (8.8, 11.9)
75th percentile	35.3 (25.6, 35.3)	14.5 (11.8, 15.9)

Source: Study 02CLLIII report.

Reviewer: The PFS analysis is still statistically significant after excluding sites 1and 2. The clinical and statistical reviewers verified applicants' sensitivity analysis and agree that the impact of sites 1 and 2 to the progression free survival is minimal.

6.1.5.2.5 Concordance between calculated and ICRA PFS analyses

The concordance between the calculated and ICRA PFS assessment are summarized as below.

Table 6-13: Concordance between the calculated and ICRA PFS assessments

ICRA PFS		Calculate PFS					
		Total		Bendamustine		Chlorambucil	
		Events	Censored	Events	Censored	Events	Censored
Total	Events	101 (34%)	12 (4%)				
	Censored	50 (16%)	138 (46%)				
Bendamustine	Events			41 (27%)	6 (4%)		
	Censored			22 (14%)	84 (55%)		
Chlorambucil	Events					60 (41%)	6 (4%)
	Censored					28 (19%)	54 (36%)

Source: Study 02CLLIII report.

Reviewer: There are 20% discordance, 18% for the bendamustine arm and 23% for the chlorambucil arm, between the verifiable calculated PFS assessment and the unverifiable ICRA PFS assessment.

6.1.5.2.6 Analyses on missing assessment/data (calculated assessment only)

The timing of tumor assessments (calculated assessment) for response and PFS were analyzed to ensure the assessment intervals were balanced between the two arms. The results are as below.

Table 6-14: Tumor assessment interval between the two treatment arms (ITT)

Assessment Number	Bendamustine (N=153)	Chlorambucil (N=148)	Total (N=301)
Assessment 1			
Missing	11	20	31
n	142	128	270
Mean	3.2	3.0	3.1
Assessment 2			
Missing	38	55	93
n	115	93	208
Mean	5.9	5.9	5.9
Assessment 3			
Missing	61	98	159
n	92	50	142
Mean	9.7	9.7	9.7
Assessment 4			
Missing	87	124	211
n	66	24	90
Mean	12.0	12.0	12.0
Assessment 5			
Missing	102	134	236
n	51	14	65
Mean	15.6	15.8	15.7
Assessment 6			
Missing	115	145	260
n	38	3	41
Mean	18.9	17.0	18.7
Assessment 7			
Missing	125	148	273
n	28	0	28
Mean	22.0	-	22.0
Assessment 8			
Missing	134	148	282
n	19	0	19
Mean	24.7	-	24.7
Assessment 9			
Missing	142	148	290
n	11	0	11
Mean	28.4	-	28.4
Assessment 10			
Missing	146	148	294

Assessment Number	Bendamustine (N=153)	Chlorambucil (N=148)	Total (N=301)
n	7	0	7
Mean	31.4	-	31.4

Source: Study 02CLLIII report.

Reviewer: The timing of tumor assessment closely followed study design and was to be conducted every 3 months for the first ten assessments. The assessment intervals were balanced between two arms until assessment 7. The control arm had no subjects remaining on study for follow up after that.

The reasons or outcomes that cause missed tumor assessments (calculated assessment) of each subject were identified and listed in the table below.

Table 6-15: Reasons or outcomes for missing assessment.

Drop out / Missing assessment	Bendamustine (N=153)		Chlorambucil (N=148)	
	Reason / outcome	ID	Reason / Outcome	ID
Missing assessment 1	Death during treatment	10303	Death during treatment	10114, 10902, 20902
	Lost to follow-up	110113	Investigator's decision	20302
	Ongoing	12614, 13610, 27202	Lost to follow-up	10109, 10110
	Other reason	12502	Ongoing	13609, 15803, 17004, 17306, 17404, 22903, 27201
	Protocol violation	22902	Other reason	10901, 11702, 13002, 22002
	Subject refusal	10407, 10507	Protocol violation	10117
	Unacceptable toxicity	12611, 12901	Subject refusal	10202, 20507
Missing assessment 2	Confirmed CR	15082	Investigator's decision	13401, 15404, 25301, 27601
	No change	21206, 22802	Lack of compliance	12103
	Ongoing	10218, 10518, 11605, 11707, 12613, 14109, 16501, 20207, 21503, 22501	Lost to follow-up	12401
	Partial response	15303	No change	11207, 11502, 12805, 17601, 21207
	during treatment	10121, 10401, 10515, 10517, 11602, 20509, 21702, 22005	Ongoing	10219, 10516, 11003, 11606, 13805, 14108, 17304, 24104
	Progression Risk/ benefit assessment no longer acceptable	17403	Partial response	12804
	Subject refusal	10111	Progression during treatment	11202, 11208, 11209, 12607, 12802, 13602, 13801, 15104, 21203, 21603, 22803, 23201, 26501
	Unacceptable toxicity	10120, 13101, 21208	Unacceptable toxicity	12601, 21205
Missing assessment 3	Confirmed CR	10217, 10703, 17002	Confirmed CR	12612
	Lack of compliance	10112	Death during follow-up	13604, 21701
	No change	11501, 17302	Investigator's decision	20206
	Ongoing	11004, 17305	No change	10505, 10513, 11503, 12403,

Drop out / Missing assessment	Bendamustine (N=153)		Chlorambucil (N=148)	
	Reason / outcome	ID	Reason / Outcome	ID
				12608, 20505
	Other reason	12402	Partial response	10124, 12504, 12505, 14107, 17003, 17402, 20203
	Partial response	10514, 13608, 17301, 17401, 24001	Progression during follow-up	12902, 21204, 22602
	Progression during follow-up	10701, 12102, 13804	Progression during treatment	10103, 10123, 10209, 10212, 10215, 10307, 10412, 10501, 10511, 10512, 11604, 15101, 17303, 20102, 20202, 20205, 20301, 20504, 21604, 22601, 24101
	Progression during treatment	10122, 12609, 20204, 20701	Unknown	13802, 23002
	Unknown	12404, 17701	-	-
Missing assessment 4	Death during follow-up	12606, 12803, 23601	Lost to follow-up	20502
	Lost to follow-up	10510, 12502	Progression during follow-up	10105, 10106, 10116, 10305, 10402, 10403, 10406, 10702, 11002, 12001, 12602, 12903, 13201, 13202, 21502
	Progression during follow-up	10107, 10118, 10127, 10304, 10408, 10409, 11705, 12604, 14201, 20101, 20402	Unknown	10216, 11601, 11706, 12610, 12701, 13605, 13607, 15401, 20901, 27101
	Progression during treatment	20508	-	-
	Unknown	10213, 11210, 14102, 15302, 15601, 17001, 17101, 21601, 22901	-	-
Missing assessment 5	Death during follow-up	11001	Progression during follow-up	10207, 10302, 10405, 10503, 12501, 22001
	Progression during follow-up	10108, 10115, 10206, 10211, 10306, 10404, 10903	Unknown	10101, 10125, 10126, 10205
	Unknown	10214, 11704, 13606, 14106, 15002, 15403,	-	-

Drop out / Missing assessment	Bendamustine (N=153)		Chlorambucil (N=148)	
	Reason / outcome	ID	Reason / Outcome	ID
		27401		
Missing assessment 6	Progression during follow-up	10208, 10210, 11204, 11603, 12905	Progression during follow-up	10411, 10508, 11203, 12002, 12101, 20401
	Unknown	15001, 15102, 15103, 15201, 15402, 15801, 22401, 24103	Unknown	10201, 11703, 14103, 14104, 14401
Missing assessment 7	Progression during follow-up	10509, 11206, 20506	Unknown	10301, 14001, 15301
	Unknown	12904, 13001, 13803, 20503, 21602, 22004, 22801	-	-
Missing assessment 8	Progression during follow-up	10102, 10410, 10506, 20303, 23401	-	-
	Unknown	12605, 21201, 23001, 24102	-	-
Missing assessment 9	Death during follow-up	22101	-	-
	Progression during follow-up	10204	-	-
	Unknown	11205, 12603, 13603, 14101, 20501, 22003	-	-
Missing assessment 10	Lost to follow-up	11701	-	-
	Progression during follow-up	10203	-	-
	Unknown	12702, 12801	-	-

Source: Study 02CLLIII report.

6.1.6 Analysis of Secondary Endpoints(s)

6.1.6.1 Duration of Response

6.1.6.1.1 Duration of Response Based on IRCA Assessment

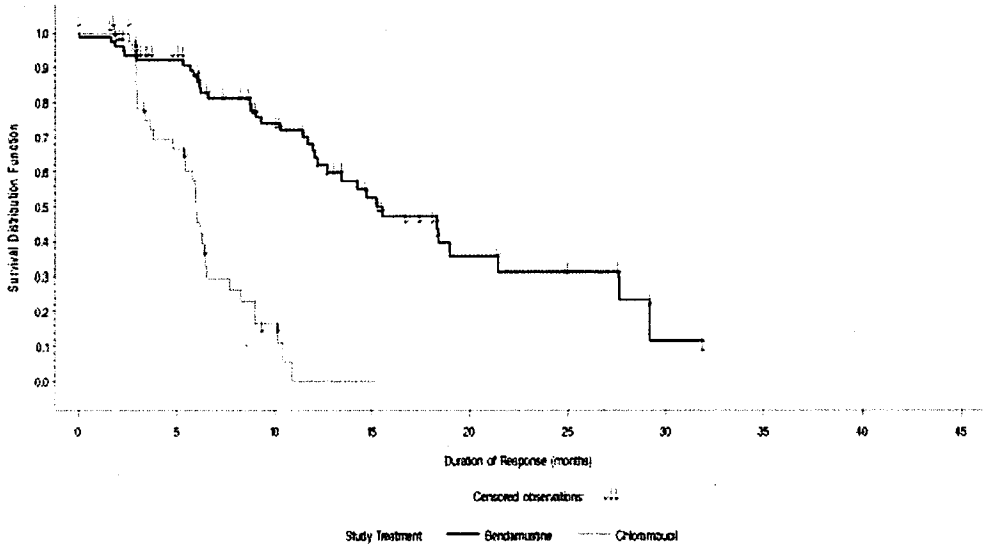
The duration of ICRA assessed response are summarized as below.

Table 6-16: Duration of response by ICRA assessment (ITT)

Duration of response	Bendamustine (N=153)	Chlorambucil (N=148)
Patients with CR, nPR, and PR combined	95	49
Patients with events, n (%)	35 (37)	31 (63)
Censored patients, n (%)	60 (63)	18 (37)
Quartiles (95% CI), months		
25th percentile	9.4 (6.4, 12.5)	3.8 (3.0, 6.0)
50th percentile (median)	15.9 (12.5, 23.9)	6.0 (5.4, 6.5)
75th percentile	29.0 (19.0, n/a)	9.0 (6.4, 10.4)

Source: Study 02CLLIII report.

Figure 9: Response duration by Kaplan-Meier estimation (ITT, ICRA)



Source: Study 02CLLIII report.

Table 6-17: Duration of each type of response (ITT, IRCA assessment)

	CR		nPR		PR	
Duration of response	BEN N = 42	CLB N = 3	BEN N = 15	CLB N= 4	BEN N = 38	CLB N = 42
All patients	42	3	15	4	38	42
Patients with events, n (%)	11 (26)	1 (33)	7 (47)	2 (50)	17 (45)	28 (67)
Censored patients, n (%)	31 (74)	2 (67)	8 (53)	2 (50)	21 (55)	14 (33)

Source: Study 02CLLIII report.

Reviewer: The study 02CLLIII was conducted by a different sponsor, and the detailed or supporting documentation of this assessment was not available to the applicant; therefore, the reviewer can not verify or confirm the reliability of the ICRA assessment.

6.1.6.1.2 Duration of Response Based on Calculated Assessment

The duration of calculated assessed response are summarized as below.

Table 6-18: Duration of response by calculated assessment (ITT)

Duration of response	Bendamustine (N=153)	Chlorambucil (N=148)
Patients with CR, nPR, and PR combined	90	38
Patients with events, n (%)	34 (38)	27 (71)
Censored patients, n (%)	56 (62)	11 (29)
Quartiles (95% CI), months		
25th percentile	9.6 (8.3, 15.5)	5.7 (5.3, 6.0)
50th percentile (median)	18.6 (15.0, 24.2)	6.5 (5.8, 10.4)
75th percentile	N/A (22.4, n/a)	11.0 (9.0, 14.0)

Source: Study 02CLLIII report.

Figure 10: Response duration by Kaplan-Meier estimation (ITT, calculated assessment)

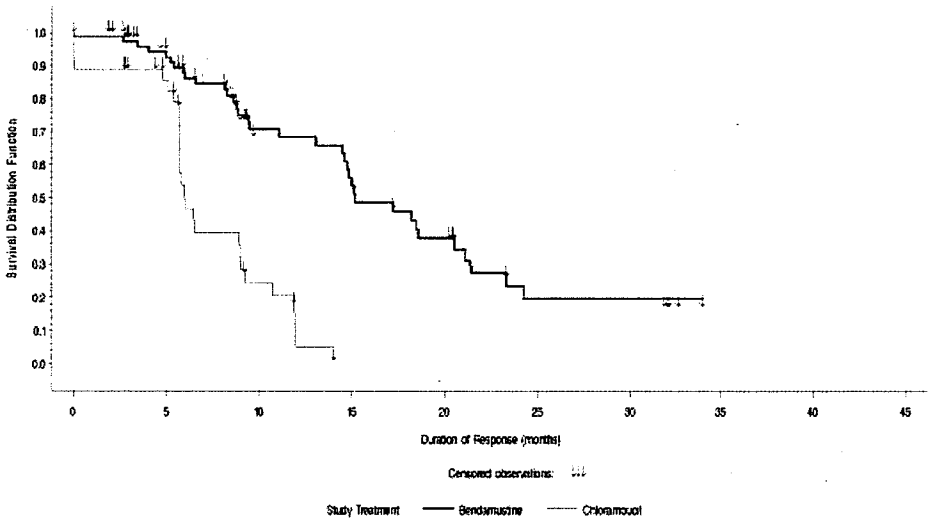


Table 6-19: Duration of each type of response (ITT, calculated assessment)

	CR		nPR		PR	
Duration of response	BEN N= 13	CLB N = 1	BEN N = 4	CLB N = 0	BEN N = 73	CLB N = 37
All patients	13	1	4	0	73	37
Patients with events, n (%)	4 (31)	1 (100)	2 (50)	0	28 (38)	26 (70)
Censored patients, n (%)	9 (69)	0	2 (50)	0	45 (62)	11 (30)

Source: Study 02CLLIII report.

Reviewer: Clinical and statistical reviewers verified result of this analysis based on the applicant provided data sets and assessment narratives. The analysis based on the calculated response duration assessment, which is the **evidence-based assessment**, is the most reliable estimate of response duration.

6.1.6.2 TTP by ICRA Assessment

The ICRA assessed TTP analysis are summarized as below.

Table 6-20: TTP by ICRA assessment (ITT)

Time to disease progression	Bendamustine (N=153)	Chlorambucil (N=148)
Patients with events	43 (28)	65 (44)
Censored patients	110 (72)	83 (56)
Hazard ratio (CLB/BEN) (95% CI)	5.050 (2.927, 8.713)	
p-value	<0.0001	
Quartiles (95% CI), months		
25th percentile	13.1 (11.4, 17.8)	5.3 (3.0, 8.6)
50th percentile (median)	21.3 (18.2, 27.6)	9.4 (8.7, 11.7)
75th percentile	34.9 (25.6, n/a)	12.7 (11.7, 14.8)

Source: Study 02CLLIII report.

Reviewer: Clinical and statistical reviewers verified result of this analysis based on the applicant provided data sets. No information was available for FDA review and verify TTP.

6.1.6.3 Overall Survival

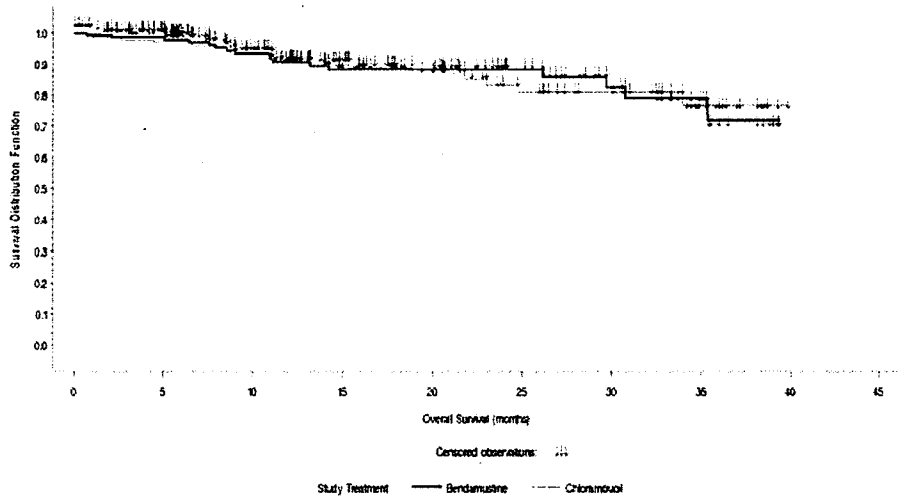
The overall survival analysis (data cut-off date as March 26, 2006) is summarized as below.

Table 6-21: Overall survival (ITT)

Overall survival	Bendamustine (N=153)	Chlorambucil (N=148)
Patients with events, n (%)	17 (11)	17 (11)
Censored patients, n (%)	136 (89)	131 (89)
HR	n/a	
p-value	n/a	
Quartiles (95% CI), months		
25th percentile	35.4 (29.9, n/a)	n/a (23.6, n/a)
50th percentile (median)	n/a (n/a, n/a)	n/a (n/a, n/a)
75th percentile	n/a (n/a, n/a)	n/a (n/a, n/a)

Source: Study 02CLLIII report.

Figure 11: Overall Survival by Kaplan-Meier Estimation (ITT)



Reviewer: Clinical and statistical reviewers verified result of this analysis based on the applicant provided data sets. The overall survival analysis was not mature; since there were only 11% death events occurred at the cut off date. At the 4 months safety update (May 31, /2007), 18.5% death events had occurred, 25 deaths for bendamustine arm and 30 deaths for chlorambucil arm.

7 Review of Safety

Summary of Safety Results and Conclusions
The randomized, multi-center comparative trial of bendamustine vs. chlorambucil in treatment-naïve patients with CLL (02CLLIII) provided the basis for the safety review of bendamustine in the CLL indication. In this trial, 296 patients received treatment (153 who were randomized to bendamustine and 143 to chlorambucil). This study was designed to compare the efficacy and safety of bendamustine to chlorambucil in the first-line treatment of CLL.

In this study, patients in the bendamustine treatment group had a higher incidence of adverse reactions (89%) than those in the chlorambucil treatment group (79%). Adverse reactions (any grade) with a frequency greater than 15% in the bendamustine treatment group were neutropenia (28%), pyrexia (24%), thrombocytopenia (23%), nausea (20%), anemia (19%), leukopenia (18%), and vomiting (16%).

The incidence of grade 3/4 adverse reactions was higher in the bendamustine group at 58% compared to 31% in the chlorambucil group. Grade 3/ 4 hematologic adverse reactions with a frequency greater than 10% in the bendamustine treatment group were neutropenia (24%), leukopenia (15%), and thrombocytopenia (13%). Grade 3/4 non-hematologic adverse reactions were reported by 52 (34%) patients in the bendamustine treatment group and 25 (17%) patients in the chlorambucil treatment group. Grade 3/ 4 non-hematologic adverse reactions with a frequency greater than 1% in the bendamustine treatment group were pyrexia (4%), pneumonia (3%), rash (3%), hypertension (3%), hypertensive crisis (2%), hyperuricemia (2%), and infection (2%).

Grade 3/4 adverse reactions by System Organ Class with a frequency ≥5% in the bendamustine group were blood and lymphatic system disorders (41%), infections and infestations (7%), general disorders and administrative site conditions (5%), vascular disorders (5%), and skin and subcutaneous disorders (5%).

Serious adverse events (SAEs) occurred with a higher frequency in the bendamustine group with 27 (18%) patients experiencing 32 SAEs compared to 16 (11%) patients experiencing 20 SAEs. SAEs by Systems Organ Class in the bendamustine group with a frequency greater than or equal to 1% were infections and infestations (5%), blood and lymphatic system disorders (3%), and immune system disorders (2%). SAEs by Preferred Term in the bendamustine group with a frequency greater than or equal to 1% were pneumonia (2%), hypersensitivity (2%), anemia (1%), vomiting (1%), and tumor lysis syndrome (1%).

The number of deaths during the treatment period was the same in both the chlorambucil and bendamustine treatment groups (17 per group). Four deaths occurred within 30 days of the last dose of study drug; 1 in the bendamustine group and 3 in the chlorambucil group. Thirty of the

34 deaths occurred more than 30 days after the last dose of study drug. Seventy-one percent of all of the deaths that occurred in each group of the study occurred more than 100 days after the last dose of study drug. Forty-one percent (7 per group) of patients who died during the study had an attribution of death from CLL placed by the investigator.

The randomized treatment groups were similar with regard to gender, age, race, height, disease specific baseline characteristics, the presence of at least one concomitant disease, and Binet stage of CLL disease.

Reviewer Overall Safety Conclusions:
This reviewer's overall assessment of the available safety data is that the adverse reactions associated with the use of bendamustine in various cancer populations is typical of that seen with other cytotoxic therapies that are already commercially available. The adverse reactions seen with bendamustine were similar to those seen with chlorambucil, though the severity and frequency of these adverse reactions were higher. This is based upon a direct comparison within a randomized trial. These adverse reactions can be expected by practicing oncologists and are monitored by standard laboratory evaluations and clinical examinations. The adverse reactions are manageable by either holding doses or symptomatic treatment. The increased efficacy over chlorambucil in the treatment-naïve CLL population makes this agent an acceptable alternative to other available therapies. A risk management program does not appear to be necessary for bendamustine, above and beyond labeling recommendations. Bendamustine will most likely be used for not only first-line symptomatic CLL patients, but refractory patients who have already received first-line agents. These patients may have received previous myelosuppressive therapy, and may be more likely to experience severe myelosuppression with the use of bendamustine.

7.1 Methods

The evaluation of safety for this application is focused primarily on study 02CLLIII. This trial provided an adequate assessment of the comparative safety and efficacy of bendamustine in an untreated population of CLL patients because it was a randomized, actively-controlled trial conducted in multiple centers. In this trial, 296 patients received treatment (153 who were randomized to bendamustine and 143 to chlorambucil). Study 02CLLIII was designed to compare the efficacy and safety of bendamustine to chlorambucil in the first-line treatment of CLL. At the time this study was conducted, chlorambucil was the only agent with U.S. FDA marketing approval for first-line treatment of CLL. The reader is referred to section 5.3.1.4 for detailed eligibility and exclusion criteria for the study.

In study 02CLLIII, the safety dataset includes all patients in the intent to treat (ITT) subset who received 1 or more doses of either study drug. Of the 301 patients who were randomized to treatment (153 to bendamustine and 148 to chlorambucil), 296 (98%) received at least one dose of study drug and were evaluated for safety in the study. Five patients who were randomized did not receive study drug; all 5 were in the chlorambucil group. Three patients (of these 5) did not meet screening criteria, one patient was prescribed or took another drug instead of chlorambucil, and one patient was withdrawn due to investigator's decision.

Reviewer Comments: The Sponsor's definition of the safety population in study 02CLLIII is acceptable. The data provided from study 02CLLIII provide an adequate assessment of the safety of bendamustine in the treatment-naïve CLL population.

A total of fifteen clinical study reports were submitted with the application. Pharmacokinetic reports were included for one of these 15 studies (SDX-105-03) and for a Japanese study (2006001) for which a study report is not available. These studies included bendamustine monotherapy trials and combination therapy trials with CLL and other oncologic conditions (including NHL, multiple myeloma, and breast cancer). Of the sixteen studies submitted, full reports were submitted for 14, an interim report of the ongoing study SDX-105-03, and bioanalytical reports (plasma, urine) for study 2006001.

7.1.1 Clinical Studies Used to Evaluate Safety

Reviewer Comments: Study 02CLLIII provides the primary basis for the safety evaluation of bendamustine in this indication. The claims made in the proposed product label regarding the safety of bendamustine in the population for the proposed indication were confirmed by review of clinical information provided for study 02CLLIII. This reviewer believes that the two phase 2 CLL studies, 99CLL2E (BG and DE), and the two phase 2 NHL studies (SDX105-01 and SDX105-02) are adequate as additional supportive evidence of the safety of bendamustine in the CLL population.

The safety review for bendamustine was performed by review of the following items submitted by the Applicant (Cephalon):

- Summary of Clinical Safety
- Summary of Clinical Efficacy
- Study protocols for 02CLLIII, 99CLL2E (DE), 99CLL2E (BG), SDX105-01, and SDX105-02

- Clinical Study Reports for 02CLLIII, 99CLL2E (DE), 99CLL2E (BG), SDX105-01, and SDX105-02
- Clinical raw and derived datasets for 02CLLIII, 99CLL2E (DE), 99CLL2E (BG), SDX105-01, and SDX105-02
- Case Report Forms for study 02CLLIII
- Patient narratives for SAE, deaths, and withdrawals
- Proposed labeling for Treanda

The major trial submitted by the Applicant to support the safety of bendamustine was 02CLLIII, a Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naïve Patients with (Binet Stage B/C) B-CLL Requiring Therapy. This study was not performed under a U.S. IND and included no U.S. patients. In September 2004, Cephalon discussed the trial with the Division and agreement was reached upon the use of chlorambucil as a comparison drug for the pivotal study.

Studies 99CLL2E (DE), 99CLL2E (BG), SDX105-01, and SDX105-02 provided additional support for the application, particularly in clarifying the occurrence of more rare adverse reactions (Table 7-2). Studies 99CLL2E (DE) and 99CLL2E (BG) (performed in Germany and Bulgaria respectively) to determine the maximum tolerated dose (MTD) in patients who had relapsed or refractory disease. These studies were followed by 02CLLIII, the major phase 3 randomized, comparator study performed in Europe with previously untreated CLL patients (Table 7-1). SDX-105-01, a phase 2 study of bendamustine monotherapy in rituximab-refractory indolent non-Hodgkin's lymphoma (NHL) was submitted in support of safety in addition to SDX-105-02, a study of bendamustine in combination with rituximab in relapsed patients with indolent NHL.

Table 7-1 Randomized Trial Providing Main Safety Population for Bendamustine

Population Group Study Number	Study Location Study Design	Bendamustine Dose and Regimen	No. of Treated Study Subjects	Significant Safety Findings or Evaluations
First-line B-CLL **02CLLIII**	International, Multi-center, Phase 3, open-label, randomized	100 mg/m^2 IV over 30 minutes on D1&2 q28d vs. chlorambucil 0.8 mg/kg PO D1&15 q28 weeks.	Bendamustine=153 Chlorambucil=143 (Total 296)	Most frequent Gr 3&4 events were hematologic (58% vs. 31%); Grade 3&4 non-heme events reported in 34% vs. 17% of patients. Equal # of deaths in each group. Most frequent events in bendamustine group were neutropenia, pyrexia, thrombocytopenia, and nausea.

Per the Applicant, the safety population pool consists of all patients who received treatment with bendamustine in clinical trials and is described in 7.2 below.

Table 7-2 Trials Providing Additional Safety Population for Clinical Studies of Intravenous Bendamustine

Population Group/ Study Number	Study Location Study Design	Bendamustine Dose and Regimen	No. of Treated Study Subjects	Significant Safety Findings or Evaluations
Rituximab-refractory NHL **SDX105-01**	Canada (12 centers) US (2 centers) Phase 2, single-group study	120 mg/m^2 IV for 30-60 minutes D1&2 every 21d. Minimum of 6 cycles.	76	Most frequent AEs: nausea, fatigue, vomiting, anemia, diarrhea, pyrexia, cough, neutropenia, constipation, and thrombocytopenia. MDS and other secondary malignancies seen.
Relapsed Indolent of Mantle Cell NHL **SDX105-02**	US (13 centers) Canada (5 centers) Australia (22 centers) Phase 2, single group study	Rituximab 375 mg/m^2 at Day -7; Followed by Rituximab 375 mg/m^2 D1 plus Bendamustine 90 mg/m^2 Days 2&3; for four 28-day cycles.	66	Common AEs: myelosuppression, nausea, vomiting, fatigue, constipation, and diarrhea. No grade 3 or 4 hypertension. SAEs: Febrile neutropenia.
B-CLL 2nd line **99CLL2E (BG)**	Bulgaria; single center Phase 2, single group study	100, 110, and 120 mg/m^2 IV over 30 minutes on two consecutive days q21 days. Up to 6 cycles.	15	DLTs: Grade 3 and 4 hyperbilirubinemia, grade 3 diarrhea, grade 4 thrombocytopenia, grade 4 anemia. SAEs: bronchopneumonia, fever, and anemia resulting in death.

Population Group/ Study Number	Study Location Study Design	Bendamustine Dose and Regimen	No. of Treated Study Subjects	Significant Safety Findings or Evaluations
				MTD 100 mg/m^2 D1&2 q28d.
B-CLL 2nd line **99CLL2E (DE)**	Germany; 5 centers Phase 2, single-group study	70, 80, 90, and 100mg/m^2 IV over 30 min on 2 consecutive days every 21 days. Up to six 3-week cycles	16	DLTs: Grade 3 edema, grade 4 hyperuricemia, grade 4 leukopenia, grade 3 infection, grade 3 dyspnea, grade 3 pneumonia, grade 3 exanthema. MTD 80 mg/m^2 D1&2 q28 days. Dose recommended was 70 mg/m^2 D1&2 every 28d for heavily pre-treated patients.

The studies included in Table 7-3 below, provided supportive safety information during the review.

Table 7-3 Other Trials Providing Supportive Safety Information

Population Group/ Study Number	Study Location Study Design	Bendamustine Dose and Regimen	No. of Treated Study Subjects	Significant Safety Findings or Evaluations
Rituximab-Refractory Indolent NHL **SDX105-03**	US (24 centers) Canada (4 centers) Phase 3, multi-center, single-group, ongoing study ***(interim report without datasets submitted)***	120 mg/m^2 D1&2 q21d (minimum of 6 cycles). Dose reductions to 90 or 60 mg/m^2 would occur for toxicity.	100 as of 07/31/07	Serious adverse reactions in 39 of 102 patients enrolled (ARDS, sepsis/infection, CHF, MI, neuropathy, infusion reaction, cholecystitis, herpes zoster, UTI, diarrhea, MDS/secondary malignancy.
Advanced Solid Tumors **20BEN03**	Belgium (1 center) Phase 1, single-group study	120-180 mg/m^2 IV days 1 & 2 q21 days (dose escalation in 20 mg/m^2 increments. Minimum of 2 cycles.	15	DLTs at 180 mg/m^2=Gr 4 thrombocytopenia. No DLTs at 160 mg/m^2. Sinus tach, PSVT, AV block, PAC, LVH, PVCs (not dose-limiting). RP2=140 mg/m^2
Advanced Solid Tumors **98B02W**	Germany (1 center) Phase 1, single-group	60, 70, and 80 mg/m^2 IV over 30 minutes weekly D1, 8, 15, 22, 29. (Up to 8 weeks of treatment).	12	DLT at 80 mg/m^2=Gr 3 asthenia, fatigue, malaise, dry mouth, and Gr 4 fever. DLT at 60 mg/m^2=atrial flutter. RP2 dose = 60 mg/m^2.
Advanced Solid Tumors (renal and hepatic impairment) **98B03**	Germany (4 centers) Phase 1, parallel-group	120 mg/m^2 IV over 30 minutes D1&2 of a 4-week cycle (dialysis patients received one dose every 4 weeks)	37	In the absence of information regarding the excretion of bendamustine, assumptions regarding dose modifications for organ impairment are not feasible.
Cholangioca-	Germany (Single	140 mg/m^2 C1D1 and	6	Gr 3 anorexia, no Gr 4. No dose

Population Group/ Study Number	Study Location Study Design	Bendamustine Dose and Regimen	No. of Treated Study Subjects	Significant Safety Findings or Evaluations
rcinoma **BE04**	center) Phase 1, single-group	100 mg/m^2 D1&2 of later cycles lasting 21 days and 4 cycles.		modification necessary with cholestasis without strong impairment of liver cell function.
Advanced Solid Tumors **98B02**	Germany (Single center) Phase 1, single group, dose escalation	100-180 mg/m^2 (dose escalating) IV for 30 minutes Days 1 and 8 q28 days. Minimum of 2 cycles.	18	DLTs at 160 mg/m^2=asthenia, fatigue, malaise, weakness, diarrhea, AV block. RP2D=140 mg/m^2 D1&8 of 4-wk cycle.
Advanced Solid Tumors **20BEN D1**	Belgium (Single Center) Phase 1, single-group	160-280 mg/m^2 IV for 30 minutes q21 days (dose escalation in 20mg/m^2 increments). Minimum of 2 cycles.	26	DLTs at 280 mg/m^2=cardiac events (QT prolongation, ischemia, T-wave changes, thrombocytopenia). 77% had new ECG findings with no dose relationship noted. RP2 =260 mg/ m^2 q21 days. Patients with history of cardiac disease should not receive bendamustine at doses of ≥260 mg/ m^2.
Advanced Centroblastic/Centrocytic Lymphomas and Lymphoplasmacytoid Immunocytomas **93BOP01**	Germany (single center) Prospective, randomized, comparative trial of BOP vs. COP	A: Bendamustine 60 mg/ m^2 IV over 30 min D1-5 plus vincristine 2mg IV D1 plus prednisone 100 mg/ m^2 D1-5 B: Cyclophosphamide 400 mg/ m^2 IV over 30 min D1-5 plus vincristine 2mg IV D1 plus prednisone 100 mg/ m^2 D1-5 Cycle=21d; up to 8 cycles	BOP=84 COP=83	BOP deaths=21 vs. 26 in COP. Cause of death in BOP group=lymphoma (14%), therapy (2%), secondary malignancy (1%), other (7%). Cause of death in COP group= lymphoma (27%), toxic pneumonia (1%), other (4%). No information regarding other SAEs provided. Not conducted in accordance with ICH-GCP.
First-line Metastatic Breast Cancer **96BMF02/1**	Multicenter (Germany, Bulgaria, UK, and Belgium) Phase 3, randomized, comparative trial of BMF vs. CMF	A: Bendamustine 120 mg/2 IV over 30-60 min D1&8 plus methotrexate	BMF=169 CMF=185	Leukopenia, stomatitis, thrombocytopenia, anemia, and fever occurred more often in the BMF group whereas alopecia, amenorrhea, constipation, and increased transaminases were more frequent in the CMF group.

Estimates provided by the Applicant, indicate that in the studies reported in this application, 862 patients were treated with single-agent bendamustine, and make up the safety population for this application. Significant post-marketing experience also exists in Europe, where bendamustine is already marketed. Cephalon estimates that approximately — patients were exposed to bendamustine between 01/01/1994-03/31/2007.

In the main study (02CLLIII), adverse reactions were defined as "any untoward medical happening (clinical or laboratory) experienced by a patient in association with a clinical study, including any signs and symptoms and intercurrent diseases and accidents, and any clinically relevant change in a laboratory value (as assessed by the Investigator), regardless of a causal relationship to the treatment under study."

Adverse reactions were classified and graded in accordance with the National Cancer Institute Common Toxicities Criteria Version 2.0 (NCI CTC V. 2.0) (1999). All adverse reactions, including changes in existing adverse reactions and their resolution, were recorded on electronic case report forms (eCRF). Each adverse reaction was classified as serious or non-serious. Patients who withdrew from the study early because of intolerable toxicity were monitored for complete recovery or final outcome was documented. Serious adverse events (SAEs) were reported, by the investigator, to the responsible contract research organization (CRO) by telephone or facsimile within 24 hours after learning of the event. The leading principal investigator (PI) was informed of all SAEs by Ribosepharm (Study Sponsor) and evaluated these, and informed the ethics committee, the competent authorities, and other participating investigators of any SAEs that would compromise study patient safety or the conduct of the study. All SAEs that occurred up to 30 days after the last dose of the study drug were reported. If a SAE occurred within 30 days of the last dose of the study drug, it was, like any other SAE, documented until resolution or definitive outcome.

The onset and end dates, treatment administered, and outcome for each adverse reaction was recorded on the eCRF. The relationship of each adverse reaction to study drug treatment, and the severity and seriousness of each adverse reaction to study drug treatment, as judged by the investigator, was recorded as described below.

- Severity of adverse reactions: Determined using the NCI CTC V. 2.0 grading criteria.
- Relationship of adverse reaction to the Study Drug: Recorded as either definite, probable, possible, unlikely, none, or not evaluable.
- Serious Adverse Event s: A SAE was any adverse reaction that resulted in any of the following outcomes or actions:
    - Was fatal or life-threatening
    - Resulted in persistent disability or incapacity
    - Required inpatient hospitalization or prolongation of existing hospitalization. Hospital admission for scheduled elective surgery, for social reasons, or due to long travel distances were not SAEs. Hospitalization or prolongation of existing hospitalization for an adverse event that was due to and/or related to the underlying disease and could be

definitely ruled out as causally related to study drug (such as due to progressive disease) was not considered a serious adverse reaction.

- Resulted in congenital abnormalities
- Caused secondary malignancies

The Sponsor monitored safety by obtaining clinical and laboratory testing at baseline and during study follow-up. Clinically relevant changes in laboratory values were recorded on eCRFs. Reference ranges were collected from each local laboratory in addition to appropriate quality documentation before the start of the study. Results of laboratory testing were graded according to NCI CTC V. 2.0 with the exception of hemoglobin, platelets, and neutrophils which were graded according to the Cheson criteria of 1996. The reader is referred to Section 5.3.1.4 for the study assessment table (Table 5-2) provided by the Applicant for this trial.

Reviewer Comments: The safety assessments performed in study 02CLLIII appear to be in accordance with the standard of care for patients with CLL and the ICH guidelines. After Cephalon acquired bendamustine, they translated the adverse reactions into MedDRA from NCI CTC V. 2.0. MedDRA is the preferred categorization for regulatory review. The categorization to MedDRA preferred terms was assessed by a direct comparison for term similarity and clinical accuracy by this reviewer. All of the verbatim terms were accurately converted to MedDRA preferred terms in this database. The safety assessments (clinical and laboratory evaluations) in the study were adequate in design and frequency to capture the expected and unexpected adverse reactions that occurred. The organ impairment study (98B03) results cannot be applied to dose modification recommendations for those with renal or hepatic impairment because of the lack of a proper ADME study.
The size of the exposed population appears to be adequate for the assessment of safety of an agent that is intended to be used for 6 months or less, for a life-threatening condition (CLL). Though the sample size (153) cannot be expected to identify all potential safety issues, it is adequate for assessment of safety in this indication. The reader is referred to Section 7.3, Major Safety Results and Discussion for further detailed review of adverse reactions from the pivotal safety study.

7.1.2 Adequacy of Data

The data submitted to this NDA is adequate to perform the safety review. Raw and derived datasets were provided so that pertinent analyses could be repeated by this reviewer. The coding plan for adverse reactions underwent some changes via amendment during the life cycle of the trial. The original protocol planned to record and grade adverse reactions per CTC v. 2.0 (or according to Cheson et al. 1996 for hemoglobin, platelets, and neutrophils). Amendment 1

called for these to be classified and graded per National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC). Amendment 3 called for these to be classified and graded in accordance with the CTC (Common Toxicity Criteria) Checklist 2.0, NCI (National Cancer Institute, Bethesda), April 30, 1999. The changes were analyzed and this reviewer does not believe that they significantly impacted the conduct of the study from a safety perspective.

Missing data can confound study results when the volume of missing data is significant or different between study groups. In study 02CLLIII, the volume of missing laboratory values was not significant and the percentage of missing laboratory values was similar between groups.

Reviewer Comments: Though the toxicity grading and categorization criteria changed during the study conduct, this should not impact the overall safety assessment because the events were translated into MedDRA after study completion by the Applicant. Additionally, NCIC CTC and NCI CTC are very similar with regard to the categorization and grading of toxicities.
The acceptable volume of missing laboratory results, given the relative equality between treatment arms, should not confound the safety analysis for bendamustine.

Assessment of Adverse Reactions Data:

All adverse reactions were summarized based on MedDRA system organ classes and preferred terms. For each adverse reaction, the following MedDRA terms information was provided in the initial application: lower level term (LLT), preferred term (PT), and system organ class (SOC). To assess the accuracy of the categorization, the Applicant was requested to provide the higher level group term (HLGT) and higher level terms (HLT). Cephalon provided new adverse reaction datasets containing the HLGT and HLT on 10/24/07.

The incidence of adverse reactions was summarized using descriptive statistics by MedDRA system organ class and preferred term. Patients were counted only once in each organ system category, and only once in each preferred term category. Treatment-related adverse reaction summaries included adverse reactions with missing relationship to study drug. For the summaries by severity, patients were counted at the greatest severity. Adverse reactions with CTC grade 3 or 4 were also summarized.

The prevalence of adverse reactions was summarized by cycle. For determination of the prevalence of adverse reactions by cycle, an adverse reaction was counted in each cycle in which it occurred; therefore, an adverse reaction may have been counted in multiple cycles for the same patient. For the prevalence analysis by cycle, the denominator was the number of patients who

received study drug for that cycle. The first day of each cycle was defined as the first infusion day of the cycle. The last day of a cycle was the day proceeding the first infusion day of the next cycle. For a patient's final cycle, the last day was open-ended. An adverse reaction was counted in a cycle if the onset day occurred prior to the first day of the cycle or during the cycle and the resolution day occurred any time during the cycle or after the last day of the cycle.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

This reviewer does not believe that the studies should be pooled for the safety analysis because of the variation in populations studied (tumor and treatment setting), variability of bendamustine doses, and the lack of appropriate controls.

7.2 Adequacy of Safety Assessments

The application contained an adequate safety assessment, in an appropriate population, with safety evaluations thoroughly assessing for not only known toxicities of alkylating agents, but most clinically important evaluations were also undertaken. The Sponsor paid particular attention to the risk for infection in these patients and prospectively collected detailed infection data. The evaluation for the potential for QT prolongation has not been fully addressed by the Applicant. This evaluation will be a post-marketing commitment.

The completeness of the safety data appears adequate. The data that was submitted appears to be complete in that the crucial information (duration, severity) regarding most adverse reactions is present. This reviewer's evaluation cannot determine if overtly missing adverse reaction data is a problem, unless the Division of Scientific Investigations identifies an issue upon inspection. The Applicant did identify problems with data from two sites in Bulgaria (sites 01 & 02). Due to these concerns, the efficacy data from these sites was excluded from the primary efficacy analyses. However, the safety data from these sites remains in the database. Individual adverse reaction rates were not significantly different when sites 01 and 02 were removed, but the overall adverse reaction rates for bendamustine did increase from 89% (all treated patients) to 94% (sites 01 and 02 removed). The adverse reaction rates differed less when sites 01 and 02 were removed in the chlorambucil group from 79% to 81% overall.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Drug Exposure

Bendamustine has been investigated for the treatment of cancer in various populations, including CLL (the proposed indication), NHL, multiple myeloma, breast cancer, and other various solid tumors (in phase 1 studies). The doses used ranged from 60 to 280 mg/m^2 in a variety of

treatment schedules. One-hundred and two patients received open label treatment with bendamustine in phase 1 and 2 studies (71 with solid tumors and 31 with CLL). In the major comparator study (02CLLIII), 153 patients with CLL received bendamustine monotherapy at 100 mg/m^2 on days 1 and 2 repeated every 28 days (the proposed dose for this application). The major NHL studies (SDX-105-01 and SDX-105-03) treated 176 patients with bendamustine monotherapy at 120 mg/m^2. This provides a total of 431 patients, from the 9 main studies, who contribute to the safety assessment in the Summary of Clinical Safety provided by the Applicant.

In Study 02CLLIII, patients in both treatment groups, who received study drug, received between 1 and 6 cycles of study drug treatment during the study. The duration of treatment was similar in both treatment groups, with the mean numbers of treatment cycles in the bendamustine and chlorambucil treatment groups 4.8 and 4.6, respectively. Ninety-two (60%) patients in the bendamustine treatment group and 80 (56%) patients in the chlorambucil treatment group received treatment for 6 cycles. Duration of exposure to study drug was similar between treatment groups. The mean duration of exposure was 114.3 days for patients in the bendamustine treatment group and 118.5 days for patients in the chlorambucil treatment group. The median number of days of treatment was 142 days in the bendamustine treatment group and 155 days in the chlorambucil treatment group. The mean total dose received was 853.4 mg/ m^2 (median 992 mg/ m^2) for patients in the bendamustine treatment group and 7.0 mg/kg (median 8 mg/kg) for patients in the chlorambucil treatment group. The mean overall relative dose intensity was 86% and 96% in the bendamustine and chlorambucil treatment groups, respectively (Table 7-4).
Similar numbers of patients between the two groups received dose reductions. Fifty-two (34%) patients in the bendamustine and 44 (31%) patients in the chlorambucil treatment group had at least 1 dose reduction. More patients in the bendamustine treatment group experience at least one dose delay. Fifty-five (36%) patients in the bendamustine treatment group and 27 (19%) patients in the chlorambucil group had at least 1 cycle of treatment delayed. The increase in treatment cycle delays in the bendamustine treatment group was most evident in cycles 2 and 3, indicating an earlier need to manage myelosuppression with bendamustine treatment than with chlorambucil treatment. In the later cycles, dose reductions were the most common form of cycle modification and were similar for the 2 treatment groups (Table 7-5).

Table 7-4 Extent of Exposure (Applicant Table)

Exposure variable Statistic	Bendamustine (N=153)	Chlorambucil (N=143)
Number of cycles treated		
n	153	143
Mean	4.8	4.6
SD	1.75	1.75
Median	6.0	6.0
Min, max	1.0, 6.0	1.0, 6.0
Total dose received[a]		
n	153	143
Mean	853.4	7.0
SD	352.58	2.93
Median	992.0	8.0
Min, max	186.0, 1270.0	0.8, 12.9
Duration of treatment (days)		
n	153	143
Mean	114.3	118.5
SD	52.50	52.30
Median	142.0	155.0
Min, max	2.0, 211.0	1.0, 199.0
Duration of treatment (days) for patients who completed 6 cycles		
n	92	80
Mean	148.5	159.3
SD	11.73	8.09
Median	142.5	156.0
Min, max	140.0, 211.0	149.0, 199.0
Overall relative dose intensity, %[b]		
n	153	143
Mean	86.40	95.52
SD	16.57	18.31
Median	92.50	98.75
Min, max	21.538, 103.735	47.765, 225.000

SOURCE: Summary 15.21, Summary 15.23, and Listing 19.
[a] The total dose received is measured in mg/m^2 for bendamustine and mg/kg for chlorambucil.
[b] The relative dose intensity=100x(actual dose intensity)/(initially planned dose intensity), where the actual dose intensity=(total actual dose received)/[(number of days on treatment/28] x 2). The initial planned dose for bendamustine was 100 mg/m^2/day and the initial planned dose for chlorambucil was 0.8 mg/kg/day (Broca's normal weight).
Min=minimum; max=maximum; SD=standard deviation.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Reviewer Comment: The size of the exposed population appears to be adequate for the assessment of safety of an agent that is intended to be used for 6 months or less, for a life-threatening condition (CLL). Though this sample size cannot be expected to identify all potential safety issues, it is adequate for assessment of safety in this indication.

The design of study 02CLLIII was an open-label comparison of the efficacy and safety of bendamustine to chlorambucil. This study design has the advantage of directly comparing bendamustine to another agent with US FDA marketing authorization for the same indication. The data collected in this study appear to provide an adequate characterization of the safety of bendamustine in the CLL population.

Table 7-5 Dose Delays and Reductions by Treatment Group (Treated Analysis Set) (Applicant Table)

Cycle Variable	Number (%) of patients	
	Bendamustine (N=153)	Chlorambucil (N=143)
Total number of patients with at least 1 cycle delayed	**55 (36)**	**27 (19)**
Total number of patients with at least 1 dose reduction	**52 (34)**	**44 (31)**
Cycle 1		
n	153	143
Median cycle length (days)	28.0	28.0
Cycle delayed	0	0
Dose reduced	3 (2)	9 (6)
Cycle 2		
n	142	133
Median cycle length (days)	28.0	28.0
Cycle delayed	32 (23)	11 (8)
Dose reduced	36 (25)	21 (16)
Cycle 3		
n	125	120
Median cycle length (days)	28.0	28.0
Cycle delayed	19 (15)	4 (3)
Dose reduced	29 (23)	18 (15)
Cycle 4		
n	114	98
Median cycle length (days)	28.0	28.0
Cycle delayed	13 (11)	6 (6)
Dose reduced	21 (18)	18 (18)
Cycle 5		
n	106	88
Median cycle length (days)	28.0	28.0
Cycle delayed	6 (6)	5 (6)
Dose reduced	19 (18)	18 (20)
Cycle 6		
n	92	80
Median cycle length (days)	28.0	28.0
Cycle delayed	15 (16)	5 (6)
Dose reduced	18 (20)	16 (20)

SOURCE: Summary 15.22.1. Listing 19.
NOTE: Cycle length was the first dose date of subsequent cycle - first dose date of the current cycle. If a cycle's length was greater than 30 days, then the subsequent cycle was considered delayed.

Data in above table was confirmed by review of raw and derived datasets and CRFs.

Reviewer Comments: The number of bendamustine patients that experienced at least one cycle delay was nearly double that in the chlorambucil arm. Both arms had similar numbers of patients who received dose reductions. Despite dose delays in the bendamustine arm, the efficacy endpoints improved.

Bendamustine was initially developed and marketed in the former German Democratic Republic, receiving approval in 1971. However, the systematic collection and retention of postmarketing data was not undertaken between 1971 and 1994. From 1994-2007, postmarketing data was systematically collected by Astellas Pharma Inc., Fujisawa, and other license partners. This data is summarized in an Overall Safety Update Report for bendamustine (marketed in Germany by Ribosapharm as RIBOMUSTIN), covering the time period of 01/01/94-03/31/07. The report