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RESEARCH**

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22-203

MEDICAL REVIEW(S)

CLINICAL REVIEW TEMPLATE

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Reviewer Name Virginia Kwitkowski, MS, RN,
ACNP-BC
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Established Name bendamustine
Trade Name Treanda ®
Therapeutic Class Alkylating Agent
Applicant Cephalon

Priority Designation S

Formulation I.V.
Dosing Regimen 120 mg/m², days 1 & 2, q 21 days
Indication Rituximab-Refractory, Indolent
NHL
Intended Population Patients with indolent NHL

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Executive Summary

This reviewer recommends on the basis of the clinical review of NDA 22303 that bendamustine (Treanda) receive regular approval for the following indication:

TREANDA is indicated for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) which has progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen

This recommendation is based upon demonstration of a clinically meaningful overall response rate of adequate duration in a refractory population in a single-arm study. The co-primary endpoints (ORR and DR) for the study were based upon an independent, central review.

Efficacy Results

The primary study (SDX-105-03) was designed to encompass a population of patients with indolent B-cell NHL who were rituximab-refractory. One-hundred patients were treated with bendamustine at a dose of 120 mg/m² IV over 60 minutes on days 1 & 2 every 21 days for 6-8 cycles. The Overall Response Rate (ORR) by the Independent Review Committee was 74% in this population with Complete Response (CR) and Complete Response unconfirmed (CRu) rates of 13% and 4% respectively. The median duration of response in this study was 9.2 months.

Table 1: Primary Study Efficacy Data

Efficacy Variable	By IRC (N=100)	By Investigator (N=100)
Overall Response Rate (%) (95% CI) P value	74 (64.3, 82.3) <0.001	80 (70.82, 87.33) <0.001
Complete Response (CR)	13	22
Complete Response Unconfirmed (CRu)	4	5
Partial Response (PR)	57	53
Duration of Response Median, months (95% CI)	9.2 (7.1, 10.8)	9.0 (7.7, 13.8)

According to the Code of Federal Regulations, section 314.126, addressing adequate and well-controlled trials, the approval of a new drug is contingent upon the demonstration of efficacy and safety by an adequate and well-controlled investigation. In September 2004, the FDA Office of Oncology Drug Products discussed with the previous Sponsor the use of single-arm trials to support the approval of bendamustine in NHL. It was agreed that, depending on the magnitude of study outcomes, approval in NHL could be based upon a single-arm study in patients with rituximab-refractory disease. Additionally, in 2001 and 2003 respectively, Zevalin and Bexxar

received regular approval for this indication with similar response rates and durations in single-arm studies of rituximab-refractory patients.

Safety Results

The data submitted support that bendamustine has an acceptable risk/benefit ratio as recommended in the labeling. Safety data from two single-arm, single agent bendamustine studies were combined for the analysis of safety. Hematologic toxicity was the most frequent type of adverse reaction observed. The most frequently occurring non-laboratory related adverse reactions among patients who received bendamustine in these two single-arm studies with an incidence of $\geq 15\%$ were: nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. The most common hematologic laboratory abnormalities with an incidence $\geq 85\%$ were lymphopenia, leukopenia, anemia, thrombocytopenia, and neutropenia. The most common non-hematologic laboratory abnormalities with a frequency of $\geq 35\%$ were hyperglycemia, hypoalbuminemia, elevated AST, and hypocalcemia.

Data submitted with this application provide adequate directions for use. The recommended safe and effective dose of bendamustine for NHL has been shown to be 120 mg/m^2 IV over 60 minutes on Days 1 & 2 in 21-day cycles for up to 6-8 cycles. The rationale for recommending up to 8 cycles is that the primary efficacy study in this population administered a minimum of 6 cycles and up to 8 cycles. Studies to evaluate for potential drug-drug interactions and the effect of renal and/or hepatic dysfunction have been previously agreed to as post-marketing commitments.

1 Recommendations/Risk Benefit Analysis

1.1 Recommendation on Regulatory Action

Cephalon has submitted New Drug Application # 22,303 for the following proposed indication:

TREANDA is indicated for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) who have progressed during or following treatment with rituximab or a rituximab-containing regimen

The clinical team recommends approval of this NDA. The basis of this recommendation are the results of a single-arm study using single-agent bendamustine in 100 patients with rituximab-refractory indolent Non-Hodgkin's lymphoma that was submitted in support of the efficacy and safety of bendamustine in this population. Study SDX105-03(hereafter referred to as the *primary study*) met its dual primary endpoints of Objective Response Rate and Duration of Response. The study was well-conducted in a North American population making the results easily extrapolated to the U.S. population. The results of the primary study indicate that bendamustine is effective in inducing sustainable, objective tumor response in 74% of patients in this treatment-refractory population.

The primary study treated 100 patients with indolent B-cell lymphoma with bendamustine at a dose of 120 mg/m² IV over 60 minutes on days 1 & 2 every 21 days for up to 6-8 cycles. The Overall Response Rate (ORR) was 74% in the Intent To Treat (ITT) population with Complete Response (CR) and Complete Response unconfirmed (CRu) rates of 13% and 4% respectively. The median duration of response in this study was 40.3 weeks (9.2 months). Three patients among these 100 did not meet the protocol definition for rituximab-refractory disease. However, the efficacy data for all 100 patients will be presented because the overall response rate is minimally changed when these non-refractory patients are removed.

The safety population for this review is comprised of 176 patients who received single-agent bendamustine in two studies at 120 mg/m² IV Days 1 & 2 of every 21 day cycle for up to 9 cycles. The safety profile of bendamustine in this combined study population appears unchanged from the previous safety review during the CLL application review.

Based upon the review of the submitted studies, the proposed indication is altered slightly as follows to more clearly identify the population studied:

Indolent B-cell non-Hodgkin's lymphoma (NHL) which has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

1.2 Risk Benefit Analysis

Based upon my review of the clinical data submitted in support of this application, the benefits of the treatment of indolent NHL with bendamustine outweigh the risks. Reduction in tumor size

of adequate duration and magnitude is believed to represent a surrogate for clinical benefit in single-arm trials of indolent NHL. Objective responses (Complete Response, Complete Response unconfirmed, and Partial Response) in the primary study were observed in 74% of patients with a median duration of response being 9.2 months.

The safety assessment of bendamustine was initially made during the review of NDA 22-249 by the comparison of adverse reactions experienced by patients with newly diagnosed CLL treated with bendamustine versus chlorambucil. The safety assessment in the single-arm studies for this application did not reveal any unexpected toxicities of bendamustine that would hinder approval of this agent in this even more heavily pre-treated and treatment-refractory population. Both single-arm studies had similar adverse reaction profiles.

Up front treatment of patients with indolent lymphoma typically involves the use of rituximab in combination with chemotherapy. Indolent lymphoma remains incurable and refractoriness to rituximab often occurs. Agents that are in the armamentarium for the treatment of rituximab-refractory patients include both FDA-approved agents for this specific population, and FDA-approved agents that are used off-label by oncologists. FDA-approved agents include Bexxar and Zevalin; two radioimmunotherapies that are underutilized by oncologists due to the difficulty of administration and the persistent hematologic toxicities observed with the use of these agents. Single-agents used off-label include chlorambucil, cyclophosphamide, fludarabine, pentostatin, and cladribine with varying efficacy and similar hematologic toxicity profiles.

1.3 Recommendations for Postmarketing Risk Management Activities

No new post-marketing risk management activities are recommended since the initial drug approval in March of 2008.

Post-Marketing Commitments Exist For:

1. Cephalon commits to providing an updated study report of Protocol 02CLLIII titled "*Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) BCLL Requiring Therapy*" at data cut off date in May 2008. Response rate, progression-free survival, overall survival and safety updates will be provided in this study report.

Protocol Submission: N/A

Study Start: N/A

Final Report Submission: February, 2009

2. Cephalon commits to submitting the results and data from the ADME Study 1039 titled "An Open-Label Study to Investigate the Pharmacokinetics (Distribution, Metabolism, and Excretion) of Bendamustine Hydrochloride Following Intravenous Infusion of [¹⁴C]Bendamustine Hydrochloride in Patients With Relapsed or Refractory Malignancy (Hematologic or Nonhematologic)". Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.

Protocol Submission: May, 2008

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NDA 22-303 /bendamustine (Treanda)

Study Start: December, 2008
PK Report Submission: December, 2009
Final Report Submission: March, 2010

3. Cephalon commits to conducting a study to assess the potential for bendamustine to prolong the QT interval in patients. The QT plan will be submitted prior to initiation for IRT review and concurrence.

Protocol Submission: July, 2008
Study Start: December, 2008
Final Report Submission: June, 2010

4. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of fluvoxamine (CYP1A2 inhibitor) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

Protocol Submission: March, 2010
Study Start: September, 2010
PK Report Submission: January, 2012
Final Report Submission: July, 2012

5. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of smoking (CYP1A2 inducer) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

Protocol Submission: March, 2010
Study Start: September, 2010
PK Report Submission: July, 2012
Final Report Submission: December, 2012

6. Cephalon commits to conducting *in vitro* screens to determine if bendamustine is a p-glycoprotein substrate or inhibitor.

Protocol Submission: March, 2008
Study Start: September, 2007
Final Report Submission: June, 2008

7. Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: sodium chloride).

Protocol submission: April 1, 2008
Study start: May 15, 2008
Final Report: September 1, 2008*

*Report submitted to NDA 22-249 to address this PMC on 08/27/08.

1.4 Recommendation for other Postmarketing Study Commitments

No additional post-marketing study requests were identified as being needed during this review.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: bendamustine

Proprietary Name: Treanda®

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

Drug Class: Alkylating drug

Applicant Proposed Indication: “TREANDA is an antineoplastic agent indicated for treatment of patients with indolent B-cell non-Hodgkin’s lymphoma (NHL) (b) (4)

Population: TREANDA is for use in adults only.

Proposed Dosage and Administration: TREANDA is intended for administration as an intravenous infusion over (b) (4) minutes. The recommended dose is 120 mg/m² administered on Days 1 and 2 of a (b) (4)-day cycle, for (b) (4) cycles.

2.2 Table of Currently Available Treatment for Proposed Indication

Table 2: Currently Available Single-Agent Therapies for Rituximab-refractory Indolent Non-Hodgkin’s Lymphoma

Established Name	Proprietary Name	FDA Approval Status	Year of U.S. F.D.A. Approval
Ibritumomab tiuxetan	Zevalin	Regular	2001
Tositumomab and Iodine ¹³¹	Bexxar	Regular	2003
Chlorambucil	Leukeran	Regular (NHL)	1957
Cyclophosphamide	Cytoxan	Regular (Malignant Lymphomas)	--
Fludarabine	Fludara	No	n/a
Pentostatin	Nipent	No	n/a
Cladribine	Leustatin	No	n/a

Only two agents have received marketing approval for the treatment of Rituxan-refractory indolent NHL; Zevalin and Bexxar. Both agents are radioimmunotherapies and eligibility for these therapies is limited. Patients with more than 25% involvement of bone marrow from lymphoma should not receive either treatment. Additionally, these agents cause severe, persistent, hematologic toxicities (Grade 3 and 4 cytopenias) in >70% of patients who receive them, sometimes limiting patients from receiving subsequent therapies. The Bexxar label contains a black box warning advising that “the Bexxar therapeutic regimen should not be administered to patients with >25% lymphoma marrow involvement and/or impaired bone marrow reserve”. The Zevalin label contains a warning to not “administer Zevalin to patients with \geq 25% lymphoma marrow involvement or impaired bone marrow reserve” and a similar black box warning indicating that “prolonged and severe cytopenias occur in most patients”.

In order to administer Bexxar, physicians must be certified by Corixa Corporation in dose calculation and administration of the regimen. These therapies require dosimetry, radiation precautions to protect family members due to gamma emissions, and the coordination of multiple hospital departments. For these reasons, and other administrative/financial concerns, according to a recent report in the New York Times, these therapies are administered to only about 10% of all patients who are otherwise candidates for the drugs (Berenson, A, Market Forces Cited in Lymphoma Drugs’ Disuse, New York Times, July 14, 2007).

Combination regimens are also used in the management of this population.

Table 3: Combination Therapies Commonly Used in Rituximab-Refractory Indolent NHL

Regimen	Components
CVP	Cyclophosphamide, Vincristine, Prednisone
COPP	Cyclophosphamide, Vincristine, Procarbazine, Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
FND	Fludarabine, Mitoxantrone, Dexamethasone
CF	Cyclophosphamide, Fludarabine
F-CNOP	Fludarabine, Cyclophosphamide, Mitoxantrone, Vincristine, Prednisone

2.3 Availability of Proposed Active Ingredient in the United States

Bendamustine is marketed in the United States for Chronic Lymphocytic Leukemia. No labeling changes have occurred since the original marketing approval in March 2008.

2.4 Important Issues with Consideration to Related Drugs

No new major safety concerns have been identified with TREANDA since the marketing approval in March 2008.

Bendamustine is a purine analog alkylating agent.

Purine Analogs

Fludarabine: The product label contains black box warnings about severe hematologic and neurologic toxicities; autoimmune phenomena; and a warning to avoid concomitant use of pentostatin and fludarabine due to the risk of severe pulmonary toxicity.

Cladribine: The product label contains a contraindication for concomitant use of alkylating agents, antimetabolites, and live vaccines. Frequent AEs: Anorexia, Bone Marrow Depression, Fatigue, Fever, Headache Disorder, Infection, Nausea, Neutropenic Disorder, Severe Anemia, Skin Rash, Thrombocytopenic Disorder, and Vomiting. Rare: MDS, nephrotoxicity, and neuropathy.

Alkylating Agents

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.

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.

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 Presubmission Regulatory Activity Related to this Submission

Bendamustine has been investigated internationally in indolent NHL, transformed NHL, and CLL. A brief regulatory history timeline is provided below.

June 11, 2003 IND 67,554 filed by Salmedix.

September 29, 2003 to August 15, 2006 Initial study SDX-105-01: Phase 2, Open-label study of patients with rituximab-refractory indolent NHL.

October 2003 (b) (4)

April 13, 2004 to December 13, 2005 (b) (4)

September 02, 2004 An EOP2 meeting was held between the applicant and FDA to discuss the clinical development plan in NHL and CLL. FDA agreed that a single randomized study might support registration and recommend use of an independent response review committee for efficacy evaluation.

March 2005 Special Protocol Assessment meeting held for study SDX-105-03. This study is referred to as “the primary study” throughout this review.

The main conclusions reached during this meeting were as follows:

- The definition of ‘rituximab-refractory’ should conform to that used in the registration trial for regular approval of Zevalin, i.e., Witzig, et al. JCO 15:3262, 2002. “Eligible patients with follicular B-cell NHL had prior treatment with rituximab, 375 mg/m² once weekly for 4 weeks, and either did not respond or had a TTP of less than 6 months.” FDA indicated a preference for a definition that would capture only those subjects who had truly progressed or not responded to a full therapeutic course (≥4 weekly doses) of rituximab.
- The FDA agreed to the minimum of 28 day delay between last rituximab dose and first Treanda dose as described in the protocol.
- The FDA stated that the target endpoints of ORR and DR as described in the protocol would be a review issue influenced by the magnitude of response, duration of response, and a risk benefit determination.
- FDA stated that whether or not the combined populations of approximately 130 patients treated with Treanda for rituximab-refractory indolent NHL would be sufficient for full approval would be a review issue.
- FDA stated that the overall acceptability of efficacy endpoints, overall response (CR + CRu + PR) rate and duration of response will be a risk/benefit judgment after review of the study data. FDA reminded the Sponsor that a finding of statistical significance may not necessarily imply its clinical relevance, especially in a single-arm study. Since there is no comparator, the proposed hypothesis formulations will be considered exploratory and whether or not the observed efficacy results are persuasive will be a review issue.

- FDA stated that, in general, all patients who have received any amount of study drug will be evaluable for response in a single arm study.
- FDA stated that, although a pre-treatment bone marrow biopsy is not essential, it is preferable.
- FDA agreed with the restricted use of corticosteroids in patients as proposed by the Sponsor.
- FDA stated that investigative site tumor measurements are essential and should be provided with the NDA.
- FDA agreed with the Sponsor's plan for collection of data regarding prior chemo-biologic therapy.
- FDA requested that results of persistently elevated LDH in a patient who otherwise meets criteria for CR, should be noted on the CRF with an alternative explanation for this elevation that would bear scrutiny by outside review. Additionally, FDA asked the Sponsor to provide any literature that they may be aware of showing evidence of durable CR in subjects with elevated LDH.
- The FDA did not concur with the Sponsor regarding the optimal time for tumor assessment because inadequate information about the typical response time in previous clinical experiences with bendamustine was provided by the Sponsor.

Reviewer Comments: *According to the Sponsor, the SPA was finalized in February 2, 2006. No SPA agreement letter was sent because this office was not issuing agreement letters at that time.*

August 2005 Sponsorship of IND transferred to Cephalon.

October 2005 Initiation of study SDX-105-03 (the primary study), a single-arm, open-label study, following a Special Protocol Assessment by the FDA.

September 13, 2006 Original Statistical Analysis Plan

August 22, 2007 Amendment 1, Statistical Analysis Plan

September 19, 2007 NDA 22,249 submitted for CLL indication.

October 29, 2007 Pre-NDA Meeting

Results of meeting:

- Statistical Analysis Plan (SAP) for SDX-105-03 (the primary study) is acceptable
- CLL NDA (22-249) cross-referenced for CMC & non-clinical sections
- Toxicology program acceptable
- Clinical Pharmacology plan reviewed and agreed upon

November 12-16, 2007 Cephalon site audit by FDA

December 28, 2007 NDA 22,303 submitted for NHL indication.

March 20, 2008 NDA 22,249 TREANDA received regular approval for CLL indication.

The Agency's acceptance of single-arm studies is consistent with the previous recent approvals of Zevalin and Bexxar in the same indication. Zevalin received regular approval in 2001 for Rituxan-refractory NHL based upon a 40-patient single-arm study. Bexxar also received regular approval in 2003 for Rituxan-refractory NHL based upon a 54-patient single-arm study. This bendamustine application contains one single-arm study that treated 100 patients with indolent NHL that was refractory to a prior rituximab regimen.

2.6 Other Relevant Background Information

2.6.1 Development History

On page 1, module 2.2, the Applicant describes the development history of bendamustine (SDX-105). 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 in Eastern Germany. The early clinical research was focused upon the activity of bendamustine in plasmacytoma, CLL, and bronchial carcinoma.

It has been 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 is presently undergoing reauthorization in Germany, because it was originally grandfathered at the time of the re-unification of Germany. A marketing authorization application (MAA) bendamustine was submitted to the Medical Products Agency (MPA) in Sweden, and also being considered for mutual recognition for the United Kingdom, France, Italy, Austria, and Spain. The application has proposed indications for NHL, Multiple Myeloma, and metastatic breast cancer.

2.6.2 Marketing History

In the NDA, Module 2.5, the Applicant describes information regarding the product development rationale. Bendamustine was marketed in Europe from 1971 through 1992 by Jenapharm as CYTOSTASAN® and from 1993 to 2006 by Ribosepharm GmbH as RIBOMUSTIN®. Mundipharma International Corp. Ltd. Acquired development and marketing rights for bendamustine in October 2006 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. 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. A clinical program has been initiated in Japan by Symbio Pharmaceuticals Co. Ltd., the licensee for Japan.

On March 20, 2008, bendamustine received regular approval for marketing by the U.S. F.D.A. for CLL via a priority review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The efficacy of bendamustine in patients with relapsed, rituximab-refractory, indolent NHL was analyzed by combining data from a single-arm study, SDX-105-03, (called the Primary Study throughout this review). The safety of bendamustine in patients with relapsed, rituximab-refractory, indolent NHL was analyzed by combining data from the primary study with a second, single-arm study, SDX-105-01, (called the Second Study throughout this review). The Primary Study treated 100 patients and the Second Study treated 76 patients. Fifteen of the 76 patients from study SDX-105-01 had transformed disease and were excluded from the primary analysis of efficacy for this study by previous agreement of the U.S. F. D. A. The Primary Study was performed at 24 study centers in the United States (US) and 4 centers in Canada by 28 investigators; with a total of 100 patients enrolled and treated in the study. The Second Study was performed at 12 centers in the US and 2 centers in Canada. According to the Applicant, this study did not prospectively collect dates of disease progression after prior rituximab-regimens. Instead, the Applicant implemented a convention whereby they derived the date of progression based upon the first dose of subsequent therapy. This derivation may not be accurate and cannot be relied upon for confirming that a patient in this study met the agreed upon definition of rituximab-refractory disease because the definition only includes patients who progressed during or within 6 months after rituximab or a rituximab-containing regimen. For this reason, only the results of the 100 patient study can be relied upon for the assessment of efficacy in this rituximab-refractory population.

The submission was a hybrid electronic submission. The submission was well organized and easy to navigate. The provided reviewer guide was helpful in locating the desired information. The electronic links were appropriately tracked.

Early in the review, it was noted that raw datasets were not submitted with the application. On January 15, 2008, the Applicant was asked to submit raw datasets for both the Primary and Second studies. These raw datasets were submitted to the NDA on January 17, 2008.

Two discrepancies were noted in the Primary Study Report between the ^{(b) (4)} reports and the derived disease assessment datasets variable “Best Response by ^{(b) (4)}”. The Applicant was asked to provide an explanation for these discrepancies. The discrepancies were not resolved to the satisfaction of the Agency so the analysis of the response rate was changed. The reader is referred to section 6.1.5.1.2 for further details of these issues.

The reader is referred to section 7.1.2 for evaluation of the coding of safety data for these studies.

3.2 Compliance with Good Clinical Practices

Per the applicant, “this study was conducted in full accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH) and any applicable national and local laws and regulations (e.g., Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314). Information regarding any investigational study centers participating in this study that do not comply with these standards is being documented”.

Before the study was initiated, the protocol was submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) according to national or local regulations. Any protocol amendments were also submitted.

Written informed, IRB-approved consent was obtained from the patients enrolled. Each patient’s willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

As discussed with DSI, the following sites essential for approval were identified for inspection, as listed below. The basis of the site selection was primarily the number of patients enrolled so that adverse inspection findings would have the potential to impact the interpretation of the studies.

Table 4: DSI Inspection Summary for Selected Sites

Study (N)	Site Number	Investigator and Affiliation	Number of Patients Enrolled	Inspection Findings	Reliability of Data
Primary Study SDX-105-03 (100)	062	Brad Kahl, Univ. of Wisconsin	15	Study conducted adequately.	Acceptable
Primary Study SDX-105-03 (100)	052	John Leonard, Cornell Univ.	8	Study conducted adequately.	Acceptable
Primary Study SDX-105-03 (100)	076	Nancy Bartlett, Washington Univ., St. Louis	8	Study conducted adequately.	Acceptable
Primary Study SDX-105-03 (100)	061	Kristen Ganjoo, Stanford Univ.	7	Study conducted adequately.	Acceptable
Second Study	005	Bruce Cheson,	11	Study conducted	Acceptable

Study (N)	Site Number	Investigator and Affiliation	Number of Patients Enrolled	Inspection Findings	Reliability of Data
SDX-105-01 (76)		Georgetown Univ.		adequately.	

No DSI inspection findings were identified that could impair the reliability of the data submitted to the NDA. The data from these studies appear to be reliable.

Reviewer Comments: The results of the Primary study can be relied upon for the assessment of efficacy and the results of both single-arm studies can be relied upon for the assessment of safety.

3.3 Financial Disclosures

In accordance with 21 CFR 54.4, the applicant acknowledges the required financial disclosure requirements and certification.

The investigators of both the Primary and Second studies completed the required financial disclosure forms.

For the Primary Study the following pertinent disclosures were received:

Dr. (b) (6) : Site (b) (6) - Reported receiving \$37,600 speaking honoraria from Cephalon

All other investigators were queried and had nothing to disclose.

All investigators in study SDX-105-01 were queried and no other disclosures were reported.

Reviewer Comments: The Applicant appears to have performed due diligence with regard to providing sufficient data on financial conflicts of interest via financial disclosures. The results for the (b) (6) studies do not appear to be impacted by any significant conflicts. The disclosure from (b) (6) is not likely to impact the results of the study because his site only enrolled (b) (6) patients. If that site were excluded from the analysis, no impact upon the study findings would result.

4 Significant Efficacy or Safety Findings Related to Other Review Disciplines

The Applicant states that they have cross-referenced their initial bendamustine application (22-249) for the CMC and Non-Clinical modules. However, new CMC and Pharm Tox information is proposed in the product label.

4.1 Chemistry Manufacturing and Controls

Minor proposed changes to the label regarding chemistry were submitted. Please refer to the Chemistry reviewer's report.

4.2 Clinical Microbiology

No new data submitted for review. The reader is referred to the review for NDA 22-249.

4.3 Preclinical Pharmacology/Toxicology

No new pre-clinical studies were submitted for review in this NDA. Updated information regarding drug mechanism of action was submitted. For further details, please refer to Dr. Anwar Goheer's review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action information was excerpted from the review of Dr. Anwar Goheer, the Pharmacology reviewer for this application.

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazol ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in understand DNA crosslink's. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells.

The exact mechanism of action of bendamustine remains unknown.

4.4.2 Pharmacokinetics and Pharmacodynamics

The information in this section was provided by Dr. Qi Liu, Clinical Pharmacology Reviewer. For further details, please see her review.

TREANDA (bendamustine hydrochloride) for Injection is an alkylating drug. Following a single IV dose of bendamustine hydrochloride, C_{max} typically occurred at the end of infusion. In humans, the mean steady state volume of distribution (V_{ss}) was approximately 25 L. Bendamustine clearance in humans is approximately 700 mL/minute. In-vitro metabolism

indicates that bendamustine is metabolized via CYP1A2 to form two active metabolites M3 and M4. Based on the clinical pharmacokinetic data, the two metabolites M3 and M4 are present at concentrations 10- and 100-fold lower than that of the parent compound, respectively. After a single dose of 120 mg/m² bendamustine IV over 1-hour, the intermediate t_{1/2} of the parent compound is approximately 40 minutes. The mean apparent terminal elimination t_{1/2} of M3 and M4 are approximately 3 hours and 30 minutes respectively. Preclinical radiolabeled bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces.

To support the approval for the treatment of NHL, the sponsor submitted data from 16 clinical studies, among which the Primary Study is considered the pivotal study and the Second Study is considered a supportive study. Both studies used the same dosage regimen for bendamustine (120 mg/m² iv infusion on days 1 and 2 of a 21-day cycle for a minimum of 6 cycles with additional cycles allowed with no evidence of disease progression).

The only new clinical pharmacology information submitted in the current submission is the pharmacokinetic/pharmacodynamic (PK/PD) analyses for the efficacy and safety in NHL patients conducted for the Primary Study. Based on logistic regression and graphical analyses, no exposure measures (AUC or C_{max}) were significant predictors of responder status within the studied exposure range. Exploratory graphical analyses demonstrated no relationship between duration of response (DR) and measures of exposure, whereas a potential relationship between progression-free survival (PFS) and exposure up to 30-60 weeks was observed. However, the relationship was not statistically significant. Among the safety endpoints evaluated in the PK/PD analyses, nausea was the only safety endpoint that was found to be statistically significantly related to bendamustine exposure. No correlation was observed between exposure and other three safety endpoints assessed (fatigue, vomiting and neutropenia) within the studied exposure range.

5 Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

The clinical studies submitted by the Sponsor in this NDA are summarized in Table 5 below. Only the Primary study and Second Study were reviewed in detail for the efficacy and safety reviews because the populations, dose administered, and study designs were the most pertinent for the indication sought by the Applicant.

Table 5: Clinical Studies

Study ID	Support	Design	US/ Canada sites	Regimen	Number of subjects
SDX-105-03 <i>Primary Study</i>	Efficacy, Safety and PK	Single arm study in Rituximab-Refractory Indolent NHL	yes	120 mg/m ² D1&2 q21d (minimum of 6 cycles).	102

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 Virginia Kwitkowski
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Study ID	Support	Design	US/ Canada sites	Regimen	Number of subjects
SDX-105-01 <i>Second Study</i>	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
2006001	Safety and PK	Single arm, dose-escalation study of treatment refractory B-cell NHL. (Japan)	None	90 or 120mg/day. Once on Day 1, and then continuous IV on Day 2. Minimum of 3 cycles.	9 (90 mg/m ² =3; 120 mg/m ² = 6)
93BOP01	Not GCP	Single center randomized study in Advanced Centroblastic / Centrocytic Lymphomas and Lymphoplasmacytoid Immunocytomas (Germany)	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 vincristine 2mg IV D1 plus prednisone 100 mg/m ² D1-5 Cycle=21d; up to 8 cycles	BOP=84 COP=83
02CLLIII	Safety	Randomized study comparing 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)
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
20BEN03	safety	Phase 1 study in advanced solid tumors (Belgium)	None	120-180 mg/m ² IV days 1 & 2 q21 days (dose escalation in 20 mg/m ² increments). Minimum of 2 cycles.	15
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
98B02W	safety	Phase 1 study in advanced solid tumors (Germany)	None	60, 70, and 80 mg/m ² IV weekly D1, 8, 15, 22, 29. (Up to 8 weeks of treatment).	12
99CLL2E (BG)	Safety & PK	Single arm 2 nd 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 2 nd line B-CLL treatment (Germany)	None	70, 80, 90, and 100mg/m ² IV on 2 consecutive days every	16

Study ID	Support	Design	US/ Canada sites	Regimen	Number of subjects
				21 days. Up to six 3-week cycles	
94BP01	Safety	Randomized study comparing bendamustine plus prednisone vs. melphalan plus prednisone in Stage II with progression and Stage III Multiple Myeloma	None (Germany)	BP= bendamustine 150 mg/m ² D1&D2 plus prednisone 60 mg/m ² D1-D4 Q29 days MP=Melpalan 15 mg/m ² D1 plus prednisone 60 mg/m ² D1-D4 Q29 days	131
SDX-105-02	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
96BMF02/1	safety	Multicenter randomized study for first line breast cancer therapy	None	A: Bendamustine 120 mg/m ² IV D1&8 plus methotrexate and 5-FU B: CMF	BMF=169 CMF=185
98B03	Safety and PK	Phase 1 parallel group study in advanced solid tumors patients with renal or hepatic impairment (Germany)	None	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 cholangiocarcinoma (Germany)	None	140 mg/m ² C1D1 and 100 mg/m ² D1&2 of later cycles lasting 21 days and 4 cycles.	6

5.2 Review Strategy

The focus of the initial review was on the larger of the two single-arm studies (SDX-105-03). This study will be called "the Primary Study" throughout the review. It was the subject of a Special Protocol Assessment and was subject to independent confirmation of the primary efficacy endpoints. The study reports, raw datasets, derived datasets, CRFs, and narratives were reviewed in detail.

Major efficacy and safety analyses were reproduced or audited using the SAS datasets submitted electronically to the NDA. A direct comparison of the efficacy datasets with confirmation by the source documentation from ^{(b) (4)} (the independent review committee) was performed. Minor discrepancies were noted and resolved by modification of the response rate to accurately reflect the existing data at the time of data cutoff. The safety data tables provided by the Applicant were confirmed by analysis of the raw adverse event datasets. Minimal discrepancies were identified during this review.

The second single-arm study (hereinafter called the Second Study) was also reviewed in detail but is not believed to provide supportive evidence of efficacy. The second study did not collect

dates of progression after previous rituximab regimens so the rituximab-refractoriness of this population could not be reliably assessed. The efficacy results were not combined with the primary study because the second study was not subject to independent confirmation of response assessments and because the overall treatment population was different. It does provide additional evidence of the safety of the proposed dose and schedule so the results from both studies can be combined for the analysis of safety. The study report, raw datasets, derived datasets, CRFs, and narratives were reviewed for the Second study. No independent assessments of the radiologic responses were performed in this study, so no comparison could be made between investigator and independent reviewers. However, the tumor measurements from the raw datasets were reviewed and were consistent with the response assessments made by the investigators. The review of efficacy will focus on the primary study with minimal detail of the results of the second study because they are not reliably applicable to the indication.

A third study (SDX-105-02) was not reviewed in detail because it did not add efficacy or safety information for this application in single-agent bendamustine. The patients in this study received both rituximab and bendamustine for relapsed indolent NHL. The dose of bendamustine was lower than the proposed dose for this indication. Patients receiving rituximab in addition to bendamustine may experience different adverse reactions than those receiving bendamustine alone. Additive activity with both agents may enhance the efficacy findings, therefore not providing additional efficacy information for single-agent bendamustine. Additionally, the population for SDX-105-02 was not similar to the intended population for the sought indication with regard to rituximab-refractoriness.

Relevant published literature was reviewed regarding Non-Hodgkin's Lymphoma and bendamustine. Multiple queries were sent to the sponsor and responses were reviewed. The Sponsor's slides during the presentation of the NDA to the FDA were also reviewed.

The designs for the primary study and the second single-arm study will be reviewed separately in Section 5.3, with the efficacy results presented independently in Section 6, and the results of the safety review combined in Section 7.

5.3 Discussion of Individual Studies

5.3.1 Study Protocol (Primary Study)

Study Title (Primary Study)

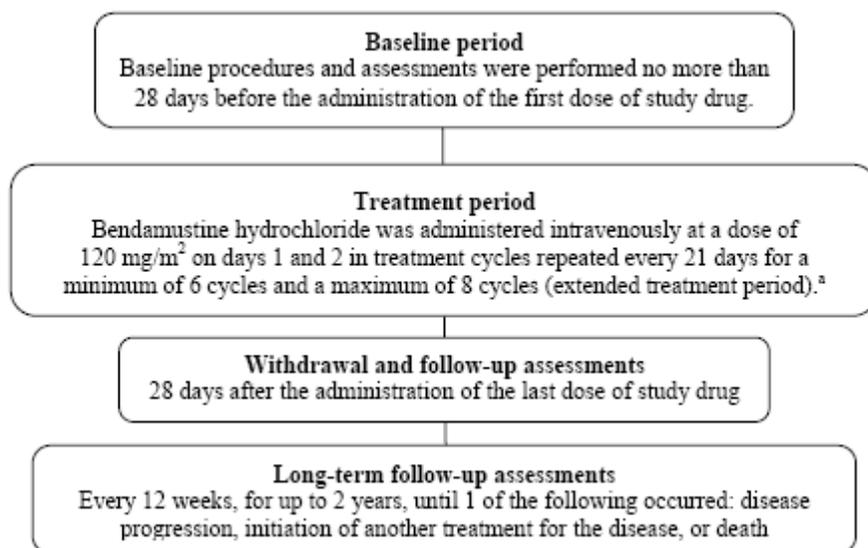
“A Multi-Center Phase III Study to Investigate the Safety and Efficacy of TREANDA™ (Bendamustine HCl) in Patients With Indolent Non-Hodgkin's Lymphoma (NHL) Who are Refractory to Rituximab”

Reviewer Comments: Though the Applicant titled this study “Phase 3”, the Agency does not agree with this because the study did not utilize a comparator arm.

5.3.1.1 Study Design (Primary Study)

The Primary Study was a single-arm trial to assess the efficacy of bendamustine in a rituximab-refractory indolent lymphoma population. The co-primary objectives of the study were Overall Response Rate (CR+CRu+PR) and Duration of Response. The secondary efficacy objective was to assess the progression free survival. The study consisted of the following 3 periods: pretreatment (screening), treatment, and follow-up. The baseline procedures and assessments were performed no more than 28 days before the administration of the first dose of study drug. All patients who met the eligibility criteria had a complete medical history review and physical examination completed within 28 days before study treatment initiation. During the treatment period, all patients received bendamustine hydrochloride I.V. at a dose of 120 mg/m² on days 1 and 2 for a minimum of six 21-day treatment cycles. Of note, the initial protocol version prescribed the treatment cycle length as 28 days. This was changed to 21 days in amendment 3 because of the findings from the phase 2 study with that cycle duration. This change occurred before any patients were treated in this study on a 28-day cycle, therefore no impact upon results has occurred as a result of this amendment. The reader is referred to Section 5.3.1.4.1 for further discussion of this change.

Figure 1: Study Schema (Primary Study) (from Applicant Clinical Summary)



5.3.1.2 Eligibility Criteria (Primary Study)

The study population was comprised of patients aged 18 years or more with rituximab-refractory indolent B-cell NHL. Diagnosis of NHL was documented by using the Revised European American Lymphoma (REAL) subcategories of NHL developed by the International Lymphoma Study Group (Harris et al 1994).

Inclusion Criteria (Primary Study)

In the Applicant provided NDA, Clinical Study Report, Section 9.3.1 describes the trial eligibility criteria.

Patients were included in the study if all of the following inclusion criteria were fulfilled:

(1) The patient had documented relapsed indolent B-cell NHL. Patients with the following subtypes of indolent NHL were eligible for this study: small lymphocytic lymphoma (absolute lymphocyte count [ALC] <5000 cells/mm³), lymphoplasmacytic lymphoma, splenic marginal zone B-cell lymphoma (\pm villous lymphocytes), extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, nodal marginal zone lymphoma (\pm monocytoid B-cells), follicle center lymphoma, and follicular (grades 1-3) lymphoma.

(2) The patient had disease documented to be refractory to rituximab treatment. Patients were considered to have disease refractory to rituximab treatment if they met any of the following criteria at any point during their treatment history. Progression was documented by scan (CT or MRI) or biopsy:

- patients who received a full course of single-agent rituximab treatment (at least 4 doses of 375 mg/m² weekly) if they had no response (did not obtain a PR or better) to treatment or progress within 6 months of the first dose of rituximab
- patients who had a history of a full course of rituximab treatment (at least 4 doses of 375 mg/m² as a single agent or in combination with chemotherapy) and were on a maintenance regimen if they progressed before the next scheduled rituximab dose or within 6 months of completing a maintenance rituximab regimen
- patients who received a full course of rituximab treatment (at least 4 doses of 375 mg/m²) in combination with chemotherapy if they had no response (did not obtain a PR or better) to treatment or progressed within 6 months of the last dose of rituximab
- For patients who had a history of a full course of rituximab treatment (at least 4 doses of 375 mg/m² as a single agent or in combination with chemotherapy), their disease was considered refractory if in a subsequent rituximab/chemotherapy combination regimen the patient had no response (did not obtain a PR or better) to treatment or progressed within 6 months of the last dose of rituximab, even if the subsequent regimen included less than 4 doses of rituximab. Patients could receive additional systemic treatment after the qualifying rituximab regimen.

(3) The patient had received treatment with at least 1 previous chemotherapy regimen with a maximum of 3 previous chemotherapy regimens. A regimen was defined as a new combination or agent. Retreatment with the identical regimen or agent did not count as a new regimen; however, change from cyclophosphamide, vincristine, and prednisolone (CVP) to cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) was counted as a new regimen. Rituximab, radioimmunotherapy, or other biologics treatment not combined with chemotherapy were not counted.

- (4) The patient had a bidimensionally measurable disease with at least 1 lesion measuring 2.0 cm or more in a single dimension. Patients who had previous involved-field irradiation could be included, provided the irradiated area was not the only source of measurable disease.
- (5) The patient was at least 18 years old at the time of informed consent.
- (6) The patient had a WHO performance status of 0 to 2.
- (7) In patients with thrombocytopenia attributable to bone marrow involvement with NHL, the patient had an ANC of 1,000 cells/mm³ or more and a platelet count of 100,000 cells/mm³ or more, or platelet count 75,000 cells/mm³ or more.
- (8) The patient had a creatinine clearance of more than 30 mL/min as determined by Cockcroft-Gault calculation.
- (9) The patient had adequate hepatic function (no more than 2.5 times the upper limit of the normal laboratory range [ULN] for aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase, and no more than 1.5 times the ULN for total bilirubin). Patients with nonclinically significant elevations of bilirubin due to Gilbert's disease were eligible.
- (10) The patient had a bone marrow biopsy within 28 days of the first dose of study treatment (results were not required before registration).
- (11) Both men and women of childbearing potential were to employ effective contraceptive measures before 2 weeks the start of study drug treatment until 4 weeks after the last dose of study drug.
- (12) The patient had an estimated life expectancy of at least 3 months.
- (13) The patient (or patient's legal representative) provided written informed consent.

Exclusion Criteria (Primary Study)

Patients were excluded from the study for any of the following reasons:

- (1) The patient had received previous radiotherapy, radioimmunotherapy, chemotherapy or immunotherapy within 28 days before cycle 1, day 1. For treatment with nitrosoureas or mitomycin, the time limit was 6 weeks before entering the study. The patient had not recovered from clinically significant adverse events due to any agents administered previously.
- (2) The patient had received treatment with investigational agents within 28 days of cycle 1, day 1.

- (3) The patient had received hematopoietic growth factors within 14 days of cycle 1, day 1. However, patients receiving chronic erythropoietin treatment were eligible for inclusion in this study.
- (4) The patient had a history of previous high-dose chemotherapy with allogeneic stem cell support (history of autologous stem cell support was permissible).
- (5) The patient was receiving concurrent treatment with therapeutic doses of systemic steroids within 14 days of cycle 1, day 1 (low doses of chronic steroids up to 10 mg/day [prednisone or equivalent] for non-neoplastic disorders were permitted).
- (6) The patient had transformed disease.
- (7) The patient had any history of central nervous system (CNS) or leptomeningeal lymphoma.
- (8) The patient had an active malignancy within the past 5 years other than the target cancer. The exceptions were localized prostate cancer treated with hormone therapy, in situ cervical carcinoma, and non-melanoma skin cancer.
- (9) A woman was pregnant or lactating. Women of childbearing potential were to have a negative serum pregnancy test.
- (10) The patient had a serious infection, medical condition, or psychiatric condition that, in the opinion of the investigator, might have interfered with the achievement of the study objectives.
- (11) The patient was known to be positive for human immunodeficiency virus (HIV).
- (12) The patient had a known hypersensitivity to mannitol.
- (13) The patient had used bendamustine previously.

5.3.1.3 Study Treatments, Concomitant Medications, and Dose Modifications (Primary Study)

Study Treatments (Primary Study)

Bendamustine was administered as a 60 minute infusion of 120 mg/m² on Days 1 & 2 every 21 days on this study. After cycle 6, if the investigator assessment was that the patient was continuing to experience clinical benefit, up to an additional 2 cycles were permitted (to a maximum of 8 cycles per patient).

The original protocol planned for patients to receive bendamustine hydrochloride I.V. at a dose of 120 mg/m² on day 1 and day 2 in treatment cycles that were repeated every 28 days for a minimum of 6 cycles. This schedule was initiated because the Sponsor reviewed data from the Phase II trial utilizing a 21-day cycle, thinking that extending the cycle length to 28-days might improve toxicity. Further review of the data demonstrated to the Sponsor that the toxicity profile

had not yet been fully characterized and that a secondary result of lengthening the cycle might be decreased response to treatment. Therefore, Amendment 3 changed the cycle frequency to every 21 days based upon findings from another study utilizing that dose and schedule. No patients were treated in cycles lasting 28 days because the first patient was enrolled to the study after Amendment 3 was in place. The reader is referred to Section 5.3.1.7.3 for further details of this change.

Bendamustine was administered as an I.V. infusion over 60 minutes. If medical conditions necessitated, e.g., fluid management issues or infusion reactions, the infusion was given over a longer period of time, though the total time for the infusion was not to be greater than 120 minutes. In-line filters were not required for administration.

Per the Applicant, the treatment regimen used in this study had been used in previous studies. In a study of patients with refractory low-grade NHL (Heider and Niederle 2001), responses (complete and partial) were seen with this regimen in 70% of patients and toxicity was low. This regimen was also used in a study of patients with refractory aggressive NHL; ORR was 44% and toxicity was felt to be acceptable (Weidmann et al 2002). In addition, in a Phase 2 study, 76 patients were administered bendamustine at a dose of 120 mg/m²/day on days 1 and 2 in treatment cycles that were repeated every 21 days for a minimum 6 cycles (study SDX-105-01). An ORR of 76% and an acceptable safety profile was observed in this study at the dosage and schedule used.

The starting bendamustine hydrochloride dose was 120 mg/m² and dose reduction was permitted if the patient experienced toxicities at the initial or subsequent doses. Section 5.3.1.4.2 describes dose modification guidelines for this study.

5.3.1.4 Bendamustine Dose Modifications (Primary Study)

Dose modifications for bendamustine were made per the following table:

Table 6: Dose Reduction Schedule for Bendamustine in Primary Study

Dose	Toxicity	Reduced Dose
120 mg/m ²	Grade 4 hematologic toxicity	90 mg/m ²
	Grade 3-4 non-hematologic toxicity	90 mg/m ²
	Grade ≥ 2 thrombocytopenia or neutropenia that lasts ≥ 2 weeks	90 mg/m ²
90 mg/m ²	Grade 4 hematologic toxicity	60 mg/m ²
	Grade 3-4 non-hematologic toxicity	60 mg/m ²
	Grade ≥ 2 thrombocytopenia or neutropenia that lasts ≥ 2 weeks	60 mg/m ²
60 mg/m ²	Grade 4 hematologic toxicity	Remove Patient from Study
	Grade 3-4 non-hematologic toxicity	Remove Patient from study
	Grade ≥ 2 thrombocytopenia or neutropenia that lasts ≥ 2 weeks	Patient can continue treatment at 60 mg/m ² as long as thrombocytopenia or neutropenia recovers to Grade 1 within 4 weeks of the scheduled start date of the next cycle

Source: Applicant Protocol SDX-105-03, 18 January 2005.

Dose modifications were required if the patient met the toxicity criteria per protocol, regardless of plans for supportive care. Dose reductions below 60 mg/m² were not permitted. If grade 3-4 non-hematologic or grade 4 hematologic toxicity occurred despite dose-reduction to 60 mg/m², the patient was removed from the study. No dose-escalations were permitted.

5.3.1.5 Concomitant Medications and Treatments (Primary Study)

The Case Report Forms (CRFs) were designed to record all previous or concomitant therapy or medication within 28 days of Cycle 1 Day 1. Additionally, medications received at the time of the end-of-study evaluation were also recorded. Generic or trade name, indication, and dosage were recorded. The sponsor encoded all therapy and medication according to the WHO drug dictionary (WHO Drug Version 2005Q1).

Supportive treatments for adverse events were permitted following an evaluation of the causal relationship of the symptom(s) to the treatment with the study drug. The onset and duration of supportive treatment was recorded in the CRF. This treatment could include antiemetic, anti-diarrheal, antipyretic, anti-allergic, anti-hypotensive, analgesic, and antibiotic medications, and other therapies, such as blood products. Chronic erythropoietin therapy was permitted.

Cytokine Use:

The prophylactic use of cytokines to stimulate white blood cells (WBCs), such as granulocyte-colony stimulating factor (G-CSF), was discouraged during the first cycle. However, cytokines were allowed in conjunction with the study drug in patients who demonstrated the need for cytokine support as a result of prolonged neutropenia (grade 4 leukopenia lasting at least 1 week, failure of WBC count to recover to at least grade 1 toxicity by the next scheduled dose, or the occurrence of febrile neutropenia in a prior cycle of treatment) following the American Society of Clinical Oncology (ASCO) guidelines.

Corticosteroid Use:

Treatment with low doses of chronic steroids (up to 10 mg/day of prednisone or equivalent) was permitted for non-neoplastic disorders. However, other on-study treatment with corticosteroids was not allowed, with the exception of single doses of steroids used as antiemetics (2 doses per cycle).

Use of Radiation:

Treatment with radiation was not allowed on study. If a patient required palliative radiation, they were removed from the study for disease progression, as lesions requiring urgent radiotherapy likely signal progressive disease. No other antitumor treatment was permitted during the course of the study.

Reviewer Comments: Concomitant use of corticosteroids or radiation can enhance the efficacy of lymphoma treatment.

5.3.1.6 Study Landmarks (Primary Study)

Four amendments were made to the protocol; three occurred before any patients were enrolled (study initiation). The study began 10/11/2005 and the data cutoff for this application was 07/16/07.

Table 7: Primary Study Duration and Timeline

Date	Important Landmarks
18 January 2005	Original Protocol (Version 1)
29 April 2005 N=0	Protocol Amendment 1 (Version 2) Performed before any patients had enrolled; changes relative to this amendment are included in the SPA review.
11 May 2005 N=0	Protocol Amendment 2 (Version 3) Revised Statistical Analysis Plan submitted to FDA. Performed before any patients had enrolled; changes relative to this amendment are included in the SPA review.
19 August 2005 N=0	Protocol Amendment 3 (Version 4) Performed before any patients had enrolled; changes relative to this amendment are included in the SPA review.
11 October 2005	Study Initiation Date & First Patient Enrolled
02 February 2006	FDA Special Protocol Assessment
17 February 2006 N=35	Amendment to reflect the SPA Agreement Meeting Discussions: Protocol Amendment 4 (Version 5) Pertinent Changes: 1) Allowance for registration to occur before results of bone marrow biopsy; LDH added as efficacy variable. 2) Entry Criteria: Eligibility criterion #2 (definition of rituximab-refractory disease) modified by requiring progression be documented by biopsy or scan; regimens of Zevalin count as only rituximab regimen; allowed enrollment of patients who progressed within 6 months of completing rituximab-maintenance therapy and patients who had no objective response to rituximab; added clarification that patients who have a history of a full course of rituximab as single agent or combination and later receive a lesser regimen of rituximab and progress within 6 months can be considered refractory; added exclusion criterion "Transformed disease"; added to eligibility criterion 2 that "patients may receive additional systemic treatment after the qualifying rituximab regimen." 3) Appendix F: The modifications to the International Working Group Response Criteria were updated. Clarification included only to add that the increase in the product of diameters required for

Date	Important Landmarks
	defining progressive disease was regarding a single lesion.
October 25, 2006	Revised Statistical Analysis Plan submitted to FDA The only change potentially relevant to the primary endpoints is the addition of a section on sample size and power
16 July 2007	Data Cut-Off Date
22 August 2007	Amended and final Statistical Analysis Plan submitted to FDA. Revisions Included: 1. "All Patients Enrolled" now also includes patients who were treated, didn't meet study criteria, and did not receive an exemption; 2. Exclusion from "Evaluable Set" patients with baseline absolute lymphocyte count >5,000 cells/mm ³ to exclude patients with CLL or leukemic transformation;
29 October 2007	FDA pre-NDA Meeting held. Pertinent clinical discussion issues: <ul style="list-style-type: none"> • Whether study SDX-105-03 was conducted in a manner that maintains the SPA agreement will be a review issue because the Sponsor did not provide safety or efficacy data from the study. • The amendments to the SAP are acceptable. • The pooled efficacy and safety analyses for the two studies (SDX-105-01 & SDX-105-03) would be supportive since the eligibility criteria for the two studies differ in the definition of rituximab refractory disease and in the NHL subtypes • The safety database may be adequate but will be a review issue. • The results (including tumor measurements) of the independent radiology review should be submitted with the NDA. • Available toxicology data is adequate to support an NDA submission.
6 December 2007	Study Report Approval Date

Source: Study SDX-105-03 Clinical Study Report

Reviewer Comments: The changes in study conduct and statistical plan were reviewed in detail for potential impact on the use of the Primary Study in supporting this application. No changes were identified that could negatively impact the study that were not previously agreed to during the Special Protocol Assessment evaluation.

5.3.1.7 Efficacy and Safety Evaluations (Primary Study)

Efficacy Evaluations (Primary Study)

Tumor assessments were performed at baseline, week 6, week 12, and then every 12 weeks thereafter within a window of ± 3 days until the patient completed treatment. A modified version of the International Workshop Response Criteria for NHL was used to assess response and disease progression. The disease status was classified as CR, CRu, PR, stable disease, progressive disease, or unknown (incomplete evaluation). Patients who achieved CR, CRu, PR, or SD were treated for a minimum of 6 cycles. Patients with evidence of clinical benefit after the first 6 cycles could continue to receive 2 more cycles of therapy. Patients who experienced progressive disease were withdrawn from the study. All patients had end-of-treatment evaluations within 28 days of the last dose of study drug and this visit included assessment of: assessment of reasons for study drug discontinuation and all baseline assessments with the exception of medical history, body height and surface area measurements, and assessment of renal function. Follow-up data was collected every 12 weeks (for up to 2 years after the last dose) on patients who did not exhibit disease progression at the end-of-treatment evaluation until one of the following occurred: disease progression, initiation of another treatment for NHL, or death.

Table 8: Applicant Schedule of Procedures and Assessments (Primary Study)

Procedures and assessments	Pretreatment	Treatment cycle ^a		End-of-treatment evaluation ^c	Follow-up ^d
	Screening/ Baseline ^b	Cycles 1-2	Cycles 3-8		
Informed consent	X				
Inclusion and exclusion criteria	X				
Medical history ^e	X				
Physical examination	X	X	X	X	
Vital signs measurements ^f	X	X	X	X	
Body weight	X	X	X	X	
Body height and surface area	X	X ^g	X ^g		
WHO performance status	X	X	X	X	
ECG	X			X	
Clinical laboratory tests ^h	X ⁱ	X	X	X	
LDH level measurement ^j	X	X	X	X	X
Assessment of renal function ^k	X				
Bone marrow aspirate and biopsy	X	X ^l	X ^l		
Concurrent medications	X	X	X	X ^m	
Study drug administration		X	X		
Samples collected for pharmacokinetic analysis ⁿ		X			
Assessment of disease ^o	X	X (day 42±3 days, day 84±3 days, and day 168±3 days [if needed])		X	X
Adverse events inquiry	X	X	X	X ^m	

^a Each 21-day cycle began on the first treatment day. For treatment delays, a new cycle started when a dose was given for the next cycle.

^b Performed within 28 days of cycle 1, day 1.

^c Patients who received less than 6 cycles of treatment or completed the study (6-8 cycles) had an end-of-treatment evaluation within 28 days after last dose of study drug, unless the patient had experienced a dose delay due to toxicity, in which case the evaluation was performed within 2 weeks of the decision to discontinue the patient from treatment. If a patient already had a tumor assessment within 28 day after the last dose of study drug, an additional tumor assessment was not necessary at study completion. For example, if a patient completed study treatment on day 154, the day-168 assessment could serve as the end-of-treatment tumor assessment.

^d Follow-up data were collected for all patients until disease progression. If a patient's disease had not progressed at the time that study drug was discontinued and the end-of-treatment evaluation was completed, follow-up data and a tumor assessment were obtained at least every 12±1 weeks. This follow-up assessment was continued until documented disease progression, until a new treatment was started for the disease, or death, whichever came first, for up to 2 years from the end of treatment.

^e Medical history with attention to past lymphoma treatment.

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- ^f Blood pressure, pulse, and temperature.
 - ^g Body surface area was recalculated during the study if there was a change in weight of $\pm 10\%$ or more.
 - ^h Hematology and chemistry evaluations were performed during the baseline period to confirm eligibility and within 3 days before dose administration on day 1 of each cycle. In addition, hematology evaluations were also performed weekly.
 - ⁱ Serum β human chorionic gonadotropin was measured at screening/baseline in women of childbearing potential.
 - ^j Measurement of lactate dehydrogenase (LDH) levels was performed during the baseline period to confirm eligibility and before dose administration on day 1 of each cycle and within ± 1 week of disease assessment, and at the end-of-treatment evaluation within 28 days after last dose of study drug, unless the patient had experienced a delay due to toxicity, in which case the evaluation was performed within 2 weeks of the decision to discontinue the patient from treatment. If a patient's disease had not progressed at the time that study drug was discontinued and the end-of-treatment evaluation was completed, LDH levels were obtained at least every 12 ± 1 weeks.
 - ^k Creatinine clearance was estimated using the Cockcroft-Gault equation.
 - ^l A bone marrow aspirate and biopsy with conventional cytogenetics were repeated once to confirm a first complete response if the patient had an initial positive response for non-Hodgkins lymphoma (NHL) at baseline.
 - ^m Include concomitant medication usage and adverse events were reported within 28 days after the end-of-treatment visit.
 - ⁿ Samples for pharmacokinetic analysis for the General Clinical Research Center group (5 mL of blood each) were collected during cycle 1 on day 1 within 2 hours before the start of study drug administration (before infusion), at midpoint through infusion, at the end of infusion, and post infusion at 15, 30, 45, and 60 minutes and 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours following the end of the study drug administration (after infusion); and during cycle 2 on day 1 within 2 hours, and 0.25 to <0.5 hours and 1 to <3 hours after the start of infusion. A maximum of approximately 4 pharmacokinetic samples were obtained from each patient in groups A, B, C, and D (see protocol for details). Five-milliliter samples of whole blood were collected into evacuated tubes containing ethylenediamine tetra acetic acid (EDTA) at each of the scheduled time points on day 1 of cycle 1, day 2 of cycle 1, day 1 of cycle 2, and day 2 of cycle 2.
 - ^o Disease assessment was at screening and within 28 days before study treatment initiation by neck, chest, abdomen, and pelvis computed tomography (CT) scan or magnetic resonance imaging (MRI), palpated disease, and assessable disease. Tumor assessments were done according to the schedule and within the windows outlined in the schedule of events regardless of any delays in dose administration.
- EKG=electrocardiography; WHO= World Health Organization.

Source: Applicant CSR Study SDX-105-03

Reviewer Comments: The standard International Working Group criteria contain a requirement that the diagnostic bone marrow biopsy sample be at least 20 mm long. In the Primary Study, this criterion was modified to not have a minimum biopsy size. An inadequately sized sample increases the risk of a false-negative result and may not accurately depict the disease involvement. Neither the standard working group criteria nor the modified protocol criteria clearly identify whether the bone marrow biopsy should be repeated at each restaging whose outcome is a Complete Response.

5.3.1.8 Statistical Plan for the Primary Study

The original statistical analysis plan for the primary study was dated 09/13/06 and submitted to FDA on 10/25/06. Amendment 1 was dated 8/22/07 and was submitted with the pre-NDA advice meeting briefing package. During the pre-NDA meeting, the Agency responded to queries about the acceptability of the original SAP and the amendment, "the SAP is acceptable". Both versions of the SAP were finalized after the study began, but before it ended.

Statistical Hypotheses and Analyses of Major Efficacy Endpoints of the Primary Study

The Applicant provided the SAP in Section 16.1.9 of the Clinical Study Report. The null hypothesis for the co-primary endpoint of overall response rate was that it is less than or equal to 40%. An assumption was made that patients treated with the study drug would have an overall response rate of at least 60%, giving the planned sample size of 100 patients more than 90% power at a 1-sided alpha of less than or equal to 0.025. The null hypothesis for the co-primary endpoint of duration of response was that the median is 4 months or less. The alternative hypothesis was that the median duration of response would be 6 months.

The exact p-value to test against the null hypothesis of ORR rate less than or equal to 40% and a 2-sided 95% exact confidence interval for the ORR was calculated using binomial distributions. The estimate of the median Duration of Response was calculated using the Kaplan-Meier method. The 2-sided 95% confidence interval was calculated using the nonparametric method of Brookmeyer and Crowley (1982). The Applicant planned to withhold claim for duration of response unless the response rate is significantly greater than 40% and the duration of response is significantly longer than 4 months.

The Applicant reports that they performed simulations that have demonstrated that the power to reject the null hypothesis is at least 90% for the primary analysis at a data cut-off point of 6 months after the last patient enrolled. They based these results on runs of 1000 simulated clinical trials each, using the following distributions:

Patient enrollment was based on a uniform distribution with a linear ramp-up period; time to onset of response was bootstrapped from Phase 2 data (Study 105-01); duration of response was drawn from an exponential distribution with a median duration of 6 months; the percentage of patients responding was kept fixed at 50% as this is the minimum percentage needed to be able to reject the null hypothesis of a 40% response rate.

Reviewer Comment: The sample size of 100 patients was discussed during the SPA meeting; the Sponsor was informed that the sample size would be a review issue.

Data Collection

Cephalon was the Sponsor of the Primary Study (SDX-105-03). Data was collected on Case Report Forms and entered into raw datasets. Raw datasets were converted into derived datasets by the rules of the protocol. The Clinical Study Report was audited by the Quality Assurance Department of Cephalon.

Statistics, endpoints and measures of Primary Study

Primary Study Objectives

Co-Primary Objectives

- Overall Response Rate (ORR) = (CR+CRu+PR)
- Duration of Response (DR)

The co-primary objectives were assessed for the Intent-to-Treat population using adjudicated responses and dates of progression from the Independent Review Committee (IRC).

Independent Review of Primary Study Efficacy Data

The tumor assessments for the primary efficacy evaluations were performed by an independent review committee (IRC), (b) (4). The IRC assessed responses on the basis of radiographic and selected clinical information received from the study centers. Two radiologists independently assessed each time point response (TPR) and certain key variables, including best response and date of disease progression. If the assessments of the 2 radiologists differed in any of these key variables, a third radiologist adjudicated the assessment. An oncologist from (b) (4) considered the assessments of the arbitrating radiologist together with selected clinical data, to determine the key variables for each patient.

Data utilized in the analysis of efficacy were based on the IRC’s oncologist’s time point response (TPR) oncologic tumor response ratings, which include a response status of CR, CRu, PR, SD, PD, or UE at each assessment, response assessment date, best response during the study, response onset date, and disease progression date.

Overall response rate was defined as the proportion of patients with a best response of CR, CRu, or PR to treatment, as defined by a modification of the International Workshop Response Criteria (IWRC) for Non-Hodgkin’s Lymphoma. This workshop was convened among U.S. and international lymphoma experts representing medical hematology/oncology, radiology, radiation oncology, and pathology in order to standardize guidelines for response assessment in trials for non-Hodgkin’s lymphoma. The results of this workshop were published in 1999. ²

The Rules used for response evaluation in the Primary Study are provided below in Figure 3, provided by the Applicant.

Table 9: International Workshop Response Committee for Non-Hodgkin’s Lymphoma Response Criteria

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or Indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse/Progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

Source: Applicant CSR SDX-105-03

INTERNATIONAL WORKSHOP RESPONSE CRITERIA (IWRC) FOR NON-HODGKIN'S LYMPHOMA AND MODIFICATIONS

Complete Response (CR) requires the following:

1. Complete disappearance of all detectable clinical and radiologic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH]) definitely assignable to NHL.
2. All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (≥ 20 mm biopsy core).

Complete Response/unconfirmed (CRu) includes those patients who fulfill criteria 1 and 3 above, but with one of more of the following features:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

Partial Response requires the following:

1. $\geq 50\%$ decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (i.e., small, lymphocytic small cleaved, or mixed small cleaved, or mixed small and large cells).
6. No new sites of disease.

Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (CR, CRu) requires the following:

1. Appearance of any new lesion or increase by $\geq 50\%$ in the size of previously involved sites.
2. $\geq 50\%$ increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following:

1. $\geq 50\%$ increase from nadir in the PD (Product of Diameters for a **single** lesion) of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

Table 10: Clinically Important Applicant Modifications to the IWRC Criteria for the Primary Study

Category	Modification	Discussion of Clinical Importance
Response Assessment	Addition of neck CT to imaging	Enhanced disease assessment
Response Assessment	Bone lesions considered non-target (not addressed at all in original criteria)	No change.
Complete Response	Bone Marrow sample size (≥ 20 mm) requirement removed.	An inadequate sample may result in false-negative results and increase the number of CRs.
Partial Response	Addition that a patient meeting criteria of CR but with bone	Limited impact.

Category	Modification	Discussion of Clinical Importance
	marrow that doesn't clear (or is indeterminate), will be classified as a PR.	
Progressive Disease	A single node reaching $\geq 50\%$ increase in diameter would need to reach 2cm to be PD; more than one node reaching $\geq 50\%$ increase in diameter would be PD.	Waiting for node to reach this size may delay diagnosis of disease progression or recurrence.
Progressive Disease	A new node of ≥ 2 cm or new non-nodal lesion of any size. A bone marrow that was previously negative and becomes positive.	Waiting for node to reach this size may delay diagnosis of disease progression or recurrence.
Recurrent Disease	A single node reaching $\geq 50\%$ increase in diameter would need to reach 2cm to be PD; more than one node reaching $\geq 50\%$ increase in diameter would be PD.	Waiting for node to reach this size may delay diagnosis of disease progression or recurrence.
Recurrent Disease	A new node of ≥ 2 cm or new non-nodal lesion of any size. A bone marrow that was previously negative and becomes positive.	Waiting for node to reach this size may delay diagnosis of disease progression or recurrence.

Source: Applicant CSR SDX-105-03

Reviewer Comments: The modifications of the IWRC response criteria were not subject to the FDA Special Protocol Assessment because the specific modifications were not the topic of Applicant questions posed to FDA. These modifications could have impact upon the efficacy analysis of bendamustine. The impact could be that the numbers of CRs could have been falsely elevated but would not be expected to change the overall response rate.

Should an inadequately sized bone marrow sample be obtained at baseline to detect bone marrow disease, and the patient achieve resolution of other disease, a follow-up marrow would not be required by the protocol. A patient in this situation would be inappropriately determined to have achieved a Complete Response instead of a true Partial Response. Additionally, the requirement for lymph nodes to reach 2 cm in order to be classified as progressive disease or disease recurrence may falsely extend the Duration of Response for that patient. The IWRC criteria were also used in the trials that supported the approval of Zevalin but not those supporting the approval of Bexxar. Whether the protocol for the Zevalin trial used the published criteria or modified the published criteria is unknown to this reviewer due to the lack of detailed

discussion of these criteria in the original FDA review and product label. The primary trial that supported the approval of Bexxar was initiated and completed before the IWRC criteria were published in 1999.

Primary Study Secondary Objectives:

- to assess the safety profile of bendamustine in this patient population
- to assess the duration of progression-free survival (PFS)

Reviewer Comment: Progression Free Survival was assessed in the Primary Study. However, PFS is not interpretable in a single-arm study, so it will not be reviewed further.

- to estimate the basic pharmacokinetic parameters and between-subject variability of bendamustine and its 2 active metabolites (gamma [γ]-hydroxy [OH]-bendamustine [M3] and N-desmethyl bendamustine [M4]) in the target population after intravenous (iv) infusion by applying nonlinear mixed effect modeling (NONMEM)
- to assess the effects of clinical and demographic covariates on the pharmacokinetics of bendamustine and its active metabolites
- to assess the effects of plasma concentrations of bendamustine and its active metabolites on the efficacy and safety of bendamustine

Safety objectives were planned to evaluate treatment-emergent adverse events, defined as adverse events that occurred after the first dose of study drug treatment. Adverse events were recorded and graded by CTCAE v 3.0. Verbatim terms on case report forms were mapped to preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of adverse events was to be displayed by system organ class, high-level term, and preferred term. For the calculation of incidence, if a patient had more than 1 adverse event mapped to the same preferred term, that adverse event were to be included only once by the highest severity and closest relationship to study drug. The total number of adverse events were also to be reported.

Primary Study Sensitivity Analyses:

For the sensitivity analysis of duration of response, undocumented disease progression and death were incorporated to modify disease progression date according to the rules specified in the section about sensitivity analyses. Details of how the response ratings were assessed, and how data irregularities were handled, were included in the IRC's charter and are summarized as follows:

- The Assessment Date is the date of the first observation indicating progression, or the last date of an assessment otherwise.
- Adequate tumor assessments must comprise scans of abdomen, chest, neck, and pelvis.

- Target lesions that are too small to be measured after baseline will be assigned a value of 5 mm x 5 mm (25 mm²) in size. Target lesions that can not be measured for other reasons are assigned a rating of unevaluable (UE).
- Tumor assessments that comprise only part of these data but are sufficient to diagnose PD are also considered adequate. Otherwise, the assessment will be labeled UE.
- Scans not occurring on the same date will be moved together for analysis; the rules for assessment date above will be used. If a target lesion is classified as UE, the response for this time point will also be UE unless disease progression can be proclaimed based on other criteria (e.g. new lesions).
- (b) (4) radiologists will note suspicious lesions in comments fields and backdate progression to the date of first suspicion if the lesions are confirmed later.

Primary Study Planned Exploratory Analyses:

The following planned exploratory analyses were found in Section 7.3 of the Clinical Study Report.

Exploratory analyses for ORR, duration of response, and PFS will be conducted by baseline features listed below. ORR will be modeled using logistic regression. Duration of response and PFS will be modeled using proportional hazard regression. The following predictors will be considered:

- Number of prior chemotherapy courses (≤ 3 vs > 3)
- Prior alkylator therapy exposure (yes vs no) (Alkylator therapies will be defined by a medical expert.)
- Prior radioimmunotherapy exposure (yes vs no)
- Refractory vs. sensitive to last prior chemotherapy regimen (refractory is defined as a best response of stable disease or progressive disease; sensitive is defined as a best response of complete response or partial response)
- Refractory vs. sensitive to last prior alkylator therapy (refractory is defined as a best response of stable disease or progressive disease; sensitive is defined as a best response of complete response or partial response)
- refractory vs. sensitive to last prior radioimmunotherapy (refractory is defined as a best response of stable disease or progressive disease; sensitive is defined as a best response of complete response or partial response)
- FLIPI (4 or less vs. more than 4 nodal areas)
- FLIPI Risk Category (low risk, intermediate risk, high risk)
- low vs. high bulk (≥ 10 cm) disease at baseline
- In addition, the distribution of the minimum values of percent change in total tumor load of target lesions will be presented graphically. Since there are 2 radiological readers ratings from the (b) (4) and each selected their own target lesions at baseline to follow during the study, the minimum value of percent change of total tumor load will be calculated for each reader and the average of the 2 minima will be graphed.

All exploratory analyses will be performed using the PAS set.

Primary Study Exploratory Safety Analyses

The Applicant proposed to perform two exploratory safety analyses to investigate known bendamustine safety issues:

- 1) Infection related adverse-events
- 2) Potential infusion reaction symptoms

Plan for Missing Data in Primary Study

Per the study report, no imputations for missing efficacy analysis data were made.

5.3.1.9 Reasons for Removal of Patients From Primary Study

Patients were free to withdraw consent for participation in the study at any time. In addition, patients were withdrawn from the study in case of disease progression, unacceptable toxicity, found ineligible for study, noncompliant with study requirements, administrative decision, or patient death.

5.3.1.10 Patient Follow-Up in Primary Study

All patients had an end-of-treatment evaluation within 2 weeks after receiving their last dose of study drug, regardless of the reason for withdrawal. The end-of-treatment scan was performed within 28 days of the last dose of study drug, unless the patient had experienced a delay due to toxicity, in which case the scan was performed within 2 weeks of the decision to withdraw the patient from treatment. Reasons for discontinuation of treatment were documented in the patient's CRF.

After the end-of-study evaluation, follow-up data were collected at least every 12 weeks (± 1 week), or more frequently, until resolution of study drug-related adverse events or until adverse events were deemed to be chronic. Patients who did not exhibit disease progression at the end-of-study evaluation were monitored at a minimum of 12 weeks (± 1 week), for up to 2 years, until 1 of the following occurred: disease progression, initiation of another treatment for the disease, or death.

5.3.1.11 Changes in Plan for Treatment Cycle Length

The standard treatment cycle length in the original protocol, Amendment 1, and Amendment 2 was 28 days. Amendment 3 (dated 8/19/05) altered the cycle length to 21 days. No patients were enrolled prior to this date, so all enrolled patients were treated on a cycle length schedule of 21 days.

The study Sponsor justified this change by the following statement:

“Upon initial review of data from the Phase II trial, which involved a 21-day cycle, it was thought that a 28-day cycle might improve toxicity. However, after further review of the data, it became clear that the toxicity profile was not yet fully characterized and that lengthening the cycle might not improve toxicity but could negatively impact patient response to treatment. The regimen was modified to repeat the cycle length used in the Phase II trial.”

Patients must have recovered their hematologic values to baseline or \leq Grade 1 in order to be eligible to receive the next cycle of treatment. Blood counts had to have recovered to ANC ≥ 1000 cells/mm³ and platelets to $\geq 75,000$ cells/mm³ to resume treatment at that time. Patients who did not receive a cycle within 4 weeks of the scheduled start date of that cycle were removed from study.

5.3.1.12 Study Sites and Enrollment (Primary Study)

Number of Patients Planned (Analyzed): For this study, 100 patients were planned to be enrolled; 102 patients were enrolled, and data from 100 patients were analyzed for safety and efficacy. Twenty-eight sites enrolled patients into the study; 24 in the U.S. and 4 in Canada. The distribution of patients enrolled was relatively evenly distributed among the sites with no single institution contributing the majority of patients to the study.

Reviewer Comments: All of the study sites were within the United States or Canada. The results of this study are easily generalized to the United States population.

5.3.1.13 Study Populations (Primary Study)

Efficacy Populations

Applicant Primary Analyses Population: All patients treated with bendamustine (n=100).

Three patients in the primary analysis population did not meet the definition of rituximab-refractory NHL. All three of these patients experienced a Partial Response as the best response.

- Patient 09078 received a complete dose and showed durable PR
- Patient 52052 had insufficient documentation of rituximab dose
- Patient 76003 did not receive the standard rituximab dose

Applicant Evaluable Population: All of the patients in the primary analyses population except patients who:

- Had transformed disease
- Had no post-baseline assessment
- Did not meet the “rituximab-refractory” definition agreed to by the FDA
- Missed a CT scan
- Did not meet inclusion criteria #3 (minimum of one and maximum of three prior treatment regimens)
- Did not have a baseline bone marrow evaluation

Only one patient was excluded from the Sponsor’s assessment of the evaluable population for lack of a baseline bone marrow evaluation (Patient 18037). However it should be noted that the

marrow sample could be less than 2 cm for it to be acceptable (unlike the IWG criteria). Bone marrow assessment is only pertinent if the patient achieves a Complete Response. During the SPA meeting for SDX-105-03 with the Sponsor, the FDA stated that “although a pre-treatment bone marrow biopsy is not essential, it is preferable”. This patient’s best response was a Partial Response and therefore can be considered in the evaluable population because the absence of a baseline bone marrow evaluation has no impact on the true response rate.

Safety Population for Primary Study

All 100 patients treated with bendamustine. The safety results from the Primary Study will be combined with the safety results from the Second study.

Reviewer Comment: This reviewer agrees with the selection of the treated population as the population for the safety analysis.

5.3.2 Study Protocol (Second Study)

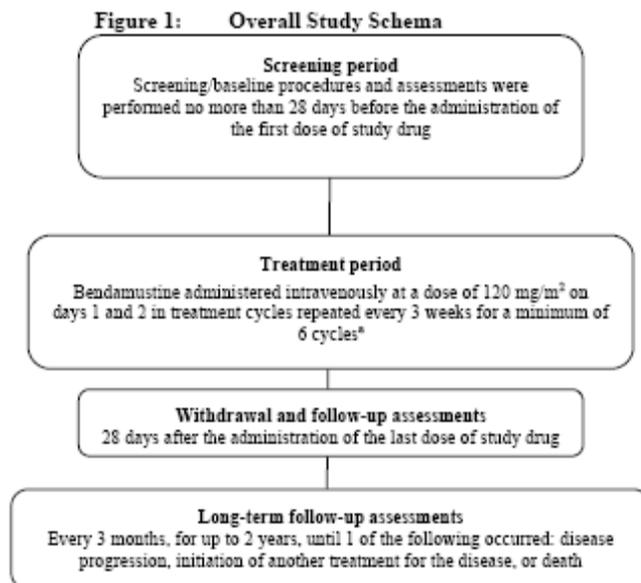
“A Multi-Center Phase II Study to Investigate the Safety and Activity of SDX-105 (Bendamustine) in Patients with Indolent Non-Hodgkin’s Lymphoma (NHL) who are Refractory to Rituximab”

5.3.2.1 Study Design (Second Study)

This study was a single-arm study of patients with Non-Hodgkin’s Lymphoma. Fifteen of the 76 treated patients had transformed disease and not indolent lymphoma; thus bringing the indolent lymphoma population down to 61 patients. This population was further reduced by 10 patients who were determined to not have disease that was refractory to rituximab. This adjustment brought the population of rituximab-refractory, indolent NHL to 51 patients from this study. Patients in this study were required to be rituximab-refractory; however, the study did not prospectively collect the dates of disease progression from the prior rituximab regimen. Therefore, the rituximab-refractory definition that was agreed upon during meetings with the Applicant and the FDA, could not be applied to this population without the date of progression after treatment with rituximab.

These patients were treated at the same dose and schedule of single-agent bendamustine as was used in the Primary Study (120 mg/m² IV on Days 1 & 2 of every 21 day cycle). This trial allowed up to 12 cycles of therapy, but the actual number of cycles received by patients was very similar to that of the Primary Study. The Sponsor of this study did not empanel an independent review committee for the response assessments (as in the Primary Study).

Figure 2: Applicant Overall Study Schema (Second Study)



Source: Applicant Study Report SDX-105-01

5.3.2.2 Eligibility Criteria (Second Study)

The intended study population was comprised of patients aged 18 years of age or more with indolent or transformed B-cell NHL who had disease refractory to treatment with rituximab. Diagnosis of NHL was documented by using the Revised European American Lymphoma (REAL) subcategories of NHL developed by the International Lymphoma Study Group (Harris et al 1994). As mentioned above, the population could not be confirmed as rituximab-refractory without the date of progression.

In Amendment 3 to the protocol, the inclusion criteria were expanded to include patients in whom further rituximab treatment was inappropriate due to adverse reactions to prior treatment with rituximab, and prior treatment with radioimmunotherapy was removed as an exclusion criterion. A patient was enrolled into the study only if all inclusion criteria and none of the exclusion criteria were fulfilled.

Study Inclusion Criteria (Second Study)

Patients were included in the study if all of the following inclusion criteria were fulfilled:

(1) The patient had documented indolent or transformed B-cell NHL (Harris et al 1994). Patients with the following subtypes of indolent NHL were eligible for this study:

- follicular B-cell lymphoma
- diffuse small lymphocytic lymphoma (chronic lymphocytic leukemia was excluded)
- lymphoplasmacytic lymphoma

- marginal zone lymphoma

(2) The patient had received prior treatment with rituximab, but further treatment was inappropriate due to the following:

- documented disease refractory to rituximab treatment given either as single-agent therapy or in combination with other agents. (NOTE: Refractory disease was defined as no response or progression within 6 months of completing rituximab treatment.)
- an untoward reaction to prior rituximab treatment making further treatment unwarranted as determined by the investigator.

(3) The patient had received treatment with a maximum of 3 prior chemotherapy regimens. A regimen was defined as a new combination or agent. Retreatment with the identical regimen or agent did not count as a new regimen; however, change from cyclophosphamide, vincristine, and prednisolone (CVP) to cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) was counted as a new regimen. Rituximab treatment alone was not considered to be 1 of the 3 prior chemotherapy regimens.

(4) The patient had bidimensionally measurable disease with at least 1 lesion measuring 2.0 cm or more in a single dimension.

(5) The patient was at least 18 years old at the screening visit.

(6) The patient had a WHO performance status of 0 to 2.

(7) The patient had an ANC of 1,000 cells/mm³ or more and a platelet count of 100,000 cells/mm³ or more. However, patients with lower counts who had more than 50% marrow involvement with lymphoma were eligible for the study.

(8) The patient had a creatinine clearance of more than 30 ml/min as determined by Cockcroft-Gault calculation.

(9) The patient had adequate hepatic function (no more than 2.5 times the upper limit of the normal laboratory range [ULN] for aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase, and no more than 1.5 times the ULN for total bilirubin).

(10) The patient had a negative pregnancy test, as determined by urine or serum β -hcg (in women of childbearing potential). In addition, both men and women were to employ effective contraceptive measures before the start of study drug treatment until 4 weeks after the last dose of study drug.

(11) The patient had an estimated life expectancy of at least 3 months.

(12) The patient (or patient's legal representative) provided written informed consent.

Study Exclusion Criteria (Second Study)

Patients were excluded from the study for any of the following reasons:

- (1) The patient had received previous chemotherapy or immunotherapy within 3 weeks before entering the study. For treatment with nitrosoureas or mitomycin, the time limit was 6 weeks before entering the study.
- (2) The patient had not recovered from adverse events due to any chemotherapy or immunotherapy agents administered previously.
- (3) The patient had received treatment with investigational agents within 28 days of entering the study.
- (4) The patient had received hematopoietic growth factors within 14 days of entering the study. However, patients receiving chronic erythropoietin treatment were eligible for inclusion in the study.
- (5) The patient had a history of prior high-dose chemotherapy with allogeneic stem cell support.
- (6) The patient was receiving concurrent treatment with therapeutic doses of systemic steroids.
- (7) A woman was pregnant or lactating.
- (8) The patient had a concurrent, active malignancy other than the target cancer. The exceptions were completely excised non-melanoma skin cancer or in situ cervical or bladder cancer.
- (9) The patient had primary or active central nervous system (CNS) lymphoma. Patients with a prior diagnosis of lymphoma active in the CNS were eligible only if the patients had been treated for the CNS lymphoma and the patient was neurologically stable, with no progressive symptoms, and was no longer receiving steroids or anticonvulsants. At least 28 days must have elapsed since treatment, and the patient must have recovered from all associated toxicities of treatment.
- (10) The patient had a serious infection, medical condition, or psychiatric condition that, in the opinion of the investigator, might have interfered with the achievement of the study objectives.
- (11) The patient had a known hypersensitivity to mannitol.

5.3.2.3 Study Treatments, Concomitant Medications, and Dose (Second Study)

Study Treatments (Second Study)

Patients were given I.V. bendamustine hydrochloride at a dose of 120 mg/m² on day 1 and day 2 in treatment cycles that were repeated every 3 weeks. Bendamustine was administered as an I.V. infusion over 30 to 60 minutes. In-line filters were not required for administration, and the infusion bags did not need not to be protected from light.

Unless the patient had documented bone marrow involvement with lymphoma of more than 50%, the patient's blood cell counts were to have recovered to an ANC of at least 1,000

cells/mm³ and platelet count of at least 75,000 cells/mm³ at the time of the next scheduled treatment cycle to continue treatment with study drug. If recovery criteria (including the recovery of CTCAE toxicities described above) were not met within 2 weeks following a treatment cycle (i.e., after a 2-week delay), the patient was re-evaluated by the investigator and sponsor and a decision made as to further continuation in the study.

5.3.2.4 Bendamustine Dose Modifications (Second Study)

Patients who experienced CTCAE grade 3 or 4 nonhematologic or grade 4 hematologic toxicity at a dose of 120 mg/m² could have their dose decreased to 90 mg/m² for the next cycle, providing the patient had recovered and toxicities were at baseline values or of grade 1 or less. Likewise, if grade 3 or 4 nonhematologic or grade 4 hematologic toxicity occurred at this reduced dose level, the dose was further decreased to 60 mg/m² for the next cycle. Patients who continued to experience toxicities at the 60 mg/m² dose were withdrawn from the study.

5.3.2.5 Concomitant Medications and Treatments (Second Study)

Case report forms were designed to capture previous therapy or medication a patient received between 14 days before the baseline visit and the first day of study drug administration. In addition, any concomitant therapy or medication a patient received during the study and at the time of the end-of-study evaluation was also recorded on the CRF. Generic or trade name, indication, and dosage were recorded. The sponsor encoded all therapy and medication according to the WHO drug dictionary (WHO Drug).

The administration of supportive treatments for adverse events was permitted following the evaluation of the causal relationship of the symptom(s) to the study drug. The onset and duration of supportive treatment was recorded in the CRF. This treatment may have included antiemetic, anti-diarrheal, antipyretic, anti-allergic, anti-hypotensive, analgesic, and antibiotic medications, and others therapies, such as blood products.

Cytokine Therapies

- Chronic erythropoietin therapy permitted
- Bone marrow growth factors not permitted during the first cycle of treatment.
- After the first cycle, the use of cytokines, such as granulocyte-colony stimulating factor (G-CSF) to stimulate white blood cells (WBC), was allowed as needed per ASCO guidelines for the use of these agents.

Corticosteroid use was not specifically addressed in excluded concomitant medications.

No other antitumor treatment was permitted during the course of the study.

5.3.2.6 Study Landmarks (Second Study)

Table 11: Important Study Landmarks

Date	Study Landmarks
12 May 2003	Original Protocol (Version 1)
8 September 2003 N=0	<p>Protocol Amendment 1 (Version 2)</p> <p>Amendment 1 to the protocol was issued before any patients were enrolled into the study. Therefore, changes relative to this amendment are reflected in the methods described in the study report and details of the change were not provided by the Sponsor.</p>
29 September 2003	Study Initiation Date & First Patient Enrolled
4 December 2003 N=14	<p>Protocol Amendment 2 (Version 3)</p> <p>Amendment 2 to the protocol was issued after 14 patients were enrolled into the study. These changes were considered to have no negative impact on the study results.</p> <p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"> • The infusion time for the study drug was increased from 30 to 60 minutes to accommodate the volume of fluid to be administered and to be consistent with administration practices in Germany. • The dose-reduction schema was clarified as being applicable to all cycles of treatment.
15 March 2004 N=63	<p>Amendment 3 to the protocol was issued after 63 patients were enrolled into the study. These changes were considered to have no negative impact on the safety of patients already enrolled into the study.</p> <p>The following major procedural changes (not all-inclusive) were made to the protocol:</p> <ul style="list-style-type: none"> • The inclusion criteria were expanded to include patients in whom further rituximab treatment was inappropriate due to adverse reactions to prior treatment with rituximab. • The inclusion criterion regarding prior chemotherapy regimens was clarified by explaining that rituximab alone was not considered to be 1 of the maximum of 3 prior chemotherapy regimens permitted for study entry. • Because the myelosuppression observed with bendamustine treatment was comparable to that observed with other therapies, prior treatment with radioimmunotherapy was removed as an exclusion criterion. The safety profile was updated to explain the reason for removing prior radioimmunotherapy as an exclusion criterion. <p>Furthermore, the purpose of the dose de-escalation schema included</p>

Date	Study Landmarks
	in the protocol was to protect those patients whose bone marrow was susceptible to severe suppression, whether from prior chemotherapy or from radioimmunotherapy agents.
15 August 2006	Data Cut-Off Date
5 April 2007	Study Report Approval Date

5.3.2.7 Efficacy and Safety Evaluations (Second Study)

Efficacy Evaluations

The Applicant provided the investigational plan for the Second Study in the Clinical Study Report for SDX-105-01 Section 9.0.

The study periods were comprised of pretreatment (screening), treatment, and follow-up. The screening/baseline assessments were performed no more than 28 days before the administration of the first dose of study drug. These procedures included the WHO performance status measurement, body weight and height measurements, body surface area calculation, vital signs measurements, physical examination, medical history including past lymphoma treatment, electrocardiogram (ECG), hematology and serum chemistry laboratory tests including serum or urine tests for beta human chorionic gonadotropin, assessments of creatinine clearance and baseline adverse events, and recording of concomitant medications usage.

Within 4 weeks before treatment initiation, tumor assessments were evaluated by using contrast-enhanced computed tomography scanning or magnetic resonance imaging for determination of measurable disease. All patients who met the eligibility criteria had a complete medical history and physical examination completed within 2 weeks before study treatment initiation. During the treatment period, assessment of disease response was performed every 9 weeks (after 3 cycles) following initiation of treatment with the study drug. Assessment was performed by clinical and radiologic evaluations of lymph nodes, nodal masses, and other organs with disease involvement, and by biochemical evaluation. Bone marrow aspirate and biopsy were performed to confirm a CR, if the bone marrow was involved before study drug treatment.

Response and progression were evaluated by the investigators using the International Workshop Response Criteria for NHL. Safety assessments in the study were conducted according to the study schedule of assessments. Blood samples for pharmacokinetic evaluation were collected during cycle 1 (days 1 and 2) and during cycle 2 (day 1 only). All patients had an end-of-study evaluation 28 days after receiving the last dose of study drug, regardless of the reason for withdrawal. Follow-up data from patients who did not exhibit disease progression at the end-of-study evaluation were collected every 3 months, for up to 2 years, until 1 of the following occurred: disease progression, initiation of another treatment for the disease, or death.

Table 12: Applicant Schedule of Procedures and Assessments (Second Study)

Procedures and assessments	Pretreatment Screening/Baseline	Treatment cycle visits					End-of-study evaluation ^e	Follow-up ^b
		Cycle 1			Cycle 2	All subsequent cycles		
		Week 1	Week 2	Week 3	Week 1	Week 1		
Informed consent	X							
Inclusion and exclusion criteria	X							
Medical history ^c	X							
Physical examination ^d	X	X			X	X	X	X
Vital signs measurements ^e	X	X			X	X	X	
Body weight	X	X (day 1)			X (day 1)	X (day 1)	X	
Body height and surface area ^f	X	X						
WHO performance status	X	X (day 1)			X (day 1)	X (day 1)	X	
ECG	X						X	
Clinical laboratory tests ^g	X ^{h,i}	X (day 1)	X	X	X	X	X	
Assessment of renal function ^j	X							
Tumor staging ^j	X							
Concurrent medications	X	X	X	X	X	X	X	
Study drug administration		X (days 1, 2)			X (days 1, 2)	X (days 1, 2)		
Samples collected for pharmacokinetic analysis ^k		X (days 1, 2)			X (day 1 only)			
Hematologic supportive care	X							
Assessment of response ^l						X ^l	X	X
Adverse events ^m	X	X	X	X	X	X	X	

- Performed 28 days after receiving the last dose of study drug. The reason for discontinuation of treatment with study drug was documented.
- Follow-up data were collected for all patients until disease progression. If a patient's disease had not progressed at the time that study drug was discontinued and the end-of-treatment evaluation was completed, follow-up data and a tumor assessment was obtained at least every 3 months. This follow-up assessment continued until documented disease progression, until a new treatment was started for the disease, or death, whichever came first, for up to 2 years from the end of treatment.
- Medical history with attention to past lymphoma treatment.
- Performed within 14 days before study initiation.
- Blood pressure, pulse, and temperature.
- Body surface area was recalculated during the study if there was a change in weight of $\pm 10\%$.
- Performed within 14 days before study treatment initiation, the first day of every treatment cycle, then weekly for the first cycle, and then within 2 days before day 1 of each treatment cycle thereafter. In the event of a dosage reduction, additional evaluations were performed weekly for the first cycle of each new dose of study drug.
- Urine or serum β HCG measured at screening/baseline in women of childbearing potential.
- Creatinine clearance estimated using the Cockcroft-Gault equation.
- Tumor staging assessed at screening and within 4 weeks before study treatment initiation by contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI). If a contrast-enhanced CT scan was not obtainable, a CT scan without contrast was acceptable.
- Samples for pharmacokinetic analysis (5 mL of blood each) were collected during cycle 1 on day 1 at 15 minutes before the start of study drug administration (pre-infusion), 15, 30, 45, 60, and 90 minutes and 2, 4, 6, 8, 10, and 12 hours following the end of the study drug administration (post-infusion); during cycle 1 on day 2 at 15 minutes before the start of study drug administration (pre-infusion); and during cycle 2 on day 1 at 15 minutes before the start of study drug administration (pre-infusion).
- Assessment of response was performed after every 3 cycles of therapy (approximately after every 9 weeks), following initiation of treatment with study drug, using the same methodology used for tumor staging at baseline and was categorized using the International Workshop non-Hodgkin's Lymphoma response criteria. A bone marrow

aspirate and biopsy were only performed to confirm a complete response if the patient had an initial positive response.

m. Adverse events were assessed 2 to 3 days after completion of administration of study drug on day 2 of each cycle by study visit or telephone call from study center personnel.

Abbreviations: WHO=World Health Organization; ECG=electrocardiogram; β HCG=human chorionic gonadotropin; CT=computed tomography; MRI=magnetic resonance imaging.

5.3.2.8 Statistical Plan (Second Study)

This was a multicenter, nonrandomized, open-label, single-agent study designed according to the 2-stage method (Simon 1989) with an initial enrollment target of 22 patients. If there were at least 6 responses, an additional 50 patients were to be enrolled for a total of 72 patients. If less than 6 responses were noted among the first 22 patients, a response rate of less than 20% was to be assumed and the study was to be stopped.

The Applicant states that a single-group design was selected for this trial because at the time the study was conducted, no widely available effective treatment for this subgroup of patients with indolent or transformed B-cell NHL who had disease refractory to treatment with rituximab was available.

Statistical Hypotheses and Analyses of Major Efficacy Endpoints (Second Study)

Sample Size Estimation

The sample size of the study was based upon the two-stage Simon design. Accrual to the first stage would occur until at least 22 rituximab-refractory patients were accrued. If 5 or fewer objective responses were observed, the study was to be closed to further accrual. If 6 or more objective responses were observed, the second stage would begin and continue until 72 patients were enrolled. A promising overall response rate would be 35% or higher, with <20% response rate would indicate that bendamustine was not worthy of further investigation in this population. Regarding rituximab-refractory patients, this design effectively discriminates between true response rates of 20% and 35%. It yields 0.80 probability of a positive result if the true response rate is 35% or higher and 0.05 probability of a positive result if the true response rate is 20% or lower.

Data Collection (Second Study)

This study was sponsored by Salmedix, Inc. until 14 June 2005 when Salmedix, Inc. became a wholly owned subsidiary of Cephalon, Inc. Effective 15 August 2005, Cephalon, Inc. assumed all rights and responsibilities to the application under Title 21 of the CFR, Section 312.

According to the Sponsor, the handling of data, including data quality assurance, was conducted according to the regulatory guidelines (e.g., ICH and GCP) and the sponsor's or CRO's SOP's and working instructions.

Statistics, Endpoints, and Measures (Second Study)

Study Endpoints (Second Study)

Primary Objective: To describe the overall response rate (ORR) to a regimen of bendamustine in patients who are refractory to rituximab treatment. The ORR was defined as a best response of a complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during the study.

Secondary objectives:

- To describe the duration of response (DR)
- To describe the progression-free survival (PFS)
- To determine the safety profile of bendamustine in this patient population,
- To describe the pharmacokinetic profile of bendamustine and its major metabolites.

Response Criteria

Disease response was assessed by the investigator every 9 weeks after initiation of bendamustine. Clinical, radiological evaluation of lymph nodes, nodal masses, and other organs with disease involvement, and laboratory evaluation of LDH were utilized to assess the disease response. If the bone marrow was involved at enrollment, this procedure was repeated to confirm a complete response. Response and progression were evaluated using the International Workshop Response Criteria for NHL². Each patient was classified as one of the following response categories:

- complete response (CR)
- complete response/unconfirmed (CRu)
- partial response (PR)
- stable disease (SD)
- relapsed disease (RD)
- progressive disease (PD)
- unknown (evaluation incomplete) (UE)

5.3.2.9 Reasons for Removal of Patients from Study (Second Study)

Patients were free to withdraw consent for participation in the study at any time. In addition, patients were withdrawn from the study for disease progression, unacceptable toxicity, trial ineligibility, noncompliance with study requirements, or administrative decision on the part of the investigator or sponsor.

5.3.2.10 Study Populations (Second Study)

Efficacy Populations

Applicant Primary Efficacy Population: All patients who received at least one dose of bendamustine were included in the Applicant's primary efficacy population. (N=76)

Applicant Evaluable Population: Of the 76 patients who received any dose of bendamustine, 15 patients had transformed disease and were not included in the primary analysis (N=61)

Rituximab-Refractory Population: All patients who had disease that met the definition for rituximab-refractory (N=51).

Safety Population (N=76)

All patients who received at least one dose of bendamustine were included in the safety population. The rationale for including the transformed patients in the safety population is that the adverse event profile is not likely to vary significantly between these two groups. An accurate assessment of the safety of bendamustine in the intended population can be assessed by analyzing safety data for all treated patients.

Reviewer Comment: The safety evaluation for this review will combine data from these patients with those from the primary study for a total treated population of 176.

5.3.2.11 Sites and Enrollment (Second Study)

This study was performed at 12 study centers in the United States (US) and 2 centers in Canada by 14 investigators enrolling a total of 77 patients. Study enrollment was relatively well distributed between centers so that no single center entered more than 15% of the study patients.

6. Review of Efficacy

Summary of Efficacy Results and Conclusions

The efficacy of bendamustine in rituximab-refractory indolent non-Hodgkin's lymphoma was demonstrated by a single-arm trial (the Primary Study) that enrolled 100 patients with indolent NHL that progressed within 6 months of a prior rituximab or rituximab-containing regimen. The Primary Study treated patients for up to 8 cycles and utilized an independent review committee for assessment of the co-primary endpoints of Overall Response Rate and Duration of Response.

The Second Study was not considered supportive for efficacy because the population of patients could not be confirmed to be rituximab-refractory as defined in the Primary Study and by agreement in pre-NDA advice meetings with the Applicant and FDA. The reason for the inability to confirm the rituximab-refractoriness of this population is because the Second study did not collect dates of disease progression for these patients after their prior rituximab regimen. The Applicant utilized a convention to derive the date of progression from the date of the next subsequent treatment initiation.

Reviewer Comments: This technique for deriving the date of progression is problematic in that patients may start subsequent for a variety of reasons; not always objective disease progression. Oncologists may delay starting subsequent therapies to await the resolution of residual toxicities from prior therapy, lack of symptoms from disease, patient preference, or other reasons. Oncologists may start subsequent therapies earlier than the availability of objective disease progression information because of patient symptoms, patient preference, or other reasons. For these reasons, the convention utilized by the Applicant cannot be relied upon to provide an accurate date of disease progression.

The reader is referred to Section 5.3 for discussion and review of the protocols, study designs, and demographics of patients in the Primary Study and Second Study.

Reviewer Comment: The study eligibility criteria for the Primary Study serve to adequately define a population similar to the target population in the proposed indication.

The Primary Study was designed with co-primary endpoints of overall response rate (ORR) and the duration of response (DR) to a regimen of bendamustine in patients with rituximab-refractory indolent lymphoma. The ORR was analyzed by the applicant based on the assessment of the Independent Review Committee^{(b) (4)}. The ORR was defined as the proportion of patients who achieved a best response (by IRC) of complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during the study, and the duration of the response (DR).

Table 13: Summary of Efficacy Results

Efficacy Variable	Primary Study TREANDA (N=100)
Overall Response Rate (%) (95% CI) P value	74 (64.3, 82.3) <0.001
Complete Response (CR)	13
Complete Response Unconfirmed (CRu)	4
Partial Response (PR)	57
Duration of Response Median, months (95% CI)	9.2

Reviewer Comments: These results demonstrate that bendamustine is effective as a single agent in a rituximab-refractory indolent lymphoma population.

6.1 Primary Study (SDX-105-03; N=100)

The Applicant proposes the following indication:

TREANDA is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma who have progressed during or following treatment with rituximab or a rituximab-containing regimen.

After review of the submitted data, the following indication is recommended for approval:

TREANDA is indicated for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) which has progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen.

6.1.2 Methods and Study Design (Primary Study)

As described in section 5.3.1, the efficacy review is based upon the Primary Study (SDX-105-03).

Protocol Deviations and Violations (Primary Study)

Eighty-three of the 100 patients who received treatment had at least one protocol deviation. The most frequent deviations were non-adherence to protocol-specific study procedures or schedules that did **not** involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines (67 patients), and disease assessments performed outside of protocol-specified time window (28 patients).

Table 14: Protocol Violations That Occurred Before Amendment 4

Criteria Violated	Number of Patients	Number of Patients with Protocol Exception Granted
Inclusion #2: Patient had disease that was refractory to a full course of rituximab therapy	13	13
Inclusion #3: The patient has had at least one prior chemotherapy regimen and a maximum of three prior chemotherapy regimens.	2	2
Inclusion # 10: The patient has had a bone marrow biopsy within 28 days of the 1st dose of study treatment.	1	1
Exclusion # 9: The patient has active malignancy within the last 5 years besides the target cancer, except localized prostate cancer treated with hormone therapy, cervical carcinoma in situ, and non-melanoma skin cancer.	1	1

Reviewer Comment: Amendment 4 revised the definition of rituximab-refractory, only three protocol violations directly related to the primary patient efficacy population occurred after the amendment. Exceptions were granted by the Sponsor to all violations in this group. A total of 6% of the patient population had at least one major protocol violation that might impact the analysis of this application. Since this is a relatively small percentage of patients, no impact is perceived.

Table 15: Protocol Violations That Occurred After Amendment 4

Criteria Violated	Number of Patients	Number of Patients with Exception Granted
<p>Inclusion Criteria #2: The patient has disease documented to be refractory to a full-course of rituximab therapy. Progression must be documented by scan or biopsy.</p> <ul style="list-style-type: none"> • Refractory after rituximab-only regimen. • Refractory after rituximab maintenance therapy or extended schedule. • Refractory after rituximab-chemotherapy combination regimen. <p>Patients may receive further treatment after the qualifying rituximab regimen.</p>	3	2
<p>Inclusion Criteria #3: The patient has had at least one prior chemotherapy regimen and a maximum of three prior chemotherapy regimens. (A regimen is defined as a new combination or agent. Retreatment with the identical regimen or agent does not count as a new regimen; however, change from CVP to CHOP would be counted as a new regimen.) Rituximab, radioimmunotherapy, or other biologics not combined with chemotherapy are not counted.</p>	1	1
<p>Inclusion Criteria #9: The patient has adequate hepatic organ function (≤ 2.5 x upper limit laboratory normal for AST (SGOT), ALT (SGPT), and alkaline phosphatase, ≤ 1.5 x upper limit laboratory normal for total bilirubin). Patients with non-clinically significant elevations of bilirubin due to Gilbert's disease are eligible.</p>	1	1
<p>Inclusion Criteria #10: The patient has had a bone marrow biopsy within 28 days of the 1st dose of study treatment.</p>	1	0
<p>Exclusion Criteria #1: The patient has received previous radiotherapy, radioimmunotherapy, chemotherapy or immunotherapy within 28 days prior to Cycle 1, Day 1 (6 weeks for nitrosoureas or mitomycin) or failure to recover from clinically significant adverse events due to any agents administered previously.</p>	1	1
<p>Exclusion Criteria #6: The patient has concurrent treatment with therapeutic doses of systemic steroids within 14 days of Cycle 1, Day 1 (low doses of chronic steroids up to 10 mg/day [prednisone or equivalent] for non-neoplastic disorders are permitted).</p>	1	1

Source: Study SDX-105-03 Study Report

Reviewer Comments: The protocol violations that were documented do not appear to have affected the overall outcome of the study due to the limited number of violations pertaining to eligibility; thus ensuring that the intended population was enrolled.

Additional Clinically Relevant Protocol Violations Not Pertaining to Eligibility Criteria:

Review of the concomitant medications datasets found that four patients were recorded as having received doses of steroids exceeding this limitation for non-oncologic indications including some who experienced an objective response around the time of the excessive steroid dosing.

A summary of these cases follows:

- Patient 21082 was recorded as having taken prednisone 10 mg twice daily for end-stage COPD starting on 11/01/06 with no stop date recorded. The CRF indicated that a hospitalist (non-investigator) prescribed this medication and the Sponsor was not notified of this violation until later. This patient was recorded as achieving an objective response of a PR on 11/29/06. This steroid dosing may have enhanced the response to bendamustine.
- Patient 05102 was recorded as taking a sliding scale of prednisone starting at 10 mg daily for Bell's Palsy from 02/21/07-02/25/07. The datasets do not clearly indicate the range for the sliding scale. One may assume that the doses may have reached above the 10 mg daily limit. An objective response of a PR was recorded on 03/01/07 followed by clinical disease progression on 04/17/07. The steroid dosing of this patient may have enhanced the response to bendamustine.
- Patient #62038 received prednisone 20 mg daily continuously for shortness of breath starting on 06/21/06. No objective response was recorded for this patient. This steroid dosing had no impact on the efficacy assessment for bendamustine.
- Patient #14090 received prednisone 20-40 mg daily from 01/08/07-02/22/07 for asthma. No objective response was recorded for this patient. This steroid dosing had no impact on the efficacy assessment for bendamustine.

The review found that no dexamethasone was used beyond the permitted anti-emetic pre-medications.

Reviewer Comments: Two patients who achieved objective response (PR) to bendamustine were recorded as having received concomitant doses of steroids that exceed the protocol allowances for the treatment of concurrent non-oncologic diseases. Both of these patients received the steroids just before diagnosis of the objective response. Because this situation is limited to two patients, this reviewer believes that no significant impact upon the overall efficacy of bendamustine is present.

6.1.3 Patient Baseline Characteristics and Demographics (Primary Study)

The population was reflective of the known demographics for patients who are diagnosed with indolent lymphoma; more common in the 6th decade of life, occurring more frequently in men in a 1.4:1 ratio with women, and more common in Caucasian populations. As is typical for this younger population, performance status was good in nearly all of the patients (93% were 0-1 WHO). All patients had received prior systemic therapy for their lymphoma as the study required that their disease be refractory to rituximab. Fifty-eight percent had received >1 prior chemotherapy regimen.

Seventy-six percent of patients in this study were staged as Ann Arbor Stage III or IV at the start of the study. Sixteen percent of patients were experiencing lymphoma B-symptoms (fever, drenching night sweats, or weight loss).

Table 16: Patient Demographics and Disease Baseline History (Primary Study)

Demographic and Disease Characteristics	SDX-105-03 (N=100)
Age, mean, years (range)	59.3 (31-84)
Sex (M/F %)	65/35
Race (white %)	88
Weight, mean (kg), (range)	86.7 (44-151)
Body surface area, mean (m ²), (range)	2.0 (1.3-2.7)
WHO performance status, n (%)	
0	51
1	42
2	6
3 or 4	0
Missing	1
Number of previous chemotherapy courses	
0	1 (1)
1	41 (41)
>1	58 (58)
Ann Arbor Stage III or IV	76 (76)
Bulky Disease \geq 10cm by IRC	
Yes	9 (9)
No	89 (89)
Unknown	3 (3)
B Symptoms at Baseline (Fever 39°, drenching night sweats, >10% wt loss)	16 (16)
Met "Need For Treatment" Criteria ^a	69 (69)
FLIPI Score for Follicular NHL Patients	(N=62)
Low Risk	18 (29)
Intermediate Risk	26 (42)
High Risk	18 (29)
Unknown	0

^a Unconfirmed, post-hoc data analysis at FDA Request

Source: Reviewer confirmed data from Applicant (except as noted in table)

A post hoc analysis was requested of the Applicant by the FDA in order to determine what percentage of patients enrolled had a “need for treatment” in addition to those who were determined to have B-symptoms. B-symptoms are not the only lymphoma-related symptoms that can lead the medical provider to determine that the patient needs treatment. Such symptoms can include pain from lymphadenopathy, significant fatigue, and/or threatened organ dysfunction secondary to bulky disease. In this analysis, the Applicant reported that 69% of patients enrolled had such symptoms that indicated a “need for treatment” determined at enrollment. The FLIPI score was calculated upon enrollment for those with follicular NHL and 71% of these patients (N=62) were rated at intermediate or high risk of relapse.

Table 17 below provides details of this post-hoc analysis of patient baseline characteristics. To be eligible to participate in this study, patients had to have received at least one prior systemic therapy and at least one containing regimen rituximab. All of the patients in the study had received prior rituximab and 99% had received prior chemotherapy. Fifty percent of patients had 2-3 prior chemotherapy regimens. Seventy-two percent of patients had received more than one prior rituximab-containing regimen. It is also important to note that 24% of patients had also received a prior radioimmunotherapy.

Table 17: Prior NHL Treatments of Enrolled Patients (Primary Study)

Baseline Lymphoma History	Bendamustine N=100
Prior Rituximab	100
Number of prior rituximab-containing regimens	
1	28
2	33
3	22
>3	17
Median (Range)	2 (1-6)
Prior radioimmunotherapy	24
Number of prior chemotherapy regimens	
Any	99
1	41
2	36
3	14
>3	8
Median (Range)	2 (0-6)

Reviewer Comment: Given the above demographic and baseline disease characteristic information on the study population, the study population was similar to the population in the

proposed indication sought by the Applicant. The patients in the study appeared to require treatment for their disease.

6.1.4 Patient Disposition (Primary Study)

In the Primary Study 100 patients were treated with single-agent bendamustine at 120 mg/m² IV on Days 1 & 2 of 21-day cycles (up to 8 cycles). Patients received between 1 and 8 cycles of treatment with a mean of 5.3 cycles and a median of 6.0 cycles. Sixty percent of patients received treatment for 6 or more cycles.

Dose reductions occurred per protocol in 24% of the patients; 20% being reduced from 120 mg/m² to 90 mg/m²; and 4% from 120 mg/m² to 90 mg/m² to 60 mg/m².

Patients were discontinued from study drug treatment because they had either received maximum benefit from treatment (52%), had adverse events (28%), had disease progression (11%), refused further treatment (2%), or for other reasons (4%). By the data cut-off date, 97 (97%) patients had end-of-treatment evaluations and 3 (3%) patients had completed study drug treatment but did not have an end-of treatment evaluation.

Median relative dose intensity for this study was 93.8% with a mean of 88.2%.

Table 18: Disposition of Patients (End of Study Treatment)

Patient disposition	Number (%) of patients ^a
Enrolled	102 ^b
Enrolled not treated	2
Primary analysis set	100 (100)
Treated and not completed end-of-treatment evaluation (ongoing extended treatment)	3 (3)
Treated and completed end-of-treatment evaluation ^b	97 (97)
Reason for discontinuation of study drug treatment ^c	
Received maximum benefit of therapy (investigator assessment) ^d	52 (52)
Adverse event	28 (28)
Disease progression	11 (11)
Patient refused further treatment (for reason other than AE)	2 (2)
Other ^e	4 (4)

SOURCE: Summary 15.1, Listing 2.

^a Percentages are based on the number of patients treated (N=100).

^b Includes patients who received treatment for less than 6 cycles (n=40), or 6 or more cycles (n=60).

^c Includes reasons for discontinuation of study drug treatment for patients who received treatment for less than 6 cycles (n=40), 6 cycles (n=39), or more than 6 cycles (n=21).

^d Includes patients who received treatment for 6 cycles or less, or more than 6 cycles, who did not discontinue due to any other reason.

^e Other reasons included delay in therapy for more than 4 weeks, referral for bone marrow transplant or the patient had 8 treatment cycles, the maximum as allowed by the protocol.

AE=adverse event.

NOTE: Data from patient 76065 is included in the database but this patient was never enrolled or treated.

Source: Applicant Clinical Study Report SDX-105-03

Reviewer Comments: The most common reason for discontinuation of treatment was that the patient had received maximum benefit of the therapy (52%). This category includes those patients who received 6 or fewer cycles, or more than 6 cycles, who did not discontinue for any

other reason. Adverse events were the second most frequent reason for discontinuation of treatment at 28% of patients.

6.1.5 Analysis of Co-Primary Endpoints (Primary Study)

The co-primary endpoints of this study were overall response rate (ORR) and duration of response (DR) as determined by the Independent Review Committee. Progression-free survival (PFS) was the secondary efficacy endpoint. PFS is not considered to be interpretable in a single-arm trial due to the lack of a comparator arm and will not be reviewed.

First the primary analyses of RR and DR will be reviewed for the IRC and investigator followed by sensitivity analyses. At the end of the efficacy analysis, exploratory analysis is presented upon this Division's request; in this analysis, the sponsor provided an analysis of lymphoma-related symptoms that would justify the need for treatment.

6.1.5.1 Overall Response Rate Assessment by Independent Review Committee and Investigator (Primary Study)

The submitted efficacy datasets and analyses were audited by review of the raw datasets and (b) (4) (IRC) report. This review identified discrepancies in the best response of two patients. Two patients' best responses were corrected by this reviewer in the final analysis because of these findings. The IRC results in Table 19 below reflect the corrections to the data.

- Patient 65036 was reported in the Applicant's CSR as having a best overall response of a CR; however, review of the (b) (4) report revealed that this patient's overall response was changed to a CRu by the oncologist and this change was not reflected in the Applicant datasets. This patient is reclassified as a CRu in this primary efficacy analysis.
- Patient 24093 was reported in the Applicant's CSR as having a best overall response of a PR; however, review of the (b) (4) report revealed that this patient's overall response was stable disease. The Applicant states that the patient was determined to have a PR two days after the data cutoff date for the application. This patient is counted as having SD in this primary efficacy analysis.

Major Efficacy Results

Table 19: Major Analyses of Efficacy for Primary Study

Efficacy Variable	By IRC (N=100)	By Investigator (N=100)
Overall Response Rate (%) (95% CI) P value	74 (64.3, 82.3) <0.001	80 (70.82, 87.33) <0.001
Complete Response (CR)	13	22
Complete Response Unconfirmed (CRu)	4	5
Partial Response (PR)	57	53

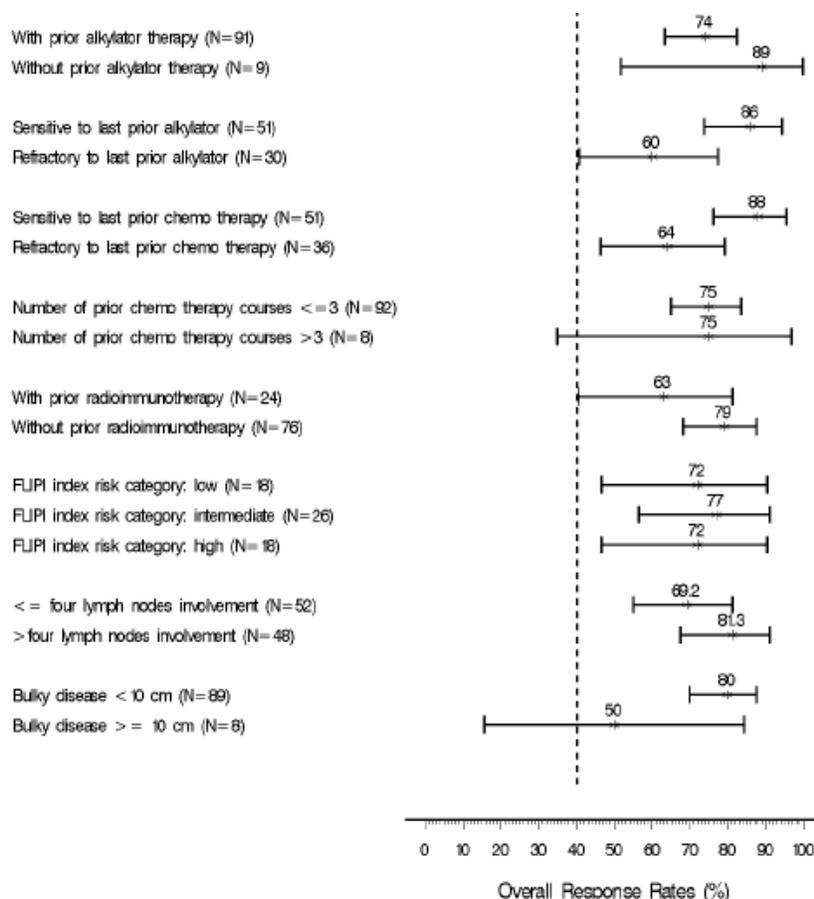
Duration of Response		
Median, months	9.2	9.0
(95% CI)	(7.1, 10.8)	(7.7, 13.8)

Reviewer Comments: The schedule for tumor assessment is adequate to assess the primary efficacy endpoints of response rate and duration of response. The follow-up duration was of sufficient length to capture the duration of response for the participating patients.

The independent review committee results had an 88% concordance rate with the investigator results. IRC reviewers were blinded to the investigator assessments, the members could choose different lymph nodes at baseline to assess response. According to the Applicant, this accounted for the majority of differences between the investigator and IRC assessments. These results are consistent across the evaluable set, sensitivity analyses, and mode of assessment (IRC or investigator). The IRC and investigator assessments are well correlated for overall responder status, with the IRC having more responses evaluated as Partial Responses. There was an 8% difference in CRs between the IRC and Investigator assessments. A similar response rate was seen in all pre-specified subset analyses. The results were statistically greater than the pre-specified protocol defined measures of minimal meaningful efficacy where the null hypothesis specified that less than 40% ORR and less than 17 weeks for DR would not be clinically meaningful.

Reviewer Comments: The independent review provides additional protection from bias. Financial conflicts of interest were assessed among the review committee participants and the results are considered reliable. The efficacy endpoints varied little between the investigator and IRC assessments.

Figure 3: Point Estimates and 95 Percent Confidence Intervals of Overall Response Rate (Independent Review Committee Assessment) by Baseline Characteristics (Primary Analysis Set) for Primary Study



SOURCE: Applicant Clinical Summary of Efficacy

Reviewer Comment: Response rates appeared to be lower in a few subsets of patients. Sixty percent of patients who were refractory to their last alkylating agent experienced an objective response compared with 86% of those who were sensitive to their last alkylating agent. Sixty-four percent of patients who were refractory to their last prior chemotherapy experienced objective response compared with 88% of those who were sensitive to their last prior chemotherapy. Sixty-three percent of patients who had received prior immunotherapy experienced objective responses compared with 79% of those without prior immunotherapy. Patients with bulky disease had a much lower response rate; 50% compared with 80% in those without bulky disease. The bulky disease group was small (n=8) with wide confidence intervals. Overall, most subgroups appeared to have received clinical benefit (in the form of prolonged objective responses) from bendamustine treatment.

FDA Assessment of Overall Response Rate Data

Derived efficacy datasets containing response data were audited by review of CRFs, data line listings, and raw datasets. The FDA assessment below varies slightly from the Applicant's

assessment because this review detected discrepancies for two patients in the derived datasets and the (b) (4) independent assessment of response. These discrepancies are as follows:

- o Patient 65036 was reported as having a CR, but the (b) (4) (Enrollment List for Protocol SDX-105-03) report indicates that the patient response was adjudicated as CRu after review by the oncologist team member (in the comments).
- o Patient 24093 was reported in the datasets as having a PR, but the (b) (4) report indicated that the patient response was Stable Disease (in the Best Radiographic Response column with nothing noted in the comments column).

Clarification was requested of the Applicant for these discrepancies on 07/24/08. The Applicant responded as follows on 07/28/08:

Patient 65036: Based on information we received from (b) (4), this patient underwent an Oncology re-read due to changes in the clinical listings. As a consequence, the Oncology and overall time point responses were changed from CR to CR-u, but unfortunately the database field for the best overall response was not updated accordingly. Therefore, the patient is still treated as a (b) (4) CR in our datasets and in the Cephalon study report.

Patient 24093: We confirmed with (b) (4) that this patient had a PR on 17 July 2007 (Listing 16.2.1 as appended to the CSR). However, 17 July 2007 is two days after the data cut-off date of 15 July 2007 and should therefore have been removed from the dataset. Without this record, the best response is SD.

6.1.5.2 Duration of Response Assessment by Independent Review Committee (Primary Study)

Table 15: Applicant Analysis of Duration of Response in Patients with Objective Response in Rituximab Refractory Set for Primary Study

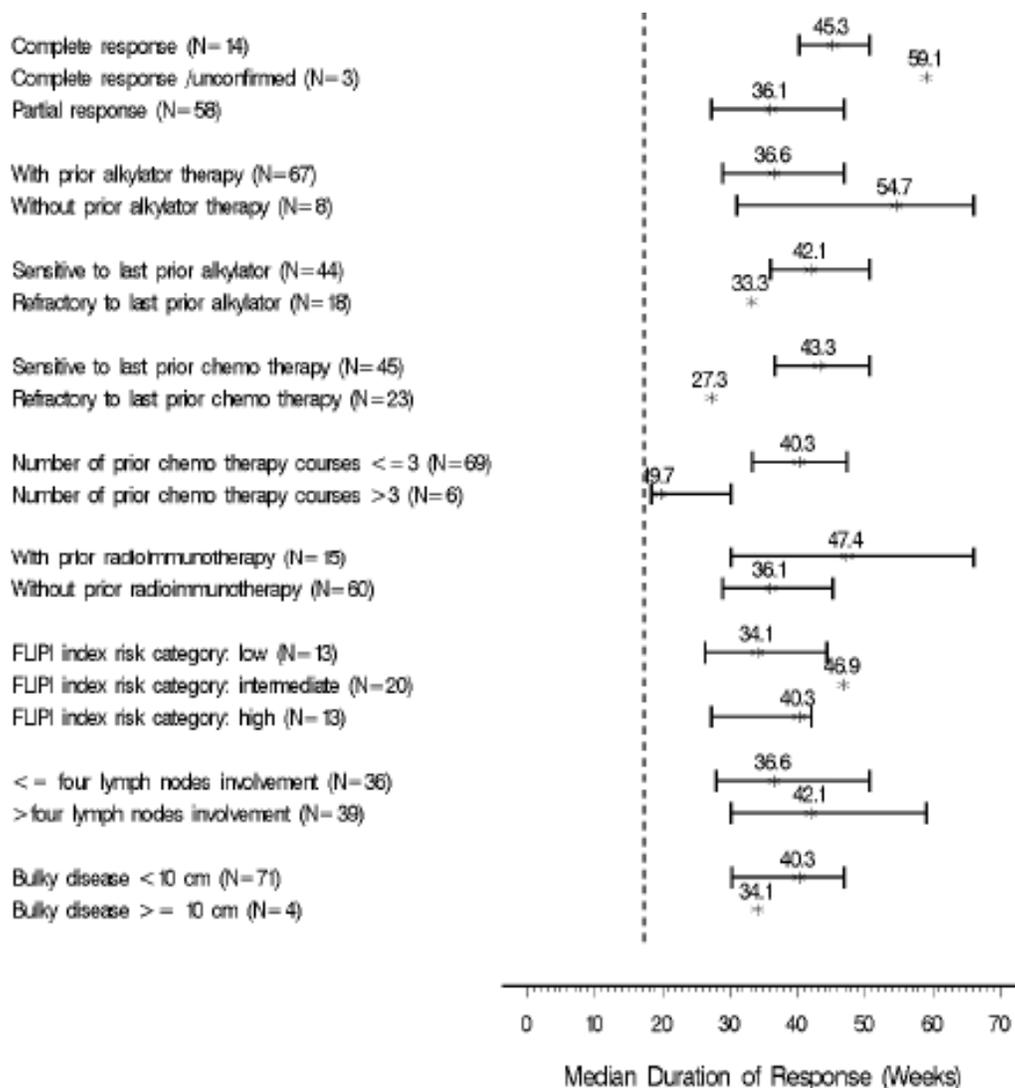
	By IRC Bendamustine (n=72)	By Investigator Bendamustine (N=78)
Number of patients with progressive disease, death, or change in therapy; N (%)	36 (50)	35 (45)
Number of patients censored; N (%)	36 (50)	43 (55)
Quartiles (95% CI) [Weeks]		
25th percentile	26.3 (18.3, 33.3)	28.0 (21.4, 31.9)
50th percentile (Median)	40.3 (31.0,47.4)	40.3 (33.0, NA)
75th percentile	66.1 (45.3, NA)	NA (60.1, NA)

Source: Applicant SCE Summary 15.15.1

Clinical Review, Division of Drug Oncology Products
Virginia Kwitkowski
NDA 22-303 /bendamustine (Treanda)

Reviewer Comment: The Applicant Analysis above was not corrected for the necessary change of patient 24093 from Partial Response to Stable Disease.

Figure 4: Point Estimates and 95 Percent Confidence Intervals of Median Duration of Response (Independent Review Committee Assessment) by Best Response/Baseline Characteristics (Patients in the Primary Analysis Set With Complete, Complete Unconfirmed, or Partial)

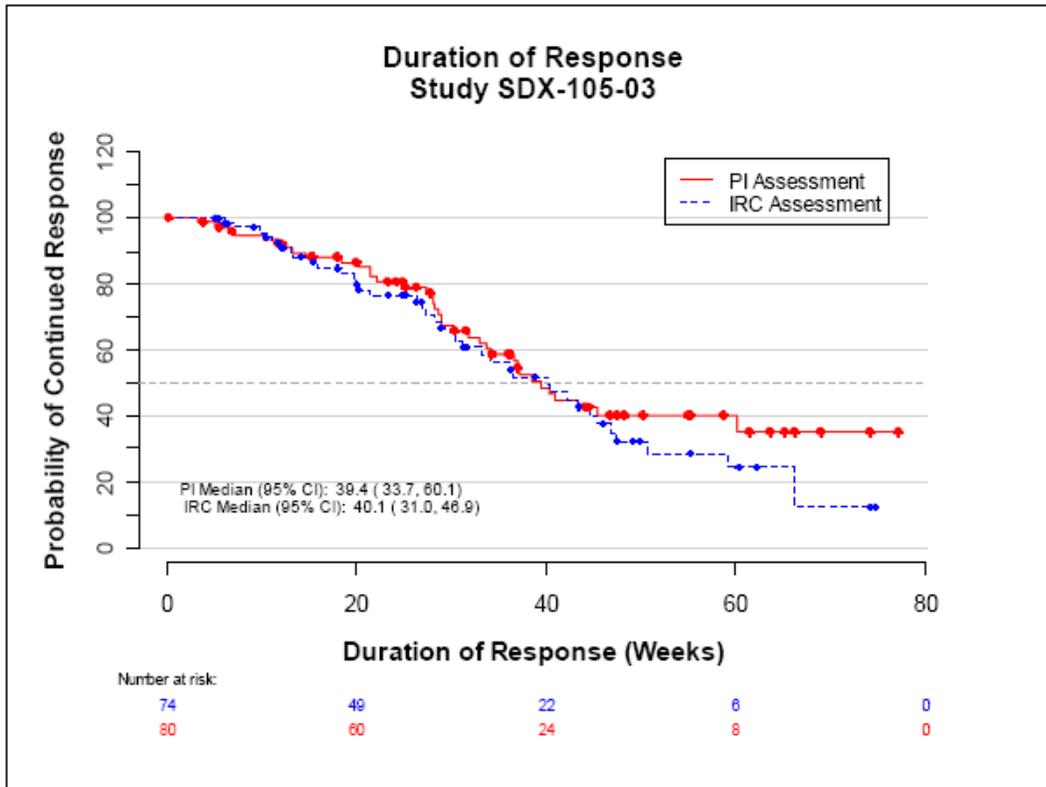


Source: Applicant CSR Study SDX-105-03

Reviewer Comment: Some subsets of patients experienced shorter durations of response. Most subset analyses were uninterpretable due to the small number of patients in each subset and resultant wide confidence intervals. Patients with CR or CRu appear to experience a longer DR (45.3 and 59.1 weeks respectively) than those with PRs (36.1 weeks). However, the subset of patients with CRu was small (N=3). Patients who were refractory to their last prior chemotherapy had a shorter DOR than those who were not refractory to their last prior chemotherapy (27.3 vs. 43.3 weeks). Patients who had received prior radioimmunotherapy experienced a longer DR than those without prior radioimmunotherapy (47.4 vs. 36.1 weeks).

Patients with more than 4 lymph node areas involved experienced a longer DR than those with 4 or less lymph node areas involved (42.1 vs. 36.3 weeks). This is an unexpected finding as it would be expected for patients with less disease involvement to respond for a longer period of time.

Figure 5: Duration of Response, Primary Study (IRC and PI Responders)

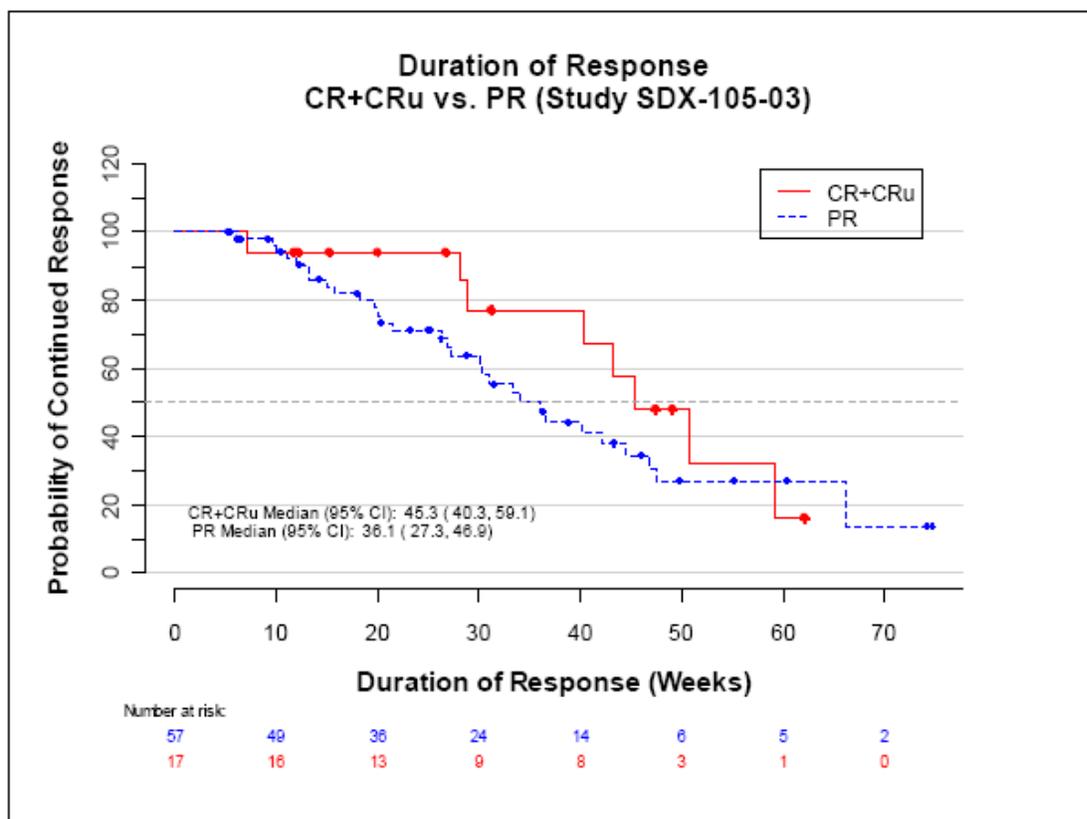


Source: FDA Biostatistician (Chris Holland)

Reviewer Comment: The duration of response was similar in the Primary Study between the Investigator and IRC assessments. The curves began to separate around week 48 when there were less patients on study.

A responder analysis of the duration of response for the Primary Study demonstrated that patients with CR or CRu had a longer duration of response than those with PRs. Figure 6 below demonstrates that relationship.

Figure 6: Duration of Response, CR+CRu vs. PR (Primary Study IRC Responders)



Source: FDA Biostatistician (Chris Holland Ph.D)

Table 20: FDA Analysis of Duration of Response in Primary Study

	Median Duration of Response	95% Confidence Interval
Population N=100 *	9.2 months	[7.1, 10.8]

*Population with corrected response of patients 65036 to CRU and 24093 to SD.

Source: FDA Clinical Biostatistics Reviewer, Chris Holland.

6.1.5.4 Missing Efficacy Data (Primary Study)

Patient 28014 had missing post-baseline imaging studies and was assessed as unevaluable due to these missed assessments. No other missing imaging time points were identified during the review.

6.1.6 Secondary Endpoints (Primary Study)

PFS was the primary secondary efficacy endpoint, which is not considered to be interpretable in a single-arm study. Therefore, results for PFS were not reviewed.

6.1.8 Subpopulations

Post-Hoc Exploratory Analyses

Assessment of “Need to Treat” Population in Primary Study

During the review of this Application, it was noted that only 16% of patients were documented to have B-symptoms within 30 days of starting the trial, and even fewer (9%) had bulky disease that might drive the decision that patients needed re-treatment. This finding brought into question whether or not the patients in the study actually needed treatment for their lymphoma at the time of enrollment.

B-symptoms can justify re-treatment of previously treated patients, but are not the only reasons to restart treatment. Bulky disease can lead to symptoms of pain, obstruction of critical organs, fatigue, edema, and others. Because the proportion of patients in the study who had B-symptoms at baseline was limited, Cephalon was asked by the FDA to assess the CRFs for other lymphoma-related symptoms that would justify the need for treatment. Cephalon was asked to perform a response analysis on patients with a sign or symptom that justified the need for treatment. The results of these analyses are demonstrated below in Table 21. These results are the result of a post-hoc, Agency requested analysis and do not meet the criteria for labeling or advertising because the data cannot be verified by the Agency.

Table 21: Presentation of Post-Hoc FDA-Requested Analysis of Need to Treat Population

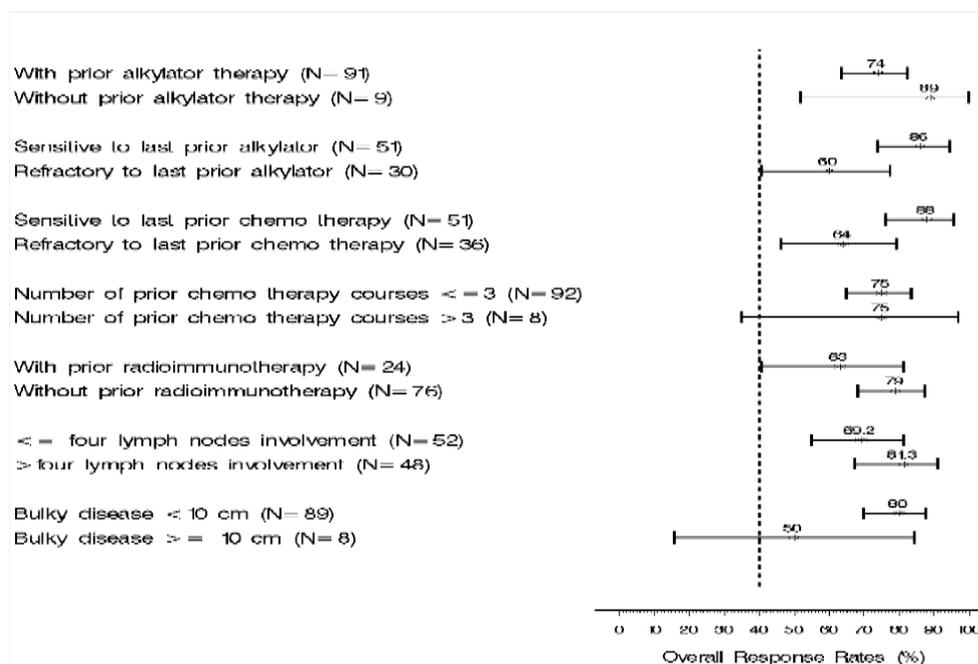
Need to Treat Criteria	Percentage of Patients
B-Symptoms	16%
Bulky lymphadenopathy	9%
Other symptoms: edema, pain from bulky tumors, threatened organ function, worsening cytopenias	69%
Ann Arbor Stage III or IV	76%
FLIPI score ≥ 2 in Follicular NHL	71%

Table 22: Efficacy Results In Need to Treat Population (Primary Study)

Efficacy Endpoint	Endpoint Type	Estimate
ORR	(Co-primary)	72.0%
Duration of Response	(Co-primary)	Median= 8.3 Months

Reviewer Comment: It appears that patients who had a “need to treat” benefitted nearly as much as the overall population of indolent lymphoma patients. Only a 2% response rate decrement and a 4 week decrement in the median duration of response were observed in the “need to treat” population compared to the overall study population. These differences are not clinically important in this indication. The IWG response criteria do not specify that objective responses (CR, CRu, or PR) should be sustained for any specific amount of time. Three of the 14 patients with CR by (b) (4) did not sustain the response for >1 assessment. All three patients with CRu by (b) (4) sustained the response for >1 assessment. Six of 58 patients with PR by (b) (4) did not sustain the response for >1 assessment. This data is captured in the analysis of Duration of Response, a primary objective of the study.

Figure 7: Applicant Subgroup Analyses of “Need to Treat” Post-Hoc Analysis Population



Source: Cephalon Amendment to NDA upon FDA Request

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations (Primary Study)

Both the Primary and Second studies provided bendamustine on the same dose and schedule (120 mg/m² IV over 60 minutes on Days 1 & 2 every 3 weeks). Dose modifications occurred only in the form of dose-delays or dose-reductions. The proposed dose appears both effective and safe in the proposed population.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects (Primary Study)

Persistence of efficacy was established for bendamustine by analysis of the duration of objective response. The duration of response was adequate; 9.2 months for the Primary Study. Tolerance, or a decrease in drug effectiveness over time, is not assessable in a single-arm study because of the lack of a comparator arm. Drug resistance information for bendamustine has not been submitted as part of this NDA.

6.2 Second Study (SDX-105-01; N=76)

Efficacy Results (Second Study)

6.2.1 Study Methods (Second Study)

As described in Section 5.3.1, Study SDX-105-01 does not provide support to the efficacy of bendamustine in the rituximab-refractory indolent NHL population, because the enrolled patients cannot be confirmed to have rituximab-refractory disease. For this reason, only limited data on this study's results will be presented.

6.2.2 Patient Baseline Characteristics and Demographics (Second Study)

The population was reflective of the known demographics for patients who are diagnosed with indolent lymphoma; more common in the 6th decade of life, occurring more frequently in men in a 1.4:1 ratio with women, and more common in Caucasian populations. As is typical for this younger population, performance status was good in nearly all of the patients (93% were 0-1 WHO). All patients had received prior systemic therapy for their lymphoma as the study required that their disease be refractory to rituximab. Forty-six percent had received >1 prior chemotherapy regimen.

Eighty-eight percent of patients in this study were staged as Ann Arbor Stage III or IV at the start of the study. Thirteen percent of patients were experiencing lymphoma B-symptoms (fever, drenching night sweats, or weight loss). The FLIPI score was calculated upon enrollment for those with follicular NHL and 63% of these patients (N=46) were rated at intermediate or high risk of relapse.

Fifteen of the 76 enrolled patients had transformed disease and were removed from the primary efficacy analyses for this reason. The Applicant stated that 10 more patients did not meet the definition as rituximab-refractory (as defined in pre-NDA meetings with FDA). However, because of the lack of collection of dates of disease progression after prior rituximab-regimens, the FDA does not believe that any of the study patients can be confirmed as rituximab-refractory.

Table 23: Patient Demographics, Underlying Disease History, and Prior Treatments of All Treated Patients (Second Study)

Demographic and Disease Characteristics	(N=76)
Age, mean, years (range)	62.7 (38-84)
Sex (M/F %)	54/46
Race (white %)	89
Weight, mean (kg), (range)	81 (44.1, 161.8)
Body surface area, mean (m ²), (range)	1.9 (1.4-2.7)
WHO performance status, n (%)	
0	41 (54)
1	30 (39)
2	5 (7)
3/4	0
Missing	0

Demographic and Disease Characteristics	(N=76)
Number of previous chemotherapy courses	
0	5 (8)
1	28 (46)
>1	28 (46)
Ann Arbor Stage III or IV	67 (88)
B Symptoms at Baseline (Fever 39°, drenching night sweats, >10% wt loss)	10 (13)
FLIPI Score for Follicular NHL Patients	(N=46)
Low Risk	12 (26)
Intermediate Risk	14 (30)
High Risk	15 (33)
Unknown	5 (11)

Source: Reviewer confirmed by review of raw datasets

Reviewer Comments: Given the above demographic information on the study population, most of these patients appeared to need treatment for their lymphoma at the time of enrollment. However, 25 patients could not be considered for the primary analysis of efficacy because of either transformed disease or non-rituximab refractory disease.

6.2.3 Patient Disposition (Second Study)

A total of 77 patients at 12 centers in the US and 2 centers in Canada were considered eligible for enrollment into the study. Forty-three (56%) patients, including the patient who did not receive any treatment, received less than 6 cycles of treatment with bendamustine. For these 43 patients, the reasons for discontinuation of study drug treatment included adverse event (23 [30%] patients), disease progression (14 [18%] patients), and patient or investigator decision (6 [8%] patients). Thirty-four (44%) patients received at least 6 cycles of treatment with bendamustine. For these 34 patients, the reasons for discontinuation of study drug treatment included completion of treatment (21 [27%] patients), adverse event (4 [5%] patients), disease progression (7 [9%] patients), and patient or investigator decision (2 [3%] patients).

Table 24: Applicant Disposition of All Study Patients (Second Study)

Patient disposition	Number (%) of patients ^a
Enrolled	77 (100)
Enrolled, but not treated	1 (1)
Primary analysis set	76 (99)
Evaluable set	64 (83)
Received at least 6 cycles of treatment	34 (44)
Reason for study drug discontinuation for patients receiving at least 6 cycles of treatment	34 (44)
Completed	21 (27)
Adverse event	4 (5)
Disease progression	7 (9)
Patient or investigator decision ^b	2 (3)
Reason for study drug discontinuation for patients not treated with at least 6 cycles of treatment	43 (56)
Adverse event	23 (30)
Disease progression	14 (18)
Patient or investigator decision ^b	6 (8)

^a. Percentages are based on the number of patients enrolled.

^b. Patient or investigator decision. Category includes patients in the consent withdrawn and other category.

Completed=completed 6 treatment cycles.

Source: Study SDX-105-01 Clinical Study Report

6.2.4 Study Protocol Deviation and Violations (Second Study)

For this study, protocol violations were defined as failing to meet the protocol-specific inclusion/exclusion criteria. Violations were to be recorded on the CRF by study center personnel. A protocol exception was granted when an ineligible patient was enrolled and exceptions were also recorded on the CRF.

Reviewer Comment: There are many other situations that should be considered protocol violations. Some examples would include use of an excluded medication or treatment, exception to proper dosing or frequency, or failure to hold drug for toxicity as called for in the protocol. None of these types of events were recorded on the CRFs as violations, so the information provided by the Applicant is not fully assessable for other impacts on the efficacy analysis of the Second Study.

The protocol violations reported by the Applicant are included in Figure 14 below.

Table 25: Individual Patients with Protocol Violations and Exceptions (Second Study; Applicant Provided)

Criteria for violation/exception	Patient number	Exception granted
Inclusion		
Disease refractory to rituximab treatment, given either as a single-agent or in combination	12017	Yes
No more than 3 prior chemotherapy regimens	01002 07044* 33048*	No No Yes
Bidimensionally measurable lesions with at least 1 lesion measuring ≥ 2.0 cm in a single dimension	03016 12033*	Yes No
ANC ≥ 1000 cells/mm ³ , platelet count ≥ 100000 cells/mm ³ , or a >50% marrow involvement with lymphoma	09011 09037	Yes Yes
Adequate hepatic organ function	09028 09041*	Yes Yes
Exclusion		
History of prior radioimmunotherapy	06013	Yes
Receiving concurrent treatment with therapeutic doses of systemic steroids	28062* 09041*	Yes Yes
Concurrent, active malignancy other than the target cancer	12055*	Yes
Received previous chemotherapy or immunotherapy within 3 weeks before entering the study (6 weeks for nitrosoureas or mitomycin) or did not recover from adverse events due to any agents administered previously	09041*	Yes

SOURCE: Listing 4.1 and Listing 4.2.

* Patients who enrolled after protocol amendment 3.

NOTE: Patient 09028 and patient 09037 enrolled after protocol amendment 3 (15 March 2004), but used the case report form from protocol amendment 2.

ANC=absolute neutrophil count.

Source: Applicant Clinical Study Report for SDX-105-01, Section 10.2

Efficacy Results (Second Study)

6.2.5 Analysis of Primary Endpoints (Second Study)

For the efficacy results of this trial, the major analyses were audited on 51 patients who represented the subset of the primary analysis set that did not have transformed disease and were rituximab-refractory (per the Applicant). Per the Applicant Clinical Study Report, dates of disease progression following previous rituximab regimens were not collected in the study. Instead, a convention was utilized by counting the first day of subsequent therapy as the date of progression for the previous regimen. This convention is not adequate for estimating the date of progression because community oncology practitioners may delay restarting treatment until the patient is symptomatic, or recovers from toxicity from previous therapy before starting the next regimen. It is possible that patients may become symptomatic before the measurable disease met the criteria for progression or recurrence. It is equally possible that the measurable disease will meet the criteria for progression or recurrence well before treatment is reinstated because of the lack of symptoms. Therefore, the use of this convention for determining missing progression dates does not meet the regulatory criteria of convincing evidence for the purpose of inclusion in labeling.

The Applicant and FDA analyses of efficacy data for the Second study varies because there were 2 patients (#05034 and #33053) were not refractory to their most recent adequate rituximab regimen and dates for disease progression were not provided for the previous rituximab regimen

where there was no objective response or a TTP of <6 months. For these reasons, these patients were excluded from the primary efficacy analysis of the study.

Table 26: Efficacy Data for Rituximab-Refractory, Indolent NHL Patients Treated (Second Study)

Efficacy Variable	Percent of Patients [95% CI]
Overall Response Rate (CR+CRu+PR)	77 [63.2, 87.5]
Complete Response (CR)	11.5
Complete Response Unconfirmed (CRu)	19.2
Partial Response	46.2
Duration of Response	9.0 months
95% CI	(5.4, 17.2)

Source: Applicant Clinical Study Report Addendum 1, SDX-105-01; Reviewers confirmed data from Applicant Line Listing 19

Reviewer Comments: The results of this study do not provide supportive evidence of the efficacy of TREANDA in a rituximab-refractory, indolent NHL population because of the lack of evidence that the patients were indeed refractory to rituximab.

6.2.6 Analysis of Secondary Efficacy Endpoints (Second Study)

Duration of response was the secondary efficacy endpoint for the Second Study. No independent review panel was used for this study so the results are based upon investigator analysis.

Table 27: Duration of Response in Patients with Rituximab-Refractory, Indolent NHL without Transformed Disease by Investigator Assessment (Second Study) (N=51)

	Median	95% CI	Range
Duration of Response (Weeks)	39.3	26.6, 72.6	9.0, 125.7

Source: Applicant SCE, Summary 15.6.1.2; Reviewer confirmed data by review of line listings in Addendum 1.

Reviewer Comment: PFS was another secondary efficacy endpoint, which is not considered to be interpretable in a single-arm study. Results for PFS will not be reviewed here for that reason.

6.2.8 Subpopulations

The relevant subpopulations were discussed in section 6.2.6 Analysis of the Primary Endpoints because the entire study population was not pertinent to the analysis of efficacy in the indolent, rituximab-refractory NHL population. Those with transformed disease and non-rituximab-refractory disease were excluded from the primary efficacy analysis.

6.2.9 Analysis of Clinical Information Relevant to Dosing Recommendations (Second Study)

The patients in this study received fixed dosing of bendamustine at 120 mg/m² IV on Days 1 & 2 of every 21 day cycle. The only dose modifications allowed were dose delay or reduction. This study provides additional support to the proposed dose and schedule for this indication.

6.2.10 Discussion of Persistence of Efficacy and/or Tolerance Effects (Second Study)

Persistence of efficacy was established for bendamustine by analysis of the duration of objective response. The duration of response was adequate; 9.0 months for the Second Study. Tolerance, or a decrease in drug effectiveness over time, is not assessable in a single-arm study because of the lack of a comparator arm. Drug resistance information for bendamustine has not been submitted as part of this NDA.

6.2.11 Additional Efficacy Issues/ Analyses

None.

7. Integrated Review of Safety

The analysis of the safety of bendamustine in the indolent NHL population was performed by a review of patients from two single-arm studies of bendamustine in patients with indolent lymphoma (Primary Study SDX-105-03 and Second Study SDX-105-01). The total number of patients in these studies is 176. These patients share similar age, gender, and racial characteristics, but differences exist in that 15 of these patients had transformed disease, and that patients in the Second Study could not be confirmed as rituximab-refractory. The patients were similar in the fact that they were previously treated for their lymphoma. Including patients with transformed disease in the safety analysis could lead to an overestimation of adverse reactions for the actual indication population of non-transformed patients. However, an analysis was performed comparing the incidence and severity of adverse reactions between the entire population (N=176) and the non-transformed patients (N=161). The maximum difference between the incidence of individual adverse reactions (all grades and grades 3-4) was 2%. These results indicate that leaving the transformed patients in the overall population did not falsely enhance the adverse reactions reported. Therefore, the safety population for the following analyses contains all patients treated in the two studies (including 15 patients with transformed disease).

Safety Populations

- One-hundred patients from the Primary study (SDX-105-03) who received bendamustine
- Seventy-six patients from the Second study (SDX-105-01) who received bendamustine

The data submitted by the Applicant was reviewed and confirmed by review of datasets, listings and select case report forms. These analyses were compared with the major safety analyses provided by the Applicant and minimal discrepancies in safety analyses were identified.

Summary of Safety Results and Conclusions

The safety of bendamustine at the proposed dose and schedule was assessed by review of two single-arm studies of 176 patients with indolent NHL who were treated at the same dose and schedule. The analyses in this section combine the safety populations from each single-arm study as noted above.

The extent and duration of exposures to bendamustine during the Second study and the Primary study are adequate for the assessment of safety for the intended use in a population with limited available therapies and a life-threatening condition. A total of 483 patients in 10 studies have been treated with bendamustine monotherapy with doses ranging from 60 mg/m² to 280 mg/m². A total of 182 patients with NHL were treated at the recommended dose of 120 mg/m² on days 1 and 2 of 21-day cycles. The dose intensity for these studies was 88%.

The safety review of the two phase 2 trials with single-agent bendamustine indicates that adverse events associated with bendamustine are typical of those seen with other cytotoxic chemotherapies. The main areas of concern with regard to the safety of bendamustine include hematologic toxicity, infections, and gastrointestinal toxicity. No significant cardiac toxicity signals were detected during this review.

Safety Issue Problem List from the Current Label:

- Hematologic Toxicity
 - Anemia
 - Thrombocytopenia
 - Granulocytopenia

These toxicities are assessed by frequent laboratory testing and clinical monitoring for adverse events related to cytopenias.

- Infections
These toxicities are assessed by monitoring of vital signs and symptoms of patients.
- Tumor Lysis Syndrome

This toxicity is assessed by monitoring clinical chemistry during the first few weeks of therapy.

- **Hypersensitivity Reactions**
These reactions are monitored by clinical observation of symptoms and vital signs during and soon after the drug infusion. Reactions have been observed during both the first dose and subsequent doses.
- **Hypertension**
This toxicity is monitored by vital sign determinations during the treatment cycles.
- **Other Cardiac Events**
These toxicities are monitored by vital sign observations, symptom reporting, and clinical diagnostics.
- **Secondary Malignancies**
These toxicities are monitored by radiographic and physical examinations.

Deaths were reported from any cause in 11% of patients on study. Deaths due to adverse event were reported in 3% of patients. This death rate is higher than that seen in the CLL study, but the population in this study received previous treatment for their cancer. The patients in the CLL study of bendamustine vs. chlorambucil were not previously treated and experienced a lower death rate.

Serious adverse events in the NHL population were reported in 37% of the combined safety population. The most frequently reported serious adverse events were febrile neutropenia (5%), pneumonia (5%), dehydration (3%), and anemia (3%).

Adverse events were reported in 100% of the combined safety population. The most frequently reported non-hematologic adverse events ($\geq 20\%$) in the combined safety population were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), pyrexia (34%), constipation (29%), anorexia (23%), cough (22%), and headache (21%). The most frequently reported hematologic adverse events ($\geq 20\%$) were neutropenia (38%), anemia (35%), and thrombocytopenia (31%).

Grade 3 or 4 adverse events were reported in 71% of the combined safety population. The most common non-hematologic Grade 3 or 4 adverse reactions ($\geq 5\%$) were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration, each reported in 5% of patients. The most frequently reported grade 3 or 4 ($\geq 10\%$) hematologic laboratory abnormalities were lymphocytopenia (94%), neutropenia (61%), leukopenia (55%), thrombocytopenia (25%), and anemia (11%).

Pertinent Negatives:

There were no reported cases of *torsades de pointes*

There were no reported cases of drug-induced liver injury.

The safety data submitted has the following limitations:

- Lack of prospectively collected serum magnesium values.
- Lack of ECG results during treatment in order to assess the risk of QT interval prolongation.

Overall, bendamustine has been demonstrated to have an acceptable risk:benefit profile in the treatment of patients with indolent NHL refractory to rituximab. Adverse reactions are very common but appear to be manageable with supportive care and dose modification. These patients should be monitored closely for toxicity so that appropriate dose-reductions can be made in case of dose-limiting toxicities. Toxicities should be managed as clinically appropriate to prevent morbidity from bendamustine. Labeling should be adequate to modify the risks of bendamustine and a REMS is not recommended at this time.

Bendamustine will likely be utilized more frequently than competing products in the indication (Bexxar and Zevalin) because of its relative ease of administration, lack of requirement for radiation dosimetry, and lack of prolonged hematologic toxicity such that is seen with the radioimmunotherapies. No comparative studies have been performed with radioimmunotherapies and bendamustine but a review of the available single-arm data suggests this.

7.1 Methods

The safety review was undertaken by combining the safety populations from the Primary study and Second Study. These populations included all patients in both trials who received at least one dose of bendamustine.

The datasets that were reviewed from this submission include:

Primary Study and Second Study: D_AE.xpt, D_DEM.xpt, D_ADMN.xpt, D_ECGS.xpt, D_LABC.xpt, D_LABH.xpt, D_LABUO.xpt, D_MED.xpt, D_MH.xpt, D_PE.xpt, D_SMED.xpt, D_TERM.xpt, D_VS.xpt, D_WHOPS.xpt.

Selected case report forms were reviewed to assess for discrepancies between CRFs and datasets. No discrepancies were found. High enrolling sites were inspected by DSI with no significant findings pertaining to reporting of adverse events. The Applicant's SCS findings were compared with datasets during the review. No significant variations were found during this audit.

The method for evaluating the safety of the study participants appears acceptable for this population.

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

Table 28: Single-Arm Trials 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
Rituximab-refractory Indolent NHL Primary Study SDX-105-03	US & Canada Single-arm fixed-dose trial	120 mg/m ² D1 & D2 of each 21 day cycle x 6-8 cycles.	100	Most frequent AEs: nausea, fatigue, neutropenia, diarrhea, vomiting, anemia, pyrexia, and thrombocytopenia. MDS and other secondary malignancies reported.
Rituximab-refractory indolent NHL* Second Study SDX-105-01	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, max of 12.	76	Most frequent AEs: nausea, fatigue, vomiting, anemia, diarrhea, pyrexia, cough, neutropenia, constipation, and thrombocytopenia. MDS and other secondary malignancies seen.

*Rituximab-refractoriness could not be confirmed for any patients in the Second Study.

The main differences between the two studies were that cough and constipation were more frequently reported in the Second Study than in the Primary Study.

Estimates provided by the Applicant in the original application, indicate that in the studies reported, 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 ^{(b) (4)} patients were exposed to bendamustine between 01/01/1994-03/31/2007.

7.1.2 Adequacy of Data

Adverse event datasets for the Primary and Second Studies were coded using the MedDRA but no Higher Level Group Terms (HLGTs) were included. These terms are necessary in the review to confirm that these events were properly mapped from the verbatim term to the MedDRA terms. New SAS transport files containing the HLGT were submitted to the NDA on January 17, 2008.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data was pooled across the Primary and Second studies to enhance the precision of the incidence estimates by enlarging the sample size. The pooling of this data is appropriate because the dose and schedule of bendamustine were the same; the patient populations were of similar age, race, and genders; safety monitoring was similar between trials; and all of the patients were previously treated for their lymphoma. There may be some increased adverse reaction incidences among the patients with transformed disease, but the small number (15) of these patients should not provide much impact upon the results. This was confirmed by the previously mentioned comparison of the groups including and excluding transformed patients. In order to pool the data, the numerator events and denominator (N) were combined to reflect an overall incidence within the safety population. This technique was selected because the size of both studies was rather similar.

7.2 Adequacy of Safety Assessments

The studies submitted were well conducted and performed an adequate assessment of the safety of bendamustine in the indolent, NHL population. The safety evaluations were frequent and similar between the studies. The demographic subsets represented a North American population that is appropriate for regulatory consideration in the U.S. Overall, appropriate physical examinations, diagnostic studies, and laboratory evaluations were performed during the conduct of the studies and during follow-up periods so that the results are considered reliable for the assessment of safety. One exception was that serum magnesium was not assessed as a safety laboratory test during this study. No prior serum magnesium assessments were performed during earlier studies of bendamustine so the clinical importance of the assessment of magnesium is unknown.

The drug exposure of both studies was adequate to assure the safety of the proposed dose in this population. The studies were not adequate to assess the risk of QT-interval prolongation with bendamustine use. ECGs were only performed at baseline and at end-of-treatment periods; not at time points during treatment with bendamustine.

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

Data on exposure was provided by the Applicant in the Summary of Clinical Safety, Section 2.7.4.

In the combined study populations from the Primary and Second studies, patients with indolent NHL received between 1 and 9 cycles of bendamustine, with a median of 6 treatment cycles. The mean total dose received was 1168.3 mg/m² (range 240 to 2160 mg/m²) and the median was 1200 mg/m². The mean absolute dose intensity was 70 mg/m²/week, which provides a dose intensity of 88%. Dose reductions were permitted for toxicity and occurred in 25% of patients. For the first 6 treatment cycles, 38% of patients had no dose reductions or cycle delays. Twenty-five percent of patients had dose reductions; 20% of patients had reductions from 120 mg/m² to 90 mg/m², and 5% had dose reductions from 120 mg/m² to 90 mg/m² to 60 mg/m².

The eligibility criteria required that patients have a creatinine clearance of at least 30 mL/min (by Cockcroft Gault) and serum bilirubin of no more than 1.5xULN. However, in the review, two patients were identified that had grade 2 bilirubin at baseline (05089 and 52063; both in the Primary Study). No patients entered the study with a creatinine clearance below 30 mL/min. Overall, the safety population contained few adults with renal or hepatic dysfunction of any grade. This analysis does not provide adequate information on the safety of bendamustine in patients with hepatic or renal insufficiency.

Some patients were enrolled with baseline cardiac dysfunction and pulmonary insufficiency (multiple prior pneumonias and COPD). Some of these patients appeared to rapidly decompensate after starting treatment. One patient with significant cardiomyopathy died from sepsis due to his inability to tolerate the cardiovascular changes associated with sepsis. This analysis does not provide adequate information on the safety of bendamustine in patients with significant cardiac or pulmonary disease, or other significant comorbid conditions.

The proposed dose of 120 mg/m² on days 1 and 2 of each 21 day cycle for NHL is higher than that for the currently approved CLL indication. The Applicant justifies the higher dose in NHL because patients with CLL typically begin treatment with marrow compromise, making a less intense dose regimen appropriate for the CLL population.

Reviewer Comments: The proposed 120 mg/m² dose for rituximab-refractory, indolent lymphoma is justified based upon these two single-arm studies with fixed dose bendamustine. Though the majority of patients required dose reductions or delays, the dose intensity of the regimen was maintained and more than half of the patients were able to receive more than the initially planned 6 cycles. Data on the frequency of dose reductions for the competing products (Bexxar and Zevalin) are not available to this reviewer but was not likely to have been an issue because neither regimen were administered repeatedly.

The extent and duration of exposure to bendamustine during the Primary and Second studies is adequate for the assessment of safety for the intended use in a population with limited available therapies and a life-threatening condition. These single-arm studies are not designed to provide a comparative safety evaluation.

Ten open-label clinical studies have been performed with bendamustine monotherapy, treating a total of 483 patients in doses ranging from 60 mg/m² to 280 mg/m². Among this total number treated, 182 patients with NHL were treated at the recommended dose of 120 mg/m² on days 1 and 2 of 21-day cycles.

Demographics

The demographic information for both study safety populations were presented individually in Section 6.1.3 & 6.2.2. The reader is referred to those sections for demographic information for both studies.

7.2.2 Explorations for Dose Response

Both studies were fixed-dose studies, allowing only for dose-reductions for toxicity. The Applicant performed analyses to assess for correlations between exposure and efficacy or safety measurements in the Primary Study. No cycle 1 exposure measures were found to be statistically significant predictors of responder status using logistic regression. Cumulative measures of exposure were statistically significant predictors of responder status. The significance of the relationship of cumulative measures of exposure to response is deemed, by the Applicant, to be related to the number of cycles completed.

Evaluations were performed to assess for any relationship and the occurrence of fatigue, nausea, vomiting, and neutropenia. Logistic regression analysis confirmed that neither exposure measures nor covariates were statistically significant predictors of the probability of fatigue, vomiting, or neutropenia. Logistic regression analysis did find that cycle 1 C_{MAX} and cycle 1 composite C_{MAX} to be equally statistically significant predictors of the probability of nausea. The use of prophylactic antiemetics in the studies likely explain the discrepancy between the relationship between exposure and these two related adverse reactions.

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical studies were submitted with this application. Non-clinical studies submitted to NDA 22-249 were reviewed previously.

7.2.4 Routine Clinical Testing

In both studies patients underwent physical examination, assessment of adverse events, laboratory studies, and vital sign determinations at baseline, before every cycle, and during each follow-up visit. This frequency is adequate and appropriate for patients with this condition and treatment. It was noted during the review that magnesium values were not assessed during the conduct of this study. ECGs were obtained at baseline and at the end-of treatment visit. This frequency is not adequate to assess for drug-related changes in the QT-interval or other asymptomatic cardiac dysrhythmias. No specific testing was undertaken to assess for changes in cardiac function.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new clinical pharmacology studies were submitted with this application. The existing fund of knowledge regarding the metabolism, clearance, and known drug-drug interactions is summarized in the NDA review for NDA 22249.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Class effects typically seen with alkylating agents include nausea, vomiting, and myelosuppression. These effects were properly evaluated in the Primary and Second studies and were some of the most commonly seen toxicities.

Reviewer Comments: The Applicant's efforts to detect class-specific adverse reactions were adequate for the indication sought. Pre-clinical testing indicated that bendamustine will not likely lead to QT prolongation. The sponsor has not conducted adequate clinical analyses to assess this potential in humans per ICH guidelines. This evaluation has been requested as a post-marketing commitment during the initial approval of bendamustine for CLL (NDA 22249).

7.3 Major Safety Results and Discussion

7.3.1 Deaths

Deaths were reported from any cause in 11% of patients on study in the combined safety population. Seven deaths are believed to be at least possibly related to TREANDA. A narrative for each of these 7 deaths in the Primary Study is presented below, followed by the reviewer assessment of attribution for each death. The deaths that are at least probably related to TREANDA will be presented first, followed by the deaths that could possibly be related to TREANDA. No narrative is provided for the deaths attributable to disease progression. The Applicant narrative for these deaths was reviewed and this reviewer agrees with the attribution.

Deaths in the Primary Study At Least Probably Related to TREANDA

1) Patient **76012** was a 71 year old white male who received one cycle of bendamustine and died on day ^(b)₍₆₎ from pulmonary alveolar hemorrhage concurrent with severe thrombocytopenia. The platelet count on the day of death was Grade 3 at $39 \times 10^9/L$, but the day before death it reached grade 4 at $19 \times 10^9/L$. This patient had a baseline history of pulmonary fibrosis, herpes zoster, AAA, and pneumonia. The patient experienced a rapid decline in health after a single cycle of bendamustine with pneumonia, severe pulmonary fibrosis, myocardial infarction, and multi-system organ failure. He was not neutropenic at the time of death (ANC 2340/ μL). Other concurrent illnesses at the time of death included pulmonary embolism, hypoxia, and multi-organ failure. This death was attributable to bendamustine due to the occurrence of severe thrombocytopenia but is potentially confounded by use of concomitant medications that can cause thrombocytopenia (Vancomycin, Motrin, and Bactrim), and a history of pulmonary fibrosis.

Reviewer Assessment of Attribution: This patient's death is probably attributable to bendamustine because the patient died from a hemorrhagic event after 5 days of grade 3 or worse thrombocytopenia. This death occurred during cycle 1.

2) Patient **04066** was a 71 year old white male who received 5 cycles of TREANDA and died ^(b)₍₆₎ days after the last dose of pneumonia developing in the presence of grade 2 neutropenia. The patient had a significant medical history of large cell carcinoma of the lung (resected in 1999), chronic maxillary sinusitis, pneumonia, and tobacco abuse. The patient experienced a dose delay after cycle 4 for grade 3 neutropenia. No causative pathogen for the pneumonia was ever identified. The investigator considered the events of neutropenia and pneumonia as possibly

related, the event of sepsis as probably related, and the event of pyrexia as definitely related to TREANDA.

Reviewer Assessment of Attribution: This death is probably related to TREANDA because the drug-induced myelosuppression put him at increased risk for life-threatening infection.

3) Patient **62046** was an 82 year-old white male who died ^(b)₍₆₎ days after the last dose of TREANDA from cytomegalovirus (CMV) infection. An assessment of the patient's hematologic laboratory status at the time of infection could not be confirmed because the last hematologic laboratory results available are from 10/11/06 and the patient died on ^(b)₍₆₎. However, the most recent laboratory results available, indicated that the patient was lymphopenic. The patient received 6 cycles of TREANDA. On Cycle 6, Day 55, the patient experienced a grade 3 CMV pulmonary infection with a low ANC per investigator but normal ANC per medical monitor. The patient subsequently received azithromycin, ceftriaxone, trimethoprim sulfa, methylprednisolone, ganciclovir, fluconazole, valganciclovir, ciprofloxacin, and piperacillin/tazobactam for the CMV infection. The patient experienced grade 3 anemia, tachycardia, grade 4 respiratory arrest, grade 2 hypotension, grade 2 pneumothorax, and oral Candidiasis. There was a progressive deterioration in health which resulted in death 18 days after the onset of CMV pneumonia. Autopsy results confirmed a diagnosis of CMV and respiratory failure.

Reviewer Assessment of Attribution: This death is probably related to TREANDA because it is secondary to an opportunistic infection in the setting of drug-related myelosuppression.

Reviewer Comments: There were three deaths in the Primary Study (3%) that were at least probably related to treatment with TREANDA. Only one of these three patients died within 30 days of their last dose of TREANDA. These deaths were related to myelosuppression which is frequently observed after treatment with TREANDA. Though this rate is higher than that seen in the CLL study, it is important to note that patients in the NHL study were previously treated with agents that can lead to myelosuppression, as compared with the CLL patients who were treatment-naïve.

Deaths in the Primary Study At Least Possibly Related to TREANDA

The following four patients died from events that could possibly be related to TREANDA and were not thought to be due to progression of the underlying NHL.

4) Patient **11076** was an 82 year old white female who died on day ^(b)₍₆₎ due to cardiopulmonary arrest. This patient entered the study with a past medical history of hypertension, congestive heart failure, tachycardia, bilateral pleural effusions, shortness of breath, and fatigue. Baseline medications included nisoldipine (for CHF). On Cycle 1, Day 2 the patient had adverse events of grade 2 peripheral edema and dyspnea exacerbation for which she received furosemide. On Day 3 a left lung thoracentesis was performed to relieve a pleural effusion. Cytology was negative for lymphoma in the fluid. The dyspnea exacerbation resolved on day 24. She died on Cycle 1, day ^(b)₍₆₎ of cardiorespiratory arrest. The patient refused further treatment after cycle 1.

Reviewer Assessment of Attribution: This death is possibly related to the drug but is most likely related to an exacerbation of baseline medical diagnoses (CHF and pleural effusions).

5) Patient **14090** was a 66 year old male who died from sepsis (b) (6) days after the last dose (b) (6) days after first dose). According to the Cephalon medical monitor, this patient developed a bacterial lung infection on day 78 (Cycle 4 Day 8) in the presence of a normal WBC and ANC. This patient's care was complicated by a history of diabetes and cardiomyopathy (which can be exacerbated during sepsis thus hindering the necessary physiological response to the cardiovascular changes associated with sepsis). Possibly confounding concomitant medications include prednisone 20 mg daily (prescribed for asthma) and inhaled steroids which can both suppress immune function and heighten the risk of infection. The inhaled steroids had been in use for more than a year and the patient had been on daily prednisone for over a month before death. This death is attributable to bendamustine but the pre-existing cardiomyopathy, steroid use, and diabetes mellitus clearly increased his risk of death from sepsis.

Reviewer Assessment of Attribution: This death was possibly related to study drug, but because there was not neutropenia or leukopenia, the baseline conditions and concomitant medications likely played a larger role in this patient's overall immune suppression.

6) Patient **21082** was a 67 year old male who died at day (b) (6) of therapy (b) (6) days after the last dose) from COPD exacerbation and pneumonia. This patient had a history of recurrent pneumonia, COPD, and hypogammaglobulinemia. He was not neutropenic at the time of pneumonia. Hypogammaglobulinemia can inhibit immune response to infectious disease. Potentially confounding concomitant medications included Advair inhaler (salmeterol and fluticasone), prednisone, and nasal fluticasone. Advair has a labeled warning about increased risk of COPD-related death compared with placebo. Steroids (prednisone and fluticasone) have class risks of increased infection incidence. This death is potentially confounded due to the patient's history of COPD, recurrent pneumonia, hypogammaglobulinemia, and concomitant medications of Advair and multiple systemic and inhaled steroids.

Reviewer Assessment of Attribution: This death is possibly related to study drug. This patient had baseline medical conditions (COPD, recurrent pneumonia, and hypogammaglobulinemia) and concomitant medication use (steroids both systemic and inhaled) that predispose him to serious infection.

7) Patient **76-068** was a 63 year old female who died (b) (6) days after her last dose of TREANDA of respiratory failure. This patient entered the study with a history of an antibiotic-resistant infection (Methicillin-Resistant Staphylococcus Aureus), baseline pleural effusions, and shortness of breath. The patient withdrew from treatment after 5 cycles with a documented partial response to treatment. No other serious adverse event (other than fatigue) was ongoing at the time of death.

Reviewer Assessment of Attribution: This death is possibly related to study drug. She did not have documented leukopenia or neutropenia at the time of her death. This patient had baseline

shortness of breath and pleural effusions that may have placed her at increased risk of respiratory failure.

There were four deaths that were believed to be secondary to progression of the underlying NHL. These patient numbers were: 09-004, 10-011, 28-014, and 72-074. The patient narratives were reviewed for these patients and this reviewer agrees with the attribution of not related to TREANDA.

This drug-related death rate of 3% is higher than the previously reported rate of 0% from the pivotal study of bendamustine in CLL (02CLLIII). Of note, the dose used in study SDX-105-03 was 20 mg higher than in the CLL study and the patients in the CLL study were not previously treated for their malignancy. The study population in SDX-105-03 was pre-treated with alkylating agents and monoclonal antibodies. In the CLL study only one patient died within 30 days of the last day of study drug due to an adverse event. This patient appeared to have died due to exacerbation of underlying baseline COPD, and was thus not attributable to the study drug. All three cases of patients who died due to adverse reactions at least possibly related to study drug in study SDX-105-03 were confounded by pre-existing conditions and concomitant medications. There are no non-confounded cases of death within 30 days of study drug. Myelosuppression is a frequent and severe toxicity of TREANDA and fatal outcomes have been observed. No new safety signal was detected in the review of deaths on study for Study SDX-105-03.

Table 29: Summary of Death Narratives (Primary Study)

Patient ID # Age/Gender	Cause of Death	Day of Death Relative to First Dose of Bendamustine	Investigator Attribution	Medical Monitor Attribution	FDA Comments
04-066 71/M	Respiratory Failure secondary to pneumonia in a setting of neutropenia	144 (b) (6) days after last dose)	Probably	Probably	Risk factors include tobacco abuse, prior lung cancer, prior pneumonia
09-004 41/F	NHL (symptomatic deterioration)	46 (b) (6) days after last dose)	Unrelated	Unrelated	Patient symptomatic at baseline
10-011 75/F	NHL	175 (b) (6) days after last dose)	Unrelated	Unrelated	Serious infusion reaction at Cycle 2
11-076 82/F	Cardiorespiratory Arrest	34 (b) (6) days after the last dose)	Unrelated	Unrelated	H/O CHF, pleural effusion (non-malig)
14-090 66/M	Sepsis, cardiomyopathy	102 (b) (6) days after the last dose)	Probably related	Probably related	Developed bacterial lung infection on Cycle 4, Day 8 with

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 Virginia Kwitkowski
 NDA 22-303 /bendamustine (Treanda)

Patient ID # Age/Gender	Cause of Death	Day of Death Relative to First Dose of Bendamustine	Investigator Attribution	Medical Monitor Attribution	FDA Comments
					normal ANC and WBC. H/O Cardiomyopathy, CHF, DVT, HTN, Asthma, crack cocaine/alcohol addictions, DM. Partial response to bendamustine obtained.
21-082 67/M	COPD exacerbation	112 (b) (6) days after last study drug)	Unlikely	Possibly	Baseline COPD, recurrent pneumonia; normal ANC at time of pneumonia diagnosis
28-014 64/M	Progression of NHL	483 (b) (6) days after last dose)	Unrelated	Unrelated	Rec'd one cycle; removed for Grade 3 persistent thrombocytopenia; progressed on D359.
62-046 82/M	CMV Pneumonitis and Respiratory Failure	194 (b) (6) days after last dose)	Definitely	Definitely	Rec'd 6 cycles.
72-074 65/F	Unknown	188 (b) (6) days after last dose)	Unlikely	Unlikely	Died one month after disease progression (new ascites and pleural effusions).
76-012 71/M	Pulmonary Alveolar Hemorrhage	15 (b) (6) days after last dose)	Definitely	Definitely	H/O pulmonary fibrosis; grade 3 thrombocytopenia concurrent.
76-068 63/F	Respiratory failure	137 (b) (6) days after last dose)	Possibly	Possibly	Baseline H/O MRSA, bilateral pleural effusion, and shortness of breath

Deaths in the Second Study

Deaths in this study were not as crucial to the overall safety review. They can be found in Appendix A.

Reviewer Comments: Eight patient deaths were reported during this study; 3 patients had adverse events leading to death and 5 patients died due to disease progression. The adverse events that led to the three deaths that were at least possibly due to bendamustine were Myelodysplastic syndrome (MDS), acute renal failure, and Chronic Myelogenous Leukemia (CML). All of these patients had prior treatment for their lymphoma and were at risk for secondary malignancies independent of bendamustine, though a relationship to bendamustine cannot be ruled out. These Adverse Reaction-related deaths do not raise new safety issues for bendamustine.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were reported in sixty-five (37%) of the combined safety population. The most frequently reported serious adverse events were febrile neutropenia (5%), pneumonia (5%), dehydration (3%), and anemia (3%).

Serious Adverse Events (SAEs) in the Primary Study

Thirty-nine (39%) of patients in the Primary Study were reported to experience a serious adverse event. The most frequently occurring SAEs were related to infection (febrile neutropenia and pneumonia) in 6 and 5 patients respectively. These effects are known effects of cytotoxic therapies and are typically reversible and managed with appropriate supportive care. Adverse events leading to study drug discontinuation occurred in 31 (31%) of patients with the most frequently reported event being thrombocytopenia (9%), fatigue (6%), and neutropenia (4%).

Table 30: Serious Adverse Events Reported (Primary Study)

Serious Adverse Event	Number/Percent (N=100)
FEBRILE NEUTROPENIA	6
PNEUMONIA	5
DIARRHEA	4
MYOCARDIAL INFARCTION	3
VOMITING	3
DEHYDRATION	3
NEUTROPENIA	2
NAUSEA	2
STOMATITIS	2
ASTHENIA	2
FATIGUE	2

Serious Adverse Event	Number/Percent (N=100)
PYREXIA	2
CYTOMEGALOVIRUS INFECTION	2
HERPES ZOSTER	2
INFECTION	2
LUNG INFECTION	2
URINARY TRACT INFECTION	2
TUMOR LYSIS SYNDROME	2
NEUROPATHY	2
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	2
PULMONARY EMBOLISM	2
RESPIRATORY FAILURE	2
ACUTE MYELOID LEUKEMIA	1
ACUTE RESPIRATORY DISTRESS SYNDROME	1

*SAEs that were clearly not related to Treanda (progression of NHL) were not included in the above table because they are not clinically important to the safety profile of the drug.

Source: Reviewer generated from Applicant Raw Datasets for Study SDX-105-03 AND 4MSU

Serious Adverse Events and Withdrawals in the Second Study

Twenty-six patients (34%) had 1 or more other serious adverse events during this study. The most common serious adverse events (those occurring in 4% or more patients overall) were anemia (5%), and febrile neutropenia, pneumonia, and dehydration (occurring in 4% of patients each). A total of 30 (39%) patients withdrew from the study and the primary reason was adverse events in 27 patients and disease progression in 3 patients. The most frequent adverse events causing withdrawal from study drug treatment were thrombocytopenia (17%), neutropenia (7%), and anemia (3%).

Severe Adverse Events in the Second Study

Forty-nine (64%) of the patients in the safety population had at least 1 grade 3 or 4 adverse event. Twenty-eight (37%) of the population experienced hematologic grade 3 or 4 adverse events. Thirty-nine (51%) of the population experienced non-hematologic grade 3 or 4 adverse events. The most frequently occurring grade 3 or 4 non-hematologic adverse events were fatigue in 6 patients (8%) and pneumonia in 4 patients (5%). Twelve (16%) patients had grade 3 or 4 infections and pneumonia was the most common event in this category (5%). The most frequently occurring grade 3 or 4 hematologic adverse events were neutropenia in 24 (32%), thrombocytopenia in 12 (16%), anemia in 8 (11%), and febrile neutropenia in 5 (7%).

Reviewer Comments: Severe (grade 3 and 4) adverse events are often more clinically meaningful to providers because they frequently lead to dose-delays or reductions. The severe adverse events that occurred are expected with a cytotoxic agent used in patients with NHL. The safety profile of bendamustine was similar between the studies. The Second Study did report

more constipation and cough than the Primary Study. No new safety signals for bendamustine were noted in this review of serious adverse events.

7.3.3 Dropouts and/or Discontinuations

Narratives and CRFs were provided by the Applicant for all dropouts/withdrawals. A total of 51 (29%) of patients in the combined safety population withdrew from the studies before completing 6 cycles of treatment due to adverse events. The most frequent causes for withdrawal were thrombocytopenia, fatigue, and neutropenia. Follow-up of the patients who withdrew continued until they developed disease progression or started another anti-cancer therapy. This follow-up is adequate to assess the occurrence and duration of adverse events.

No particular pattern was noted for time-dependency, drug-drug interactions, or drug-demographic interactions of the dropouts.

7.3.4 Significant Adverse Events

Hematologic toxicity is an expected effect of cytotoxic chemotherapy because it damages rapidly dividing cells. Significant hematologic adverse reactions were seen in both studies, with the need for transfusion support being common.

Adverse events that led to dropouts most frequently were thrombocytopenia, fatigue, and neutropenia. These are expected toxicities of alkylating agents. Oncologists are aware of these class effects and they can be appropriately monitored on an outpatient basis.

Myelosuppression: Neutropenia, leukopenia, thrombocytopenia, and anemia occurred frequently with bendamustine. These events were captured via complete blood counts with differential. These adverse reactions may lead to serious and life-threatening infections and hemorrhage in this population which already has an increased risk of infection from the disease NHL and previous cancer treatments. Infections were captured by notations of increased temperature, symptoms of localized infection, radiological studies, and microbiological laboratory test results.

Infections: Infections, typically related to myelosuppression, including pneumonia and sepsis, have been reported in patients in bendamustine clinical studies and in postmarketing reports. In rare cases, infection has been associated with hospitalization, septic shock, and death. Six percent of patients in the combined safety population experienced febrile neutropenia and 19% experienced at least one infection. Patients with neutropenia and/or lymphopenia following treatment with bendamustine are more susceptible to infections. Patients with myelosuppression following bendamustine treatment should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms. The use of granulocyte growth factors for the prevention of chemotherapy-induced neutropenia may be used, which may reduce the risk of infection.

Tumor Lysis Syndrome: Two cases of grade 3 or 4 tumor lysis syndrome were reported in the combined safety population. Both patients (70050 & 76068) were enrolled into the Primary Study and neither patient experienced renal insufficiency or death related to this adverse

reaction. Patient 76068 experienced a grade 4 elevated serum creatinine on day 14 of bendamustine treatment. This patient was also experiencing significant elevations in BUN and uric acid. Allopurinol was begun on day 13 for “tumor lysis syndrome”. This case of elevated serum creatinine is likely related to tumor lysis syndrome. The creatinine returned to grade 0 four days later with institution of treatment for tumor lysis syndrome. Tumor lysis was also reported in the CLL study. The onset tends to be within 48 hours of the first dose of bendamustine and, without intervention, may lead to acute renal failure and death. Tumor lysis syndrome was detected by laboratory analysis of serum uric acid, phosphorus, potassium, calcium, creatinine, and BUN.

Hypersensitivity Reactions: Patients receiving TREANDA should be observed closely for symptoms of infusion reactions. Reactions suggestive of infusion reactions to bendamustine have occurred commonly in clinical studies. Symptoms are generally mild and include fever, chills, pruritis, and rash. Hypersensitivity reactions were more common in the second and subsequent cycles of therapy. Thirty-five patients (20%) had events consistent with infusion reactions during both studies. There were five (3%) grade 3-4 events of hypersensitivity in the combined safety population. These events are typically considered anaphylactoid. Most of the hypersensitivity reactions appeared to be dermatologic in nature. Hypersensitivity reactions were more common in the second and subsequent cycles of therapy. The lower grade (1 & 2) reactions were improved with the use of systemic antihistamines and both topical and systemic corticosteroids. No patients with grade 3 allergic or hypersensitivity reaction were rechallenged with bendamustine. Most patients with significant rash discontinued therapy. No deaths resulted from hypersensitivity reactions to bendamustine in the combined safety population.

Hypertension: Patients receiving bendamustine should be observed for the development of hypertension. In the CLL study, hypertensive events were more commonly observed in the bendamustine treatment group patients than in the chlorambucil patients. In this combined safety population, a trend was also observed in reviewing the vital sign evaluations for these patients. Hypertension of all grades occurred in 21 patients; however there was only 1 grade 4 and no grade 3 events.

Other Cardiac Events: Cardiac-related events were reported in 27 (15%) patients in the combined safety population. Grade 3 or 4 cardiac disorders were reported in 9 patients. All but one of these patients had a previous history of cardiac disorders. The most common cardiac-related events were tachycardia in 13 (7%) patients and palpitations in 4 (2%) patients.

Secondary Malignancies: Five (3%) patients in the combined safety population were reported as developing new malignancies after treatment with bendamustine. The patients in the Primary study had myelodysplastic syndrome and squamous cell carcinoma. Two patients in the Second study had MDS and 1 patient had CMML. All patients had received prior therapies that have been associated with secondary malignancies.

7.3.5 Submission Specific Primary Safety Concerns

No new submission-specific safety concerns were identified during this review.

7.4 Safety Results and Discussion

The analyses of adverse reactions were performed by combining the safety populations of the Second study and the Primary Study. The total number of patients in this combined safety population is 176.

7.4.1 Common Adverse Reactions

The analyses below combine the safety populations from each single-arm study as noted above.

Adverse events were reported in 100% of the combined safety population. The most frequently reported non-hematologic adverse events ($\geq 20\%$) in the combined safety population were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), pyrexia (34%), constipation (29%), anorexia (23%), cough (22%), and headache 21%). The most frequently reported hematologic adverse events ($\geq 20\%$) were neutropenia (38%), anemia (36%), and thrombocytopenia (31%).

Grade 3 or 4 adverse events were reported in 71% of the combined safety population. The most frequently reported ($\geq 5\%$) non-hematologic grade 3 or 4 adverse events were fatigue (11%), febrile neutropenia (6%), and hypokalemia, pneumonia, and dehydration (each 5%). The most frequently reported ($\geq 10\%$) hematologic adverse events were neutropenia (38%), anemia (35%), thrombocytopenia (31%), and leukopenia (10%).

Table 31: Adverse Reactions in the Combined Safety Population $\geq 5\%$ (N=176)

Preferred Term (MedDRA)	All Grades N	All Grades %	Grades 3-4 N	Grades 3-4 %
Nausea	132.0	75.0	7.0	4.0
Fatigue	101.0	57.4	19.0	10.8
Vomiting	71.0	40.3	5.0	2.8
Neutropenia	66.0	37.5	59.0	33.5
Diarrhea	65.0	36.9	6.0	3.4
Anemia	62.0	35.2	17.0	9.7
Pyrexia	59.0	33.5	3.0	1.7
Thrombocytopenia	55.0	31.3	27.0	15.3
Constipation	51.0	29.0	1.0	0.6
Anorexia	40.0	22.7	3.0	1.7
Cough	38.0	21.6	1.0	0.6
Headache	36.0	20.5	0.0	0.0
Weight Decreased	31.0	17.6	3.0	1.7
Dyspnea	28.0	15.9	3.0	1.7
Rash	28.0	15.9	1.0	0.6
Stomatitis	27.0	15.3	1.0	0.6
Back Pain	25.0	14.2	5.0	2.8

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Preferred Term (MedDRA)	All Grades N	All Grades %	Grades 3-4 N	Grades 3-4 %
Dizziness	25.0	14.2	0.0	0.0
Chills	24.0	13.6	0.0	0.0
Dehydration	24.0	13.6	8.0	4.5
Edema Peripheral	23.0	13.1	1.0	0.6
Insomnia	23.0	13.1	0.0	0.0
Abdominal Pain	22.0	12.5	2.0	1.1
Decreased Appetite	22.0	12.5	1.0	0.6
Dyspepsia	20.0	11.4	0.0	0.0
Asthenia	19.0	10.8	4.0	2.3
Leukopenia	18.0	10.2	14.0	8.0
Gastroesophageal Reflux Disease	18.0	10.2	0.0	0.0
Herpes Zoster	18.0	10.2	5.0	2.8
Upper Respiratory Tract Infection	18.0	10.2	0.0	0.0
Urinary Tract Infection	17.0	9.7	4.0	2.3
Dry Mouth	15.0	8.5	1.0	0.6
Sinusitis	15.0	8.5	0.0	0.0
Hypokalemia	15.0	8.5	9.0	5.1
Pneumonia	14.0	8.0	9.0	5.1
Anxiety	14.0	8.0	1.0	0.6
Pharyngolaryngeal Pain	14.0	8.0	1.0	0.6
Tachycardia	13.0	7.4	0.0	0.0
Dysgeusia	13.0	7.4	0.0	0.0
Febrile Neutropenia	11.0	6.3	11.0	6.3
Chest Pain	11.0	6.3	1.0	0.6
Infusion Site Pain	11.0	6.3	0.0	0.0
Nasopharyngitis	11.0	6.3	0.0	0.0
Oral Candidiasis	11.0	6.3	2.0	1.1
Arthralgia	11.0	6.3	0.0	0.0
Pruritis	11.0	6.3	0.0	0.0
Pain	10.0	5.7	0.0	0.0
Depression	10.0	5.7	0.0	0.0
Hypotension	10.0	5.7	2.0	1.1
Dry Skin	9.0	5.1	0.0	0.0
Night Sweats	9.0	5.1	0.0	0.0
Abdominal Distention	8.0	4.5	0.0	0.0
Abdominal Pain Upper	8.0	4.5	0.0	0.0
Catheter Site Pain	8.0	4.5	0.0	0.0
Bone Pain	8.0	4.5	0.0	0.0
Pain in Extremity	8.0	4.5	2.0	1.1
Nasal Congestion	8.0	4.5	0.0	0.0

Preferred Term (MedDRA)	All Grades N	All Grades %	Grades 3-4 N	Grades 3-4 %
Wheezing	8.0	4.5	0.0	0.0
Hyperhidrosis	8.0	4.5	0.0	0.0

Source: Reviewer Assessment of Adverse Event Datasets

The safety review of the two phase 2 trials with single-agent bendamustine indicates that adverse events associated with bendamustine are typical of those seen with other cytotoxic chemotherapies. The main areas of concern with regard to the safety of bendamustine include hematologic toxicity, infections, and gastrointestinal toxicity. No significant cardiac toxicity signals were detected during this review.

Less Common Adverse Events in the Combined Safety Population

Adverse reactions with a 10% or higher incidence were reported in Section 7.4.1. Myocardial infarction was reported in 1% (2 cases) of patients in the combined safety population. Cardio-respiratory arrest occurred in 1 patient.

Unilateral deafness and hearing impairment occurred in one patient each.

Three patients (2%) were reported to experience an adverse event related to visual impairment (vision blurred, decreased visual acuity, and visual disturbance).

Two cases each of mental impairment and memory impairment were reported (a total of 2%).

7.4.2 Laboratory Findings

The laboratory datasets were reviewed and analyzed for both studies. The results are combined in Table 32 below. Hematologic laboratory abnormalities were quite common as expected with a cytotoxic agent. A significant percentage of the hematologic laboratory abnormalities were of Grade 3-4 severity. Chemistry laboratory abnormalities were also frequent but were mostly of low severity. Grade 3-4 chemistry abnormalities were infrequent.

Reviewer Comment: Serum magnesium was not prospectively collected in either study. The magnesium results were not in the datasets. The results may have been collected by investigators because of a clinical condition that warranted its evaluation. Because it was not prospectively assessed, the effect of bendamustine on serum magnesium cannot be evaluated.

Table 32: Hematology Laboratory Abnormalities in Combined Safety Population

Laboratory Abnormality	All Grades %	Grade 3%	Grade 4 %
Low ALC	99	24	70
Low WBC	94	45	10

Low Hemoglobin	94	9	2
Low Platelets	86	18	7
Low ANC	86	35	24

Source: Reviewer confirmed Applicant provided laboratory datasets LAB_H

Table 33: New or Worsening Laboratory Chemistry Abnormalities Data from the Combined Studies

Laboratory Result	All Grades %	Grades 3/4 %
Creatinine (µmol/L)	18	2
Albumin (g/L)	34	1
SGOT (AST) (u/L)	26	<1
SGPT (ALT) (u/L)	18	0
Alkaline Phosphatase (u/L)	16	0
Total bilirubin (µmol/L)	15	0
Carbon Dioxide (mmol/L)	10	0
Sodium (mmol/L) Low Values	21	2
Sodium (mmol/L) High Values	10	0
Potassium (mmol/L) Low Values	26	5
Potassium (mmol/L) High Values	12	2
Glucose (mmol/L) Low Values	9	0
Glucose (mmol/L) High Values	42	3
Calcium (mmol/L) Low Values	30	2
Calcium (mmol/L) High Values	5	1

Source: Reviewer Confirmed Applicant Chemistry Laboratory Datasets (LAB_C)

Reviewer Comments: The clinical significance of high glucose values in this analysis is unknown because the laboratory samples were not prospectively collected as fasting samples. Low serum albumin is also not clinically significant because it is common in patients with cancer and while undergoing cancer treatment due to anorexia and vomiting. Carbon dioxide has limited clinical importance in a cancer treatment population. TREANDA's impact on serum potassium is not clearly demonstrated in these single-arm studies because both abnormalities occurred, with somewhat more patients experiencing hypokalemia. This may be impacted by the use of potassium-wasting diuretics to treat the peripheral edema that can occur with TREANDA. It is also unclear as to how or whether TREANDA impacts serum calcium.

Overview of laboratory testing in the development program

In the Second Study, clinical chemistries were performed at baseline, weekly x3, then once per cycle, and at the end-of-treatment visit. In the Primary Study clinical chemistries were obtained with less frequency: at baseline, once per cycle for cycles 1-8, and at end-of treatment visit. Clinical chemistries in both studies included sodium, potassium, chloride, carbon dioxide, glucose, BUN, creatinine, AST, ALT, Alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, calcium, and LDH. Serum magnesium and urinalysis were not prospectively performed in either study.

In the Second Study clinical hematology labs consisted of CBC with differential and platelet count and were obtained at baseline, weekly x3, then per cycle and at end of treatment visit. In the Primary study, clinical hematology labs were the same but were assessed at baseline, weekly throughout the treatment period, and at the end of treatment visit.

Table 34: Range of Number of Patients Per Week with Missing Hematology Laboratory Values Per Cycle In Primary Study

Test Value	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
ALC	4	7-14	4-11	6-12	6-14	6-11	6-15	2-4	2-8
ANC	4	6-11	3-7	3-10	4-13	5-9	4-13	1-4	2-8
Hemoglobin/ Hematocrit	1	4-8	1-6	0-6	0-8	1-6	1-11	1-4	2-8
Platelets	1	4-9	2-6	0-6	0-9	2-7	1-11	1-4	10-18
WBC	1	4-8	1-6	0-6	0-8	1-6	1-11	1-4	2-8

Table 35: Number of Patients In Primary Study With Ranges of Missing Chemistry Laboratory Values By Frequency In Primary Study

Test Value	0 Missing	1-5 Missing	6-12 Missing	14-17 Missing
Chemistry Lab	62	21	4	2

In both studies, 176 (all) patients had baseline ECGs obtained but only 137 of the total of 176 patients had an ECG at the end-of-treatment visit. Most patients in the Primary study had baseline chemistry and hematology values. Chemistry and hematology laboratory testing data were missing on <10% of required time points.

The hematology and chemistry datasets were evaluated for missing data. The amount of missing data is not considered significant for the evaluation of the safety of bendamustine in rituximab-refractory indolent NHL.

Selection of studies and analyses for drug-control comparisons of laboratory values

This analysis is not applicable because both studies supporting this NDA are single-arm, uncontrolled studies. Comparative analyses for drug-control comparisons of laboratory values were performed during the review of NDA 22249 where bendamustine was compared to chlorambucil in a CLL population.

Standard analyses and explorations of laboratory data

Laboratory values were analyzed using JMP 7.0.1 to identify abnormalities of all grades. Per the Applicant, there was no evidence of an increase in number or severity of CTC laboratory abnormalities over time. Datasets D_LABH.xpt and D_LABC.xpt from the Primary and Second studies were reviewed and this analysis was confirmed.

Chemistry Testing:

Grade 4 serum chemistry values were experienced by 4 patients (3 patients in the Primary Study and 1 in the Second Study). All but one of these events resolved within 15 days (range 3-14) of the first grade 4 result. The resolution of the last patient's abnormality could not be assessed because he was removed from study and had no subsequent laboratory tests.

Nine patients had grade 3 or 4 adverse events associated with hypokalemia; 2 patients had grade 3 or 4 adverse events associated with hyperkalemia, 3 patients had grade 3 or 4 adverse events associated with hypomagnesemia, and one patient each with grade 3 or 4 adverse events associated with hyponatremia, hypoglycemia, hypercalcemia, hypocalcemia, hypoalbuminemia, and increased blood creatinine. No grade 3 or 4 adverse events were reported related to elevations in liver enzymes or bilirubin, though there was one case of grade 3 AST identified in the laboratory datasets. There were no cases of grade 3-4 elevated ALT in the laboratory results. These results were from a single patient (76012; also discussed in death narratives in Section 5.3.1.13) who experienced a rapid decline in health on Day 15 of bendamustine, developed multi-organ system failure, and dying from pulmonary hemorrhage.

Upon initial review of the datasets, one case of grade 3 hyperbilirubinemia (Patient 09101) was identified in the laboratory datasets. However, upon analysis it was discovered that the NCI CTCAE grading had been documented improperly; possibly because the units of measure were not in mg/dL. CTCAE for bilirubin is based upon the number of increases above the ULN, therefore, the patient's baseline was just below the ULN for the UMOL/L. After treatment started, the bilirubin rose maximally to 1.8x ULN which is considered a Grade 2 toxicity by CTCAE. No potential cases that would be consistent with Hy's Law were identified during the review.

Hematologic Testing:

Anemia, thrombocytopenia, neutropenia, and lymphopenia are common with the use of bendamustine and with other alkylating agents. Twenty-four percent of patients in the combined safety population (N=176) experienced grade 4 neutropenia while 35% experienced grade 3 neutropenia. However, the overall cycle frequency was low; in 13% of cycles patients experienced grade 3 neutropenia and in 6% of cycles patients experienced grade 4 neutropenia.

Use of prophylactic granulocyte growth factors was discouraged during the first cycle. After the onset of neutropenia, 37% of patients received these agents. No trend was observed over time for increasing number or severity of hematologic laboratory abnormalities.

Thrombocytopenia was also seen with significant frequency and severity in both studies. Grade 3 thrombocytopenia was observed in 18% of patients and grade 4 in 7% of patients. But, just as with neutropenia, few cycles were affected; grade 3 in 6% of cycles and grade 4 in 2% of cycles were affected. Thrombocytopenia was the most frequent adverse reaction leading to treatment discontinuation and the second most frequent event leading to dose delay.

Almost half (48%) patients had grade 3 or 4 neutropenia. Six percent had febrile neutropenia and 1 patient in the Primary Study died from this Adverse Reaction. One patient in the Primary Study had the study drug discontinued because of this Adverse Reaction.

Urine Testing:

Urinalysis was not routinely collected in the safety data for both studies. There are no known effects of bendamustine that would be uniquely identified during urinalysis.

Analyses focused on measures of central tendency

Analyses of maximum change of chemistry and hematology laboratory values were performed and no particular patterns of clinical importance were observed.

Reviewer Comments: No significant patterns were observed during this analysis that would provide additional information to the previously presented frequency and severity assessments regarding the laboratory changes in these patients.

Analyses focused on outliers or shifts from normal to abnormal

Table 36: Patients With Grade 4 Serum Chemistry Values Reported in Combined Studies (Applicant Analysis)

Study Patient number	Parameter, unit	Baseline value (grade)	Grade 4 value	Day of grade 4 value ^a	Subsequent grade 0 or lowest grade value (grade)	Day of subsequent grade 0 or lowest grade value ^a
SDX 105-03						
14090	Sodium, mmol/L	139 (0)	(b) (4)		NAV	NAV
70083	Potassium, mmol/L	3.7 (0)			3.8 (0)	107
76068	Creatinine, µmol/L	44.2 (0)			97.24 (0)	18
SDX 105-01						
02064	Calcium, mmol/L	2.725 (1)			2.625 (0)	54

SOURCE: Report for study SDX 105-01, Listing 8.

^a Relative to start of study drug treatment.

NAV=not available (no further laboratory test results).

Patients were selected who had grade 4 chemistry value changes. Detailed review of the chemistry datasets and CRFs identified alternative causes for nearly all cases.

Patient 14090 experienced grade 4 hyponatremia on day 98 of bendamustine treatment. In the same time period, the patient developed ground glass opacities on the chest CT and significant respiratory difficulty. Pulmonary conditions are frequent causes of hyponatremia. This case of hyponatremia is not likely to be a result of bendamustine toxicity. The patient did not have further labs performed before he died.

Patient 70083 experienced grade 4 hypokalemia on Day 93 of bendamustine therapy. The hypokalemia recovered to grade 0 within 14 days of starting oral potassium replacement. No concomitant medications were noted in the reviews that are known to cause hypokalemia. The attribution of this case of hypokalemia is possibly related to bendamustine.

Patient 76068 experienced a grade 4 elevated serum creatinine on day 14 of bendamustine treatment. This patient was also experiencing significant elevations in BUN and uric acid. Allopurinol was begun on day 13 for “tumor lysis syndrome”. This case of elevated serum creatinine is likely related to tumor lysis syndrome. The creatinine returned to grade 0 four days later with institution of treatment for tumor lysis syndrome.

Patient 02064 experienced grade 4 hypercalcemia on Day 51 of bendamustine treatment. This patient had developed progressive disease, received Aredia 90 mg IV on the day 51, with resolution of the hypercalcemia on Day 54. This case of hypercalcemia was likely related to the underlying malignancy and it responded to appropriate medical care.

Marked outliers and dropouts for laboratory abnormalities

Seventy-one patients (40%) dropped out of the study treatment before completing 6 cycles. Forty-five (63%) of these were due to adverse events. No patients withdrew for chemistry laboratory changes.

Additional analyses and explorations

None.

Special assessments

None.

7.4.3 Vital Signs

Overview of vital signs testing in the development program

In the Primary and Second studies, vital signs (pulse, systolic and diastolic blood pressure, and temperature) and body weight were measured at baseline, during treatment, and at the end-of-treatment evaluation; the exception was height which was measured at baseline only.

Selection of studies and analyses for overall drug-control comparisons

N/A

Standard analyses and explorations of vital signs data

In the combined analysis set, there were no significant changes in mean pulse, systolic and diastolic blood pressure, or temperature from baseline to endpoint. There was a decrease in body weight from baseline to endpoint; 38% of patients had grade 1 loss in body weight, 13% had grade 2 loss in body weight, and 3% had grade 3 loss in body weight. Weight loss is not only common in cancer (it is a known “B Symptom” in NHL), but it frequently occurs during cancer treatment due to anorexia, nausea, and vomiting.

Analyses focused on measures of central tendencies

The Applicant submitted this analysis of vital sign changes in the Primary and Second Studies. The data were reviewed by review of datasets and accurately represent the experiences with these studies.

Table 37: Newly Diagnosed Vital Signs Abnormalities by CTCAE Grade in Bendamustine Monotherapy Studies in Patients with NHL (Primary and Second Studies)

[Applicant Table]

Category	Number (%) of patients			
	Bendamustine (N=176)			
	Grade 1	Grade 2	Grade 3	Grade 4
Patients with postbaseline body weight measurement (n=174)				
Patients with weight change ^b	73 (41)	25 (14)	5 (3)	0
Weight gain	8 (5)	2 (1)	0	0
Weight loss	66 (38)	23 (13)	5 (3)	0
Patients with postbaseline temperature measurement (n=174)				
Patients with temperature increase	4 (2)	3 (2)	0	NA ^a
Patients with postbaseline measurement of blood pressure (n=174)				
Patients with hypertension	17 (10)	3 (2)	0	1 (<1)
Patients with hypotension	5 (3)	1 (<1)	2 (1)	2 (1)
Patients with postbaseline measurement of pulse (n=174)				
Patients with abnormal pulse rate	14 (8)	2 (1)	0	0

SOURCE: Summary 15.14.

^a For vital sign of temperature increase, grades 3 and 4 events were combined as grade 3 events.

^b A patient could have both a weight gain and a weight loss during the study.

CTCAE=Common Terminology Criteria for Adverse Events; NA=not applicable.

NOTE: If a patient reported more than 1 postbaseline vital sign CTCAE grade, the highest grade was presented for that vital sign. Patients were counted only once in each vital sign category and only once for each vital sign, with the highest grade presented for each.

Analyses of adverse events related to vital sign changes were reviewed in Section 7.0.

Analyses focused on outliers or shifts from normal to abnormal

N/A

Marked outliers and dropouts for vital sign abnormalities

Reviewed in Section 7.0.

Additional analyses and explorations

N/A

7.4.4 Electrocardiograms (ECGs)

Overview of ECG testing in the development program, including brief review of preclinical results

Neither study prospectively collected ECG data in a schedule that would be adequate to capture any ECG-related events. ECGs were collected only at baseline and at the end-of-treatment visit. Quantitative ECG data related to interval length were not captured in these studies. ECGs were not performed at C_{max} and 43% of patients across both studies had missing post-baseline ECG assessments. In the absence of appropriately timed ECGs, conclusive statements can not be made regarding QT changes. The ECG abnormalities that were detected at baseline and at the end of study were those typical of an older population with multiple co-morbidities.

A post-marketing commitment was made during the initial approval of bendamustine.

Pre-clinical results indicated that bendamustine is not likely to affect the QT interval.

Selection of studies and analyses for overall drug-control comparisons

N/A. These studies were uncontrolled.

Standard analyses and explorations of ECG data

Inadequate data was provided to perform this analysis.

Analyses focused on measures of central tendency

Inadequate data was provided to perform this analysis.

Analyses focused on outliers or shifts from normal to abnormal

Inadequate data was provided to perform this analysis.

Marked outliers and dropouts for ECG abnormalities

Inadequate data was provided to perform this analysis.

Additional analyses and explorations

N/A

7.4.5 Special Safety Studies

No special studies were performed during the development program pertinent to this review.

7.4.6 Immunogenicity

There were 35 patients who experienced symptoms of hypersensitivity reactions during Primary and Second Studies. This adverse reaction was also recognized during the review of NDA 22249 and this issue is addressed in the current Warnings & Precautions section of the product label. Patients who experience low grade reactions to bendamustine are frequently pre-medicated with antihistamines or corticosteroids.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

These studies were fixed-dose studies based upon body mass. No dose-dependency for adverse reactions can be assessed in this situation.

7.5.2 Time Dependency for Adverse Findings

No specific time dependency was observed for adverse reactions to bendamustine.

7.5.3 Drug-Demographic Interactions (gender, race)

No significant differences were observed between men and women enrolled in these studies regarding efficacy or safety. No evaluation for race can be made in these studies as nearly all patients were Caucasian.

7.5.4 Drug Disease Interactions

Hematologic adverse events, symptoms of respiratory infections, falls, anorexia, and musculoskeletal symptoms were slightly more common in patients with abnormal liver enzymes at baseline. The number of patients with abnormal liver function tests at baseline were limited to 2 patients with Grade 2 bilirubin, and one patient each with Grade 2 AST and ALT. These frequencies are too small to conclude anything about the use of bendamustine in hepatic-impaired patients. The most frequently reported adverse events in the 138 patients with normal liver enzymes at baseline and in the 37 patients with abnormal liver enzymes at baseline were nausea (77% and 68%, respectively) and fatigue (56% and 65%, respectively).

7.5.5 Drug-Drug Interactions

No formal clinical assessments of pharmacokinetic drug-drug interactions between bendamustine and other drugs have been conducted. There were no studies conducted to evaluate extrinsic factors such as alcohol or nicotine consumption on patients treated with bendamustine but based upon the properties associated with bendamustine's pharmacologic class, there are no specific safety concerns associated with the use of this product and specific extrinsic factors.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Bendamustine is an alkylating agent and is likely to be carcinogenic. Patients in the lymphoma population are already at risk for other malignancies due the nature of their impaired immune system. Myelodysplasia (MDS) was the most frequently observed secondary pre-malignant condition occurring in 3 patients between the two studies. MDS has been observed after treatment with alkylators. One case each of squamous cell carcinoma and CMML were observed. CMML often develops in patients with MDS. Patients in the bendamustine studies reviewed did experience secondary malignancies, but also had prior treatment with agents that are known to induce secondary malignancies. A direct relationship between bendamustine and the reported secondary malignancies is not assessable in this situation.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant or lactating women and women of child-bearing potential were excluded from the bendamustine clinical studies. The use of bendamustine during pregnancy has not been studied in humans; however, the use of bendamustine in pregnant rats and mice resulted in fetal malformations and embryoletality. Women of childbearing potential are therefore advised to avoid becoming pregnant.

7.6.3 Pediatrics and Assessment and/or Effects on Growth

Since 04/01/1999, it has been required that at approval, NDA's must have either a pediatric assessment, pediatric waiver, or a pediatric deferral (21 C.F.R. § 314.55(c)).

The Applicant has requested a Pediatric Waiver with the following language submitted with this NDA:

In accordance with 21 CFR 314.55 (c)(2)(ii), Cephalon is requesting a waiver for pediatric studies for all age groups since the indication that is being applied for, Indolent non-Hodgkin's lymphoma (NHL) does not occur in a pediatric population. The FDA acknowledge that a waiver under the Pediatric Rule for studies in this population would be appropriate during an End-of-Phase 2 meeting that occurred on September 2, 2004 and was stated in the minutes (September 14, 2004) from this meeting.

Reviewer Comments: This reviewer concurs with the pediatric waiver request per 21 C.F.R. § 314.55(c)7.6.4 because the pediatric population is not affected by indolent non-Hodgkin's Lymphoma.

7.6.4 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

Doses as high as 280 mg/m² have been administered during the bendamustine development program. No specific antidote for bendamustine overdose is known. Management of overdosage should include general supportive measures to sustain the patient through any period of toxicity that might occur. Toxicities that have occurred in doses this high are severe, prolonged hematologic toxicities, cardiac dysrhythmia, and prolonged QT interval.

No nonclinical or clinical studies have been conducted to investigate the dependence potential of bendamustine. Bendamustine is an intravenous medication only available by prescription by a physician. Bendamustine is not a psychoactive drug, has significant toxicities, and is unlikely to have drug abuse potential. No withdrawal or rebound phenomena have been reported.

7.7 Additional Submissions

On 4/29/08, the Applicant submitted the 4 month Safety Update Report as required by 21 CFR 314.50(d)(5)(vi)(b). The cutoff date for this report was 12/7/07. New or updated data was available from the Primary Study, the Second Study, or the CLL randomized study.

No new exposure data was available for the Primary or Second studies.

One new death >30 days after last dose of study drug was reported in the Primary Study. This death was due to MDS at day 418 after the last dose of study drug. This death may be related to the receipt of prior alkylating agents, including bendamustine. There was no change in the number of deaths for the Second Study.

Overall, no significant changes or findings in the safety profile of bendamustine were identified since the submission of the NDA.

Serious adverse event information and death information is updated in Section 7.0.

8 Postmarketing Experience

Treanda became available for use in the U.S. in April of 2008. No significant new safety issues have been identified in the post-marketing period to date. 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 (b) (4) 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 consists of individual reports, a report of a 398 patient postmarketing study, and an Overall Safety Update Report (SUR). According to (b) (4), approximately (b) (4) patients were exposed to bendamustine during this time period. Reliance on postmarketing reports for estimation of adverse reaction incidence and severity is limited due to the passive nature of the collection of spontaneous reports, the voluntary nature of reporting, the insufficient detail contained in these reports, and difficulty calculating event rates due to the relatively unknown safety population denominator.

The most commonly reported adverse events from all postmarketing sources have been the following: hypersensitivity (23 patients), leukopenia (12), pyrexia (11), pneumonia (9), thrombocytopenia (9), and dysgeusia (7). A total of 32 postmarketing spontaneous reports associated with fatal outcomes, assessed as related or possibly related to bendamustine, and medically confirmed by health care providers, have also been received. The main causes of death include disease progression (8 patients), infections/immune suppression (9), pulmonary embolism (2), pulmonary fibrosis (1), sudden cardiac death (1), respiratory failure (1), tumor lysis syndrome (1), CLL transformation (1), and hepatocellular damage (1).

Review of the postmarketing reports reveals the following medical events of special interest: acute renal failure, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, cardiac failure, cardiogenic shock, depressed level of consciousness, hypersensitivity, pulmonary embolism, pulmonary fibrosis, and tumor lysis syndrome.

9 Appendices

9.1 Literature Review and other Important Relevant Materials/References

Information regarding indolent NHL was reviewed from the published literature.

The existing label, approved March 20, 2008, for bendamustine in CLL was utilized during this review.

9.2 Labeling Recommendations

Review of the trade name is not indicated as bendamustine currently holds the trade name TREANDA after approval of NDA 22249.

The Applicant submitted a proposed label. Agency amendments to this proposal are described below with added text underlined and deleted text as strikethrough. Comments about the changes to the Applicant proposals are in highlights. At the time of the completion of this review, labeling negotiations were ongoing. For finalized content, please refer to the finalized label.

Proposed Applicant Label

(b) (4)



24 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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9.3 Advisory Committee Meeting

No advisory committee meeting was deemed necessary for this application.

9.4 Existing Post-Marketing Commitments

1. Cephalon commits to providing an updated study report of Protocol 02CLLIII titled "*Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) BCLL Requiring Therapy*" at data cut off date in May 2008. Response rate, progression-free survival, overall survival and safety updates will be provided in this study report.

Protocol Submission: N/A
Study Start: N/A
Final Report Submission: February, 2009

2. Cephalon commits to submitting the results and data from the ADME Study 1039 titled "An Open-Label Study to Investigate the Pharmacokinetics (Distribution, Metabolism, and Excretion) of Bendamustine Hydrochloride Following Intravenous Infusion of [¹⁴C]Bendamustine Hydrochloride in Patients With Relapsed or Refractory Malignancy (Hematologic or Nonhematologic)". Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.

Protocol Submission: May, 2008
Study Start: December, 2008
PK Report Submission: December, 2009
Final Report Submission: March, 2010

3. Cephalon commits to conducting a study to assess the potential for bendamustine to prolong the QT interval in patients. The QT plan will be submitted prior to initiation for IRT review and concurrence.

Protocol Submission: July, 2008
Study Start: December, 2008
Final Report Submission: June, 2010

4. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of fluvoxamine (CYP1A2 inhibitor) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

Protocol Submission: March, 2010
Study Start: September, 2010
PK Report Submission: January, 2012
Final Report Submission: July, 2012

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5. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of smoking (CYP1A2 inducer) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

Protocol Submission: March, 2010
Study Start: September, 2010
PK Report Submission: July, 2012
Final Report Submission: December, 2012

6. Cephalon commits to conducting *in vitro* screens to determine if bendamustine is a p-glycoprotein substrate or inhibitor.

Protocol Submission: March, 2008
Study Start: September, 2007
Final Report Submission: June, 2008

7. Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: sodium chloride).

Protocol submission: April 1, 2008
Study start: May 15, 2008
Final Report: September 1, 2008

9.5 Appendix A: Death Narratives Provided by Applicant for Second Study

Death Narratives Provided by Applicant:

Patient Number: 03-065

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycles 1-3)

Adverse Event(s) Leading to Death: Unknown (the cause of death was not recorded)

Patient 03-065 was an 81-year-old white man with asymptomatic, stage IV asymptomatic follicular lymphoma. On day 22 (cycle 2, day 1), the patient experienced an adverse event of grade 2 rash that resolved on day 64 (cycle 3, day 22), which was considered probably related to study drug treatment by the investigator. On day 36 (cycle 2, day 15), he experienced an adverse event of grade 3 chest pain (verbatim: left-sided chest pain), which interrupted study drug administration in cycle 3 for one week. The patient was treated with naproxen sodium and paracetamol, local injections of lidocaine and a lidoderm patch, oxycocet, and gabapentin for the chest pain. He also experienced an adverse event of grade 1 anemia on day 36, and was treated with darbepoetin alfa. The anemia resolved on day 43 (cycle 3, day 1) and was considered probably related to study drug treatment by the investigator. On

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day 50 (cycle 3, day 8), the patient experienced a second adverse event of grade 1 anemia; treatment with darbepoetin alfa continued. The anemia resolved on day 56 (cycle 3, day 14) and was considered probably related to study drug treatment by the investigator. On day 87 (cycle 3, day 45), the patient experienced adverse events of grade 2 anemia (hemoglobin 9.4 g/dL; normal range: 12 to 18 g/dL) and grade 2 thrombocytopenia. He was transfused with 2 units packed red blood cells the next day. The grade 2 anemia was considered probably related to study drug treatment by the investigator, and the thrombocytopenia was considered possibly related to study drug treatment. Due to the adverse events of anemia and thrombocytopenia, study drug was permanently discontinued (last dose: day 44 [cycle 3, day 2]). Progressive disease was noted on day 58. On day 89 (cycle 3, day 47), the patient experienced grade 1 dysarthria (verbatim: slurred speech). The dysarthria was considered not related to study drug treatment by the investigator. Study drug treatment was discontinued on day 87. No follow-up information was available for this patient as he died on (b) (6) prior to the follow-up visit. No cause of death was recorded.

Patient Number: 05-008

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycles 1-6)

Adverse Event(s) Leading to Death: Myelodysplastic syndrome

Patient 05-008 was an 80-year-old white woman with stage IIIE asymptomatic follicular lymphoma. The patient completed 6 cycles of therapy and received the last dose of study drug on day 114 (cycle 6, day 2). Her last day on study was day 128 (cycle 6, day 16), per protocol. During follow-up, on day (b) (6), the patient experienced a serious adverse event of grade 4 adrenal hemorrhage (verbatim: bilateral adrenal hemorrhage), which was considered possibly related to study drug treatment by the investigator. She was admitted to the hospital that day after presenting to the emergency room with fever, abdominal pain, hypotension, nausea, vomiting, and a change in mental status (data on file). A computed tomography scan of the chest, abdomen, and pelvis revealed bilateral adrenal hemorrhage. She was also noted to have developed worsening anemia and thrombocytopenia, and she was treated with intravenous fluids, antibiotics and intravenous hydrocortisone. On day (b) (6), the adrenal hemorrhage resolved with sequelae, and the patient was discharged from the hospital. On day (b) (6), the patient presented to the clinic with complaints of nausea, vomiting, and back pain. She was subsequently admitted to the hospital for treatment including hydration, supportive care, and disease assessment (data on file). A bone marrow aspiration was performed, which revealed myelodysplastic syndrome (recorded as a grade 4 serious adverse event). Upon admission, her laboratory results showed the following: white blood cell count of 4.8 K/ μ L, neutrophils 73%, lymphocytes 19%, monocytes 3%, hemoglobin of 9.8 g/dL, hematocrit of 29.4%, and platelets of 62 K/ μ L. During hospitalization, she required multiple blood and platelet transfusions. The patient also developed nosocomial pneumonia and steroid-induced diabetes mellitus during her stay. On day (b) (6), the patient was discharged to a subacute rehabilitation facility where she continued to require platelet support. She was re-admitted to the hospital on day (b) (6) due to back and neck pain. The patient continued to be thrombocytopenic and received several transfusions during her second hospitalization. She was discharged from the hospital to home hospice support on day (b) (6), and she subsequently died from the

myelodysplastic syndrome on day (b) (6). The myelodysplastic syndrome was considered possibly related to study drug treatment by the investigator.

Patient Number: 06-012

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycle 1), 90 mg/m² (cycles 2-3)

Adverse Event(s) Leading to Death: Progression of disease

Patient 06-012 was a 74-year-old white woman with stage IV asymptomatic lymphocytic lymphoma. The patient received the first cycle per protocol. However, cycle 2 was delayed to day 43 cycle 2, day 1) and the dose was reduced to 90 mg/m² due to thrombocytopenia. Study drug dosage continued at the lower dose for the remainder of the study. The patient took her last dose of study drug on day 65 (cycle 3, day 2) and was noted as having a partial response to study drug treatment on day 79 (cycle 3, day 16). Due to progression of disease she was withdrawn from the study on day 109 (cycle 3, day 46). On day (b) (6) (125 days after last dose of study drug), the patient died due to progression of disease. Other adverse events of note included grade 2 thrombocytopenia on day 85, which was continuing at the time the patient died.

Patient Number: 07-015

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycle 1)

Adverse Event(s) Leading to Death: Renal failure acute

Patient 07-015 was a 58-year-old white man with asymptomatic, stage IV asymptomatic follicular lymphoma. Significant ongoing medical history included worsening hydronephrosis, cardiomyopathy, and lower extremity edema. At screening (day -7), the patient's creatinine clearance was low and creatinine level was elevated (see table below). Screening diagnostic tests (a computed tomography scan of the abdomen and a renal ultrasound) revealed a large mass near the proximal left ureter causing hydronephrosis (data on file). A left ureteral stent was placed after the patient experienced an adverse event of grade 3 renal impairment (verbatim: altered renal function) on day -2 (data on file). The renal impairment was considered not related to study drug treatment by the investigator. On day 1 of cycle 1, the patient experienced adverse events of grade 3 ascites and grade 1 lung crackles. His oral intake decreased markedly after the first infusion of study drug, and he was noted as hypotensive (data on file). He underwent paracentesis on day 3 with removal of 2 to 3 liters of fluid (data on file). On day 3 of cycle 1, the renal impairment worsened and became a serious adverse event of grade 4 acute renal failure. The patient also had grade 2 hyperkalemia. (Note: Although the adverse event is listed as hypokalemia, the laboratory results document it as hyperkalemia.) His creatinine levels continued to be elevated, and a renal consultation was ordered (data on file). Upon examination, the physician felt that the elevated creatinine levels were caused by pre-renal factors, including hypotension and hypovolemia (data on file). Study drug was discontinued due to the renal failure after the final infusion on day 2, cycle 1. The patient was slowly rehydrated but continued to be anemic (data on file). On day 6, cycle 1 he experienced a serious adverse event of grade 4 pulmonary edema

and remained 2 hyperkalemic. The patient became anuric by day 7 (cycle 1) and his family requested that no heroic measures be performed (data on file). He received treatment with diuretics (chlorothiazide plus an unknown diuretic) and oxygen (via a non-rebreather oxygen mask). The patient died on (b) (6) as a result of the acute renal failure. The investigator considered the acute renal failure and pulmonary edema unlikely related to study drug treatment, and the ascites, lung crackles, and hyperkalemia not related to study drug treatment. The investigator felt that the acute renal failure was likely secondary to hypovolemia/hypotension, which had caused decreased renal blood flow, and that the pulmonary edema was due to volume overload that occurred following infusion with packed red blood cells (data on file).

Selected serum chemistry values for patient 07-015 are listed below.

Day	Creatinine (0.7 to 1.3 mg/dL)	Blood urea nitrogen (6 to 19 mg/dL)	Potassium (3.3 to 5.1 meq/L)	Uric acid (3.9 to 8.1 mg/dL)
-7	(b) (4)			
1 (cycle 1, day 1)				
3 (cycle 1, day 3)				
5 (cycle 1, day 5)				
7 (cycle 7, day 7)				

Source: Applicant SCS

Patient Number: 07-073

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycles 1-5)

Adverse Event(s) Leading to Death: Unknown (death due to disease progression)

Patient 07-073 was a 52-year-old black woman with stage II asymptomatic follicular lymphoma. Significant medical history included urinary tract infection, hypertension, diabetes mellitus type 2, chronic renal failure, and recent nephrostomy tube placement. Prior to administration of study drug, the patient experienced adverse events of grade 1 urinary tract infection (day -7) and grade 1 pyrexia (day -2), both of which were considered not related to study drug treatment by the investigator. The urinary tract infection likely resulted from a recent stent and/or nephrostomy tube placement. The pyrexia resolved 1 day prior to the first dose of study drug. On day 1 of cycle 1, the patient experienced an adverse event of grade 2 post-procedural hemorrhage (verbatim term: bleeding from nephrostomy). The following day (b) (6) she was hospitalized for a serious adverse event of grade 1 pyrexia, which was believed to be caused by the continuing urinary tract infection. On the same day, she experienced a nonserious adverse event of grade 2 hematuria. The pyrexia, post-procedural hemorrhage, and hematuria were considered not related to study drug treatment by the investigator. Study drug was held on day 2 of cycle 1 due to pyrexia. The patient was treated with acetaminophen. The pyrexia, post-procedural hemorrhage, and urinary tract infection resolved on (b) (6) and the patient was then discharged from the hospital that same day. The hematuria resolved on day 48 (cycle 3, day 1). The patient experienced 2 additional adverse events of grade 1 urinary tract infection (day 22

[cycle 1, day 22]; and day 48 [cycle 3, day 1]). Both events resolved within 1 month of onset (exact date not available) and were considered not related to study drug treatment by the investigator. Other adverse events of note included grade 1 back pain (cycle 1, day 1), grade 1 chills (cycle 1, day 2), and grade 1 fungal infection (verbatim term: yeast infection; day 36 [cycle 2, day 10]). The chills and fungal infection resolved; the back pain continued throughout the study. On day 109 (cycle 5, day 13), the patient experienced an adverse event of grade 2 thrombocytopenia ($51 \times 10^9/L$; normal range: $140-440 \times 10^9/L$), which was considered possibly related to study drug treatment by the investigator. Study drug was discontinued due to this adverse event (last dose: day 98 [cycle 5, day 2]). On day (b) (6), the patient was hospitalized for a serious adverse event of grade 2 hematuria, which required bladder irrigation and was considered not related to study drug treatment by the investigator. During the week prior to admission, the patient had noted blood in her nephrostomy bag and large clots in her urine (data on file). She was treated with levofloxacin for a presumed urinary tract infection. The patient, however, had also passed the left ureteral stent, which possibly caused trauma and bleeding and could have been the source of the hematuria (data on file). She was found to be anemic (hemoglobin 6.5 g/dL; normal range was not available [data on file]) and was treated with 3 units of packed red blood cells. Upon resolution of the hematuria on (b) (6), the patient was discharged from the hospital. The thrombocytopenia continued throughout the patient's hospitalization and later resulted in patient's withdrawal from the study on day 127 (cycle 5, day 31), at which time the thrombocytopenia continued. Approximately 3 months after the patient discontinued from the study (b) (6) 2005; exact date unknown) the patient died due to disease progression.

Patient Number: 09-011

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycles 1-3), 90 mg/m² (cycles 4-6)

Adverse Event(s) Leading to Death: Lymphoma

Patient 09-011 was a 47-year-old white man with stage IV asymptomatic follicular lymphoma. Significant medical history included an autologous bone marrow transplant. On day 22 (cycle 2, day 1), the patient experienced adverse events of grade 2 fatigue and grade 3 anemia. Both events were considered probably related to study drug treatment by the investigator. The anemia (hemoglobin: 82 g/L; normal range: 140-180 g/L) resolved on day 23 (cycle 2, day 2), following the transfusion with 2 units of packed red blood cells. The event of fatigue continued throughout the study. On day 36 (cycle 2, day 15), the patient experienced adverse events of grade 1 chills and grade 1 hot flush, both of which were considered possibly related to study drug treatment by the investigator. He was treated with paracetamol with codeine for the chills and hot flush, and both events resolved on day 40 (cycle 2, day 14). On day 64 (cycle 3, day 22), the patient experienced an adverse event of grade 4 neutropenia (absolute neutrophil count: $0.78 \times 10^3/\mu L$; normal range: $2.0-8.6 \times 10^3/\mu L$), which was considered almost certainly related to study drug treatment by the investigator. The patient was treated with filgrastim for the neutropenia beginning on day 74, and the event resolved on day 75 (cycle 3, day 32). Study drug treatment was reduced to a dose of 90 mg/m² due to the neutropenia, and cycle 4 was delayed until day 78. On day 78 (cycle 4, day 1), the patient experienced an adverse event of grade 2 hemoglobin decreased (hemoglobin: 86 g/L), which was

considered probably related to study drug treatment by the investigator. The patient received 2 units of packed red blood cells on day 80. After completion of cycle 6 (last infusion on day 124), the patient began treatment with cyclophosphamide, prednisone, and etoposide for disease progression (data on file). On ^{(b) (6)}, the patient was admitted to the medical unit that day to receive a thoracentesis after experiencing dyspnea on exertion for several days (data on file). Following the thoracentesis, the patient was admitted to the hospital for pain management and palliation. While hospitalized, he experienced continuing increased sternal pain and leg pain, and he developed a fever on day 162 (cycle 6, day 40). On ^{(b) (6)}, the patient died as a result of grade 4 lymphoma (disease progression). During the patient's hospitalization, he was treated with meperidine, hydromorphone, metoclopramide, diphenhydramine, morphine, lorazepam, senna, potassium supplement, docusate sodium, fentanyl, vancomycin, prednisone, vitamin K, midazolam, scopolamine, furosemide, dexamethasone, and ceftriaxone (data on file).

Patient Number: 11-024

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycles 1-3)

Adverse Event(s) Leading to Death: Chronic myelomonocytic leukemia

Patient 11-024 was an 82-year-old white man with stage IV asymptomatic follicular lymphoma. Relevant medical history included history of anemia, basal skin cancers, squamous cell skin cancers, and colon cancer. On day 43 (cycle 3, day 1), the patient experienced adverse events of grade 2 anemia (verbatim term: worsening anemia) and grade 3 neutropenia. The patient continued to have anemia throughout the study, and the neutropenia continued for approximately 1 month. On day 47 (cycle 3, day 5), the patient experienced an adverse event of grade 3 thrombocytopenia, which continued and caused interruption of study drug. The patient was treated with epoetin alfa and 2 units of packed red blood cells for the anemia and pegfilgrastim for the neutropenia. All 3 adverse events were considered almost certainly related to study drug treatment by the investigator. The neutropenia resolved on day 65 (cycle 3, day 23); however, at this time the patient was diagnosed with grade 4 monocytosis, which was considered a serious adverse event. He presented to the clinic several days later for his cycle 4, day 1 visit and was determined to have abnormal hematology results (see table below), which resulted in study drug being held for 1 week. On day 68 (cycle 3, day 26), the patient experienced an adverse event of grade 1 pyrexia, and received treatment with acetaminophen and ciprofloxacin. One week later on day ^{(b) (6)} the patient returned to the clinic in order to receive treatment in cycle 4 but was admitted to the hospital for a serious adverse event of grade 4 sepsis. He was treated initially with piperacillin/tazobactam, then fluconazole and bactrim DS were added as treatment for the sepsis. On ^{(b) (6)}, the patient underwent a bone marrow aspiration/biopsy that showed chronic myelomonocytic leukemia in transformation to acute leukemia (data on file). He received 2 units of packed red blood cells for continuing anemia. Study drug was discontinued as a result of the monocytosis, sepsis, and chronic myelomonocytic leukemia (last dose: day 42 [cycle 3, day 2]). Both the sepsis and pyrexia resolved on day 80 (cycle 3, day 38) and were considered almost certainly related to study drug treatment by the investigator. The patient was discharged from the hospital on day ^{(b) (6)}

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in stable condition and did not appear to be developing acute leukemia at the time of discharge (data on file). Without treatment, the patient's WBC count and platelet counts decreased ($16 \times 10^9/L$ and $27 \times 10^9/L$ respectively; data on file). The chronic myelomonocytic leukemia resulted in the patient's death on day ^{(b) (6)} days after the last dose of study drug) and was considered possibly related to study drug treatment by the investigator.

Patient Number: 14-014

Study Drug: Bendamustine hydrochloride (CEP-18083)

Assigned Dosage: 120 mg/m² (cycles 1-6)

Adverse Event(s) Leading to Death: Progression of disease

Patient 14-014 was a 64-year-old white man with stage III asymptomatic follicular lymphoma. Significant medical history included an initial diagnosis of indolent lymphoma on 28 January 1999, with a most recent recurrence on 19 February 2004. The patient's first dose of study drug was on 25 February 2004, and he completed 6 cycles of study drug therapy on day 107 (cycle 6, day 2). The patient was withdrawn from the study due to disease progression on day 122 (cycle 6, day 17) and had his final study visit on day 125. He was subsequently treated with radiation therapy. The patient died on day ^{(b) (6)}.

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/s/

Virginia Kwitkowski
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Amna Ibrahim
10/28/2008 04:21:44 PM
MEDICAL OFFICER

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Safety Update

See MOR dated 10-22-08.

Alice Kacuba

Alice Kacuba 1023-08

NDA 22-303

Financial Disclosure Reviews

See MOR dated 10-22-08.

Alice Kacuba

Alice Kacuba 10-23-08

NDA 22-303

Other Reviews Requested by Clinical

This section is Not Applicable.

Alice Kacuba

Alice Kacuba 10-23-08

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