CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-249

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	*March 20th, 2008*
From	Amna Ibrahim MD
Subject	Cross-Discipline Team Leader Review
NDA # (Supp #)	22249 (S-000)
Proprietary / Established (USAN) names	Bendamustine (Treanda)
Dosage forms /strength	100-mg vials of bendamustine HCL as white to off-white lyophilized powder
Proposed Indication(s)	For the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
Recommended:	Approval

This an amended CDTL review. The additions are provided in italics in this review and are based on the new information.

1 Introduction

A single, open-label, multicenter, randomized trial has been submitted as the major trial to support the approval of bendamustine (Treanda®) for the treatment of patients with CLL. The clinical team recommends approval of this NDA on the basis of an improvement in Overall Response Rates (ORR) and Progression-free Survival (PFS).

In this study, Bendamustine was compared to Chlorambucil as a comparator in a treatment-naïve population. The choice of comparator was influenced by the drugs approved in Europe for this indication, where the trial was conducted. Fludarabine, one of the most active drugs for this disease was approved only for second-line use. FDA does not require the use of a standard of care in a randomized study.

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

CLL is a disease that mainly affects the older population, the median age being 72 at diagnosis. Over the past few decades, there has been little progress in prolonging survival of patients with CLL, and it remains an incurable disorder. Because the patients generally have a good long term prognosis and treatment does not change the outcome of disease, a "watch and wait" approach is often used before initiation of treatment. Factors which generally prompt the initiation of therapy include the presence of disease-related symptoms, massive and/or progressive lymphadenopathy or hepatosplenomegaly, bone marrow failure, or recurrent infections. The lymphocyte doubling time should be considered in the total clinical picture but not used as the primary criterion. The routine availability of peripheral blood lymphocyte immunophenotyping has facilitated the diagnosis of CLL in patients with a monoclonal lymphocytosis. Three main phenotypic features define B-CLL: the predominant population shares B-cell markers (CD19, CD20, and CD23) with the CD5 antigen, in the absence of other pan-T-cell markers; the B cell is monoclonal with regard to expression of either κ or *h;* and surface immunoglobulin (sIg) is of low density. Not only are these characteristics generally adequate for a

precise diagnosis, but, importantly, they distinguish CLL from uncommon disorders such as PLL, hairy-cell leukemia, mantle-cell lymphoma, and other lymphomas[1].

The National Cancer Institute-Sponsored Working Group (NCI-WG) published guidelines for the diagnosis and criteria for response for CLL[1]. The peripheral blood should exhibit an increase in the number of small mature-appearing lymphocytes to >5,000/μl. The bone marrow aspirate smear must show >30% of all nucleated cells to be lymphoid. Although a bone marrow examination is rarely required to make the diagnosis of CLL in general practice, it may be evaluable prior to the start of treatment in order to define prognostic factors. Subsequently, a bone marrow examination is indicated primarily to evaluate response to treatment or to assess normal elements if there is an unexplained anemia or thrombocytopenia[1]. Although not approved for this indication, Fludarabine-based regimens are generally used for treatment-naïve patients in the US. Chlorambucil and cyclophosphamide are approved for this patient population. For further details regarding first-line treatment options, please see Medical Officer's Review (MOR).

2. **Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status**

Bendamustine hydrochloride was developed in the 1960s in former East Germany, but was never systematically studied in patients until the 1990s[2]. Per applicant, although it has been used for a variety of malignancies in Germany for over 30 years, re-approval was required by the German law post reunification due to regulatory requirements in the German Democratic Republic. Bendamustine is currently marketed in Germany and Bulgaria.

This randomized study was conducted entirely in Europe by Ribosepharm GmbH, and per applicant, is Cephalon Inc. acquired the rights and using their own statistical analysis plan (SAP), analyzed and submitted the NDA to FDA. This SAP and its approach were discussed with the FDA in a preNDA meeting. FDA asked for details of the SAP, and did not agree (or disagree) to the design due to insufficient information. In an earlier EOP2 meeting with Cephalon, FDA agreed to accept a single randomized study and encouraged the use of an independent response review committee for efficacy evaluation. For further details regarding the regulatory history, please see Dr. Qin Ryan's Medical Officer's Review (MOR). There was no Special Protocol Assessment (SPA) conducted for the protocol.

3. **CMC/Microbiology**

The CMC review was completed by Ravindra K. Kasliwal Ph.D., and cosigned by Ravi Harapanhalli on 2/27/2008. Their recommendation is as below:

"The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided trademark and labeling acceptability has been determined by Office of Drug Safety (DMETS) and provided the manufacturing sites are deemed acceptable for cGMP compliance. The product quality microbiology has recommended approval on 06-Feb-2008. The recommendation for Office of Compliance regarding the acceptability of the manufacturing facilities is pending as of the date of this review."

3.1 General product quality considerations

According to the microbiology reviewer, Anastasia G. Lolas, M.S., and co-signed by Stephen Langille Ph.D., this NDA is recommended for approval (Date archived: 2/6/2008) from microbiology point of view.

3.2 Facilities review/inspection

According to C. Cruz, the facilities inspection was found acceptable (memo dated March 17th, 2008).

3.3Other notable issues

Per CMC review, the company has not provided data showing compatibility of the constitution solution, Sterile Water for Injection, USP, with other commonly available diluents such as [redacted] .The data (assay and impurity profile) should be provided as part of the phase 4 commitment within 6 months of approval of the application (comment for company is provided at the end of this review).

It is recommended in the CMC review that the following be included in the action letter:

"We remind you of your agreement in an amendment dated 12-Feb-2008 to initiate change controls for all the documents impacted by the revision to the maximum hold time not to exceed [redacted] and to submit appropriate post-approval correspondence reflecting this change."

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology Review and Evaluation was signed by Anwar Goheer Ph.D. and cosigned by team leader John Leighton Ph.D. on 2/27/2008. According to the review, the nonclinical studies are sufficient to support the approval of this NDA. Excerpt from his review states:

"A. Recommendation on approvability: The non-clinical studies submitted to this NDA provide sufficient information to support the use of Treanda ® (bendamustine hydrochloride) for the treatment of patients with chronic lymphocytic leukemia (CLL)."
"B. Recommendation for nonclinical studies: No additional non-clinical studies are required."
"C. Recommendations on labeling: A separate review will be conducted."

4.1 General nonclinical pharmacology/toxicology considerations

According to Dr Goheer's review, "Bendamustine hydrochloride [Treanda®, Cytostasan® (Germany), and Ribomustine® (Germany)] belongs to bifunctional nitrogen mustards. Nitrogen mustard and its derivatives are alkylating agents which dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage produced can lead to cell death via several pathways. The precise mechanism of action of bendamustine has not been fully characterized."

4.2 Carcinogenicity

As observed in Dr. Goheer's review, bendamustine is a genotoxic alkylating agent. Oral administration for four days induced mammary carcinoma and pulmonary adenomas in mice."

4.3 Reproductive toxicology

Dr. Goheer's review also stated that embryo-fetal developmental studies were not conducted by the sponsor. During embryo-fetal developmental toxicity study, intraperitoneal administration of bendamustine produced embryotoxic and teratogenic effects in mice.

4.4 Other notable issues

Per Dr. Goheer's review, nonclinical safety issues relevant to clinical use were reduction in WBC and lymphocytes were observed in a dose related manner during pivotal repeat dose toxicity studies in rats and dogs. Treatment related microscopic changes were seen in kidneys (tubular degeneration/necrosis) in both species. Cardiomyopathy (focal/multifocal) was observed in male rats only. Heart rates of dogs at 6.6 mg/kg/day were reduced during cycle 2 (2 males & 1 female, 3/6 animals). A vigilant monitoring of QT prolongation is warranted until more clinical experience is gained. Bendamustine is mutagenic, carcinogenic, and teratogenic like other nitrogen mustard alkylating agents. There are no outstanding issues noted in Dr Goheer's review.

5 Clinical Pharmacology/Biopharmaceutics

Julie Bullock, Ph.D. was the clinical pharmacology reviewer for this NDA. Her recommendations were as follows:

"This NDA is considered to be deficient from a clinical pharmacology perspective due to the lack of data available regarding pharmacokinetics at the proposed dose, dose proportionality, human excretion and metabolism, effect on QT prolongation, in-vivo drug-drug interactions, and in-vitro p-glycoprotein screens." She recommended that the NDA will be considered acceptable pending the sponsor's agreement to four Phase 4 commitments. "No pharmacokinetic data was obtained at the proposed dose (100 mg/m2 IV over 30-mins) in the proposed CLL patient population. In addition, there were no formal PK dose ranging studies, and no multiple dose pharmacokinetic assessments. A mass-balance study in humans was initiated in 2008. Completion of the mass balance study, assessment of QT prolongation, [redacted], in-vitro p-gp substrate and inhibition screens, and in-vivo interaction studies with a CYP1A2 inhibitor and inducer will be phase 4 commitments. The completion of renal and/or hepatic studies will depend on the outcome of the mass balance evaluation." Dr. Bullock's review was cosigned by Brian Booth Ph.D. on 2/22/2008.

5.1 General clinical pharmacology/biopharmaceutics considerations:

The Clinical pharmacology assessments were mostly based on Studies conducted in patients with Non-Hodgkin's Lymphoma (NHL). As noted by Dr. Booth, Team Leader/Deputy Director, Clinical Pharmacology, "the dose in this patient population is 20% higher than the dose used for CLL patients (100 mg/m^2). In the NHL patients, the higher dose was infused for 1 hour (twice as long as CLL patients) and had an elimination half-life of about 5 hours. The Cmax was approximately 5600 ng/ml, and the AUC was approximately 6600 ng·hr/ml. No information is available from these studies regarding the dose proportionality of bendamustine. Bendamustine generates two active metabolites, named M3 and M4. However, concentrations of these metabolites in vivo appear to be 1/10 (M3) and

1/100th (M4) of the concentrations of the parent, and are not likely to contribute significantly to the activity of the drug."

5.2 Drug-drug interactions

Per Dr Booth, "Based on in vitro studies, cytochrome P-450 1A2 (CYP 1A2) appears to mediate the metabolism of bendamustine. No in vivo drug-drug interactions were conducted to assess the impact of co-administering medications that induce CYP 1A2 (e.g. smoking, omeprazole) which could reduce bendamustine plasma concentrations to sub-therapeutic levels. Also, no in vivo studies were conducted to assess the effect of CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin), which might be expected to cause toxicity via increased plasma levels of bendamustine. The role of P-glycoprotein and other transporters in the fate of bendamustine was not assessed."

5.3 Pathway of Elimination

No "mass balance" study was conducted, and the routes of elimination and the extent that these routes play in the elimination of the drug were not determined. Therefore, although metabolism plays some role in the elimination of the drug, extent of renal elimination remains unknown. Therefore, the need for studies to assess the effect of organ dysfunction on drug elimination has not yet been assessed."

5.4 Demographic interactions/special populations

According to Dr. Booth, a pharmacokinetic study of bendamustine in Japanese patients was also undertaken. This study revealed a similar disposition of bendamustine, but Japanese patients had a mean clearance that was 20% lower than the North American population. The clinical significance of this finding is unclear.

5.5 Thorough QT study or other QT assessment

QT assessment has not been conducted and will be a post-marketing commitment

5.6 Other notable issues

See post-marketing commitments.

6 Clinical Microbiology

Not Applicable.

7 Clinical/Statistical

7.1 Efficacy

7.1.1 Dose identification/selection and limitations

Per applicant, two dose finding studies were conducted in previously treated patients with refractory or progressive Binet stage B or C CLL with 15 and 16 patients respectively. In one study in which bendamustine was administered every 21 days, MTD was 70 mg/m^2/day administered on day 1 and 2. Based on these results, it was recommended that the treatment cycle be prolonged to 28 days. In the

second study with younger and less heavily treated patients, the MTD was 100 mg/m^2 on day 1 and 2, when given every 21 days. A recommendation was made in this study as well, to prolong the treatment cycle to 28. Later, in a Scientific Protocol Review Board Meeting, experts recommended that 100 mg/m^2 be administered on days 1 and 2 and repeated every 28 days.

7.1.2 Randomized, Phase 3 clinical study

The applicant submitted a single randomized study titled "*Title of Study: Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naïve Patients With (Binet Stage B/C) B-CLL Requiring Therapy*". This study was conducted from 5th November 2002 through 26th March 2006. The safety and efficacy of bendamustine were evaluated in trial comparing bendamustine to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

Table: Dose and schedule of bendamustine and chlorambucil

Treatment Arms	Dose and Schedule
Treanda N=153	100 mg/m^2 on days 1 and 2 during each 28-day cycle.
Chlorambucil N=148	0.8 mg/kg (Broca's normal weight) orally on days 1 and 15 or, if necessary, divided doses on days 1 and 2 and on days 15 and 16 during each 28-day cycle.

Co-primary endpoints:
- Overall response rate (ORR) based on the criteria as defined by the NCI-WG on CLL (original protocol)
- Progression-free survival (PFS)

The primary efficacy endpoints were overall response rate (ORR) and progression-free survival (PFS) assessed for the intent-to-treat (ITT) population. Originally, these were based on the NCI-WG criteria for CLL. In amendment #4, the primary endpoints were to be based on ICRA assessment. Overall response rate (ORR) was defined as the proportion of patients in each treatment group with a best response of complete response (CR), nodular partial response (nPR), or partial response (PR) to treatment. Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first.

Analysis of the co-primary endpoints will be described using three different major analyses, i.e., as assessed by Independent Response Assessment Committee (ICRA), investigator's assessment and "calculated assessment". The "calculated assessment" was the applicant's efficacy assessment that used a computer programmed algorithm based on NCI-WG criteria for CLL with elements obtained from the source documents.

Secondary endpoints were:

- time to progression (TTP)
- duration of response
- overall survival (OS)
- infection rate
- quality of life
- toxicities

The secondary endpoints will not be discussed further in this review. Please see MOR for details.

Results:

The demographics were unremarkable except that all but one patient were Caucasians. Seventy percent had Binet Stage B disease and 30% had stage C disease. Ninety percent patients had co-expression of CD5, CD23 and either CD19 or CD20 or both. Two of the largest enrolling centers were found by the applicant to have several major deviations from the protocol. These sites enrolled 54 patients.

Efficacy

Applicant's table

Primary Efficacy Variable	**TREANDA (N=153)**	**Chlorambucil (N=148)**	**p-value**
Response Rate by Independent Review, n (%)			
Overall response rate	95 (62)	49 (33)	<0.0001
(95%CI)	(54.40, 69.78)	(25.53, 40.69)	
Complete response (CR)	42 (27)	3 (2)	
Nodular partial response (nPR)	15 (10)	4 (3)	
Partial response (PR)	38 (25)	42 (28)	
Response Rate by Calculated Analysis, n (%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95%CI)	(51.03, 66.62)	(18.64, 32.71)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)	4 (3)	0	
Partial response (PR)	73 (48)	37 (25)	
Progression-Free Survival by Independent Review			
Median, months	21	9	
Hazard ratio (95% CI)	0.23 (0.13 – 0.39)		<0.0001
Progression-Free Survival by Calculated Analysis			
Median, months	18	6	
Hazard ratio (95% CI)	0.27 (0.17 – 0.43)		<0.0001

CI=confidence interval

*CR only assigned in patients with requisite bone marrow sample for confirmation.

Table: Efficacy Data based on Calculated Algorithm based on NCI-WG Criteria for CLL
FDA Statistical Reviewer's table

	TREANDA (N=153)	Chlorambucil (N=148)	p-value
Response Rate n(%)			
Overall response rate	90 (59)	38 (26)	**<0.0001**
(95% CI)	(51.03, 66.62)	(18.64, 32.71)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)	4 (3)	0	
Partial response (PR)	73 (48)	37 (25)	
Progression-Free Survival			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		**<0.0001**

*CR was defined as peripheral lymphocyte count $\leq 4.0 \times 10^9$/L, neutrophils $\geq 1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L, hemoglobin > 110g/L, , absence of palpable hepatosplenomegaly, lymph nodes $\leq$ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms

Response Rate (RR):

The overall response rate was approximately 60% in the bendamustine arm and 26% -33% in the chlorambucil arm as assessed by ICRA or by the calculated algorithm based on NCI-WG CLL criteria respectively (see tables above). The CRs were 27% according to ICRA assessment and 8% according to the calculated algorithm. For RR according to investigator's assessment, please see MOR. The clinical and statistical teams recommend that the efficacy findings be based on the calculated algorithm that used NCI-WG criteria for CLL for the labeling for reasons discussed below.

ICRA assessed versus calculated algorithm-based analysis:

According to applicant, the original sponsor supplied the ICRA with the tumor evaluations from all patients blinded for patient name, center, treatment arm and overall response assessment. Each ICRA member evaluated all patients separately. The assessments were provided to the sponsor who compared the assessment of the ICRA members. Patients with identical assessments were to have analysis entered directly. Responses assessed differently underwent a discussion and consensus process between the ICRA members. The analysis with the consolidated overall response was used. However, no records on the decision making were kept, and therefore, the results based on the ICRA assessment can not be verified.

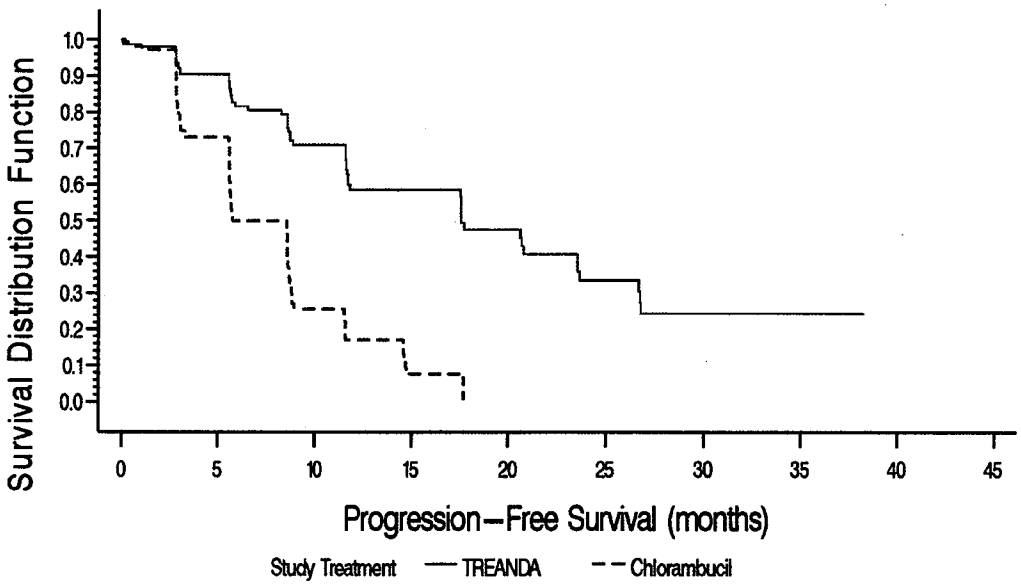
e the ICRA-assessed analyses The RR by this assessment has a markedly higher number of CRs, although the ORR is similar to that obtained by the calculated algorithm. However, the results according to ICRA assessment are not verifiable

, ICRA did not adhere to the NCI-WG criteria as specified in the original protocol. The reasons for deviation from NCI-WG criteria for individual patients were not captured. The results based on ICRA assessment are not verifiable.

Progression-free Survival:

The median PFS based on the ICRA assessment was 21 months in the bendamustine arm and 9 months in the chlorambucil treatment group; the difference between treatment groups in PFS was statistically significant in favor of bendamustine treatment. Hazard ratio for this difference was 0.23. For the NCI-WG criteria based calculated analysis, the median PFS was 18 months on the Bendamustine arm and 6 months on the chlorambucil arm with a hazard ratio of 0.27. The difference in median PFS was 12 months between the two groups in both analyses.

Figure: PFS based on prespecified algorithm based on NCI-WG criteria



7.1.3 Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical efficacy reviewer Dr. Qin Ryan and clinical safety reviewer Ms. Virginia Kwitkowski M.S., R.N., C.R.N.P., both recommend approval of bendamustine for CLL pending completion of financial disclosure by the applicant.

The efficacy analyses of the primary endpoint were statistically significant in favor of bendamustine and these included the following

- RR and PFS based on prespecified NCI-WG criteria,
- RR and PFS based on ICRA,
- RR and PFS based on analyses excluding of the 2 sites with major violations.

As noted by Ms Kwitkowski, the requirements for blood transfusions (20% on Treanda arm), decreased with increasing number of treatments. This improvement in anemia was most likely due to disease response. Patients with Patients with complete responses (CRs) had more improvement in hemoglobin than those with partial responses (PRs).

Overall survival was immature at the time of data cut-off.

7.1.4 Pediatric use/PREA waivers/deferrals

CLL is a disease that generally affects older individuals. A pediatric waiver was given to Treanda for this indication.

7.1.5 Discussion of notable efficacy issues

The efficacy of bendamustine has been demonstrated by a clinically and statistically significant improvement in response rate and progression-free survival. The response rate improved to 59% with an 8% CR rate. A twelve month improvement in median progression-free survival was observed. No drug has demonstrated an unequivocal improvement in overall survival to date.

7.2 Safety

7.2.1 General safety considerations

The safety population included 153 patients treated on the Treanda arm. The population was 45-77 years of age, 63% male, 100% white, and had treatment naïve CLL. Adverse reactions were reported according to NCI CTC v.2.0.

According to the safety reviewer Virginia Kwitkowski, "Non-hematologic adverse reactions were mostly of low grade (1-2). Eighty-eight (58%) patients in the bendamustine treatment group and 44 (31%) patients in the chlorambucil treatment group reported at least one grade 3 or 4 adverse reaction. Both grade 3 and 4 adverse reactions occurred more frequently in the bendamustine treatment group than in the chlorambucil treatment group. Grade 3 events were reported in 33% of the bendamustine patients as compared to 22% in the chlorambucil patients. Grade 4 events were reported in 25% of patients in the bendamustine group as compared to 8% of patients in the chlorambucil group"

7.2.2 Safety findings from submitted clinical trials

In the randomized CLL clinical study, hematologic adverse reactions (any grade) in the Treanda group that occurred with a frequency greater than 15% were neutropenia (28%), thrombocytopenia (23%), anemia (19%), and leukopenia (18%). Non-hematologic adverse reactions (any grade) in the Treanda group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%). Grade 3 or greater hematology laboratory test abnormalities were anemia (13%),

thrombocytopenia (11%), and decreased neutrophils (43%). The incidence of febrile neutropenia was 6% and 20% of the patients were transfused with RBCs. The most frequent adverse reactions leading to study withdrawal for patients receiving Treanda were hypersensitivity (2%) and pyrexia (1%).

"Grade 3/ 4 hematologic adverse reactions with a frequency greater than 10% in the bendamustine treatment group were neutropenia (24%), leukopenia (15%), and thrombocytopenia (13%). Grade 3/4 non-hematologic adverse reactions were reported by 52 (34%) patients in the bendamustine treatment group and 25 (17%) patients in the chlorambucil treatment group. Grade 3/ 4 non-hematologic adverse reactions with a frequency greater than 1% in the bendamustine treatment group were pyrexia (4%), pneumonia (3%), rash (3%), hypertension (3%), hypertensive crisis (2%), hyperuricemia (2%), and infection (2%). Five patients (3%) in the bendamustine treatment group experienced febrile neutropenia compared with none in the chlorambucil group. Neutropenic infection occurred in 10 bendamustine patients compared with 1 in the chlorambucil group. There were 2 events of grade 3 sepsis, both in patients in the bendamustine treatment group. Both patients recovered. Grade 3/4 hematologic adverse reactions with a frequency greater than 5% in the chlorambucil treatment group were neutropenia (9%) and thrombocytopenia (8%)".

Myelosuppression, infections related to myelosuppression, tumor lysis syndrome, hypersensitivity reactions, hypertension and other cardiac events and secondary malignancies were identified as significant adverse reactions in the safety review.

"Thirty-four deaths occurred during the conduct of study 02CLLIII. An equal number (17) of deaths occurred in each treatment group" and "The most common attribution for death was progression of disease (41% of patients in each group). Four patients died during the treatment phase of the study or within 30 days of the last study drug dose, one patient in the bendamustine group and three patients in the chlorambucil group."

According to Ms Kwitkowski, "Twenty-two patients were withdrawn from the study because of adverse reactions; 17 (11%) patients who received bendamustine and 5 (3%) patients who received chlorambucil. The most frequent adverse reactions causing withdrawal were hypersensitivity (occurring in 3 bendamustine patients and 1 chlorambucil patient) and pyrexia (occurring in 2 bendamustine patients and 1 chlorambucil patient)."

She also comments: "Non-clinical studies described dose-related cardiac toxicity in animals. The clinical dose-escalation studies demonstrated dose-related cardiac toxicities. Though the overall incidence of cardiac toxicity in the bendamustine arm was low (and similar to the chlorambucil arm); bendamustine may have cardiac toxicities, particularly at higher doses than those utilized in the pivotal trials for CLL and NHL. The large variety of cardiac events reported in these smaller studies make it difficult to provide firm attribution to bendamustine. ECG monitoring in this study was not adequate to evaluate the potential for QT prolongation because ECGs were only obtained at baseline and end of study; and interval measurements were not obtained."

In the amended Medical Officers' Review, Ms. Kwitkowski observed "In the dataset exploration, no cases that met Hy's law criteria were found. These results do not exclude the potential for DILI due to the small sample size, but no evidence for DILI was identified during this data exploration."

7.2.3 Safety update

Per Ms Kwitkowski: "The postmarketing data provided by the Applicant does not provide new safety concerns that would affect the regulatory decision to approve bendamustine for CLL."

7.2.4 Discussion of primary reviewer's comments and conclusions

I concur with the primary reviewers' conclusions.

7.2.5 Pre-Approval Safety Conference

A Pre-Approval Safety Conference was conducted on 2/27/2008. The findings of the safety reviewer were discussed and are included in this review above and in Ms. Kwitkowski's review of safety.

7.2.5 Discussion of notable safety issues

See section 7.2.1.

Statistics Review Team's comments:

According to Shenghui Tang, Ph.D., primary statistics reviewer, "A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries. The sponsor reported that the proportion of patients with ORR was 62% in the bendamustine treatment group compared with 33% in the chlorambucil treatment group ($p<0.0001$) as determined by the Independent Committee for Response Assessment (ICRA). The primary PFS analysis showed that the bendamustine treatment was superior to chlorambucil treatment (median 21 vs. 9 months, hazard ratio (HR) 0.23, $p<0.0001$). Based on the data submitted by the sponsor these results were confirmed by this reviewer and the data support the efficacy claim."

"Whether the endpoints and the sizes of the effects on these two endpoints in this phase III study are adequate for approval is a clinical decision." (Review dated 2/19/2008, concurrence signatures provided by Dr. Sridhara and Dr. Chakravarty on the same dates).

According to Rajeshwari Sridhara Ph.D., Team Leader and Deputy Director for Biometrics, "I concur with the primary reviewer, Dr. Tang's conclusion that the data submitted supports the claim that bendamustine has demonstrated superior overall response rate (ORR) and progression-free survival (PFS) compared to chlorambucil (ORR of 59% vs. 26% and PFS HR = 0.52, p-value < 0.0001)."

"Progression-free survival was assessed by a panel of three independent expert hematologic oncologists and also objectively calculated using an algorithm based on NCI working group criteria. According to the sponsor, in performing the review the members of the independent panel were allowed to exercise clinical judgment in determining response." and "The FDA reviewers were able to verify the calculated response rates and PFS, but could not verify the same as determined by the independent panel due the subjective nature of the independent evaluation. Therefore, it is recommended that the calculated response rates and PFS estimates be included in the product label." Her review is dated 2/25/2008 and was cosigned on the same day by Aloka Chakravarty Ph.D.

8 Advisory Committee Meeting

None held.

9 Other Relevant Regulatory Issues

None.

10 Financial Disclosure

Per applicant, many of the studies contained in this NDA, including the pivotal trial Study 02CLLLIII were conducted by another sponsor, Astellas, at clinical sites in Europe only; they were not conducted under an IND. Therefore, the sponsor of these studies did not prospectively request financial disclosure information from any investigator. The applicant asked representatives from Astellas if it were possible to obtain information from the investigators in support of this application. Astellas responded that they would be unable to obtain the required information for this randomized study.

The applicant obtained financial disclosure from the investigators on FDA's request. According to the amended Medical Officers review, "Among the 45 principal investigators (PIs), 43 of them as well as the available sub-investigators from their sites submitted financial disclosures indicating no personal financial interest in the study drug. Of the 2 remaining PIs, one was deceased and one is on vacation. Based on the information provided in this NDA, there were 11 patients enrolled from the sites of the 2 PIs whose financial disclosures are not yet available. Excluding enrollments from the deceased PI, 6 patients (or 2% of the total enrollment of study 02CLLIII) were treated by an investigator who has not provided financial disclosure information. The applicant will continue to collect this information and submit it to the Agency as soon as the last one is available."

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

11 Labeling

Labeling has been completed and agreement has been reached with the applicant.

11.1. Proprietary name

There were no objections to the use of Treanda as the proprietary name by OSE/DMEP.

11.2. Physician labeling

Labeling has been completed. Revised labels were submitted and are acceptable.

11.3. Carton and immediate container labels

CMC and OSE/DMEP recommendations for changes in the carton and container labels were communicated to and accepted by the applicant.

11.4 Patient labeling/Medication guide

This is an intravenous formulation that will not be self-administered by the patient. Patient labeling is not required.

12. DSI Audits

In the DSI review dated 2/29/2008, Lauren Iacono-Connors, Ph.D. concludes that the study data collected at the 4 sites inspected appear reliable. The inspection of Cephalon Inc., did not identify any critical issues. Only the sponsor inspection has completed the EIR and provided that to DSI for support of the CIS. The 4 CIs final reports (EIRs) have not been completed to date. While 2 of the of the 4 clinical investigators inspected were issued Form FDA 483 inspection observations, it does not appear that the compliance deviations would significantly alter overall study outcome.

Dr. O'Connor stated that "DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits".

13. Conclusions and Recommendations

13.1. Recommended regulatory action

All disciplines recommend approval of Treanda for CLL. A statistically significant improvement in response rate, and progression free survival was observed. The adverse event profile is acceptable.

13.2. Safety concerns to be followed Postmarketing

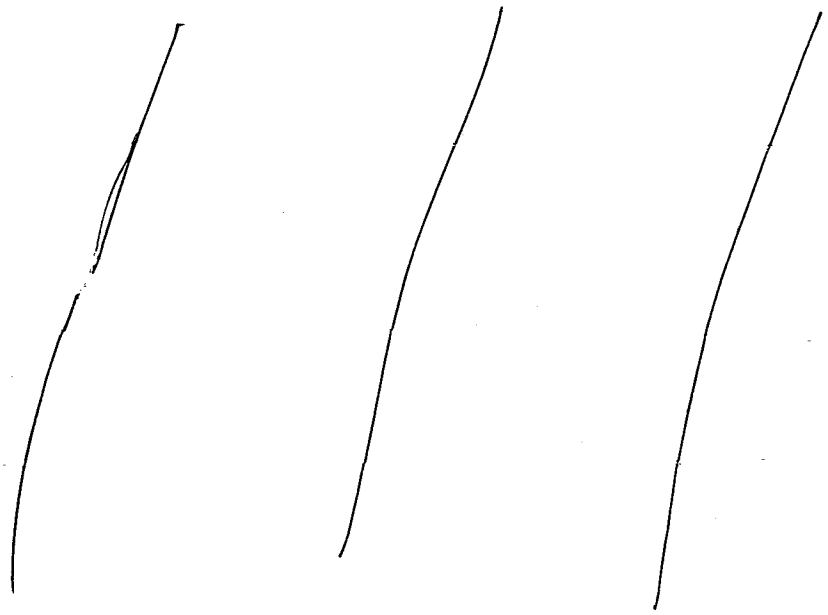
As noted in Ms. Kwitkowski's review, a risk management program does not appear to be necessary for bendamustine, above and beyond labeling recommendations.

13.3. Risk Minimization Action Plan, if any

None.

13.4. Postmarketing studies

Please see the action letter for the finalized PMCs. PMC under discussion at this time are:



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1. Cheson BD, Bennett JM, Kay N et al. National Cancer Institute-Sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;12,4990-4997
2. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Annals of Oncology* 13:1285-1289, 2002

Amna Ibrahim MD
Clinical Team Leader
Cross-Disciplinary Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amna Ibrahim
3/20/2008 10:44:26 AM
MEDICAL OFFICER
Amended CDTL review

Cross-Discipline Team Leader Review

Date	February 29, 2008
From	Amna Ibrahim MD
Subject	Cross-Discipline Team Leader Review
NDA # (Supp #)	22249 (S-000)
Proprietary / Established (USAN) names	Bendamustine (Treanda)
Dosage forms /strength	100-mg vials of bendamustine HCL as white to off-white lyophilized powder
Proposed Indication(s)	For the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.
Recommended:	Approval (pending completed reviews from all disciplines and financial disclosure from the applicant)

1 Introduction

A single, open-label, multicenter, randomized trial has been submitted as the major trial to support the approval of bendamustine (Treanda®) for the treatment of patients with CLL. The clinical team recommends approval of this NDA on the basis of an improvement in Overall Response Rates (ORR) and Progression-free Survival (PFS).

In this study, Bendamustine was compared to Chlorambucil as a comparator in a treatment-naïve population. The choice of comparator was influenced by the drugs approved in Europe for this indication, where the trial was conducted. Fludarabine, one of the most active drugs for this disease was approved only for second-line use. FDA does not require the use of a standard of care in a randomized study.

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

CLL is a disease that mainly affects the older population, the median age being 72 at diagnosis. Over the past few decades, there has been little progress in prolonging survival of patients with CLL, and it remains an incurable disorder. Because the patients generally have a good long term prognosis and treatment does not change the outcome of disease, a "watch and wait" approach is often used before initiation of treatment. Factors which generally prompt the initiation of therapy include the presence of disease-related symptoms, massive and/or progressive lymphadenopathy or hepatosplenomegaly, bone marrow failure, or recurrent infections. The lymphocyte doubling time should be considered in the total clinical picture but not used as the primary criterion. The routine availability of peripheral blood lymphocyte immunophenotyping has facilitated the diagnosis of CLL in patients with a monoclonal lymphocytosis. Three main phenotypic features define B-CLL: the predominant population shares B-cell markers (CD19, CD20, and CD23) with the CD5 antigen, in the absence of other pan-T-cell markers; the B cell is monoclonal with regard to expression of either κ or *h;* and surface immunoglobulin (sIg) is of low density. Not only are these characteristics generally adequate for a

precise diagnosis, but, importantly, they distinguish CLL from uncommon disorders such as PLL, hairy-cell leukemia, mantle-cell lymphoma, and other lymphomas[1].

The National Cancer Institute-Sponsored Working Group (NCI-WG) published guidelines for the diagnosis and criteria for response for CLL[1]. The peripheral blood should exhibit an increase in the number of small mature-appearing lymphocytes to >5,000/μl. The bone marrow aspirate smear must show >30% of all nucleated cells to be lymphoid. Although a bone marrow examination is rarely required to make the diagnosis of CLL in general practice, it may be evaluable prior to the start of treatment in order to define prognostic factors. Subsequently, a bone marrow examination is indicated primarily to evaluate response to treatment or to assess normal elements if there is an unexplained anemia or thrombocytopenia[1]. Although not approved for this indication, Fludarabine-based regimens are generally used for treatment-naïve patients in the US. Chlorambucil and cyclophosphamide are approved for this patient population. For further details regarding first-line treatment options, please see Medical Officer's Review (MOR).

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Bendamustine hydrochloride was developed in the 1960s in former East Germany, but was never systematically studied in patients until the 1990s[2]. Per applicant, although it has been used for a variety of malignancies in Germany for over 30 years, re-approval was required by the German law post reunification due to regulatory requirements in the German Democratic Republic. Bendamustine is currently marketed in Germany and Bulgaria.

This randomized study was conducted entirely in Europe by Ribosepharm GmbH, and per applicant, is _____. Cephalon Inc. acquired the rights and using their own statistical analysis plan (SAP), analyzed and submitted the NDA to FDA. This SAP and its approach were discussed with the FDA in a preNDA meeting. FDA asked for details of the SAP, and did not agree (or disagree) to the design due to insufficient information. In an earlier EOP2 meeting with Cephalon, FDA agreed to accept a single randomized study and encouraged the use of an independent response review committee for efficacy evaluation. For further details regarding the regulatory history, please see Dr. Qin Ryan's Medical Officer's Review (MOR). There was no Special Protocol Assessment (SPA) conducted for the protocol.

3. CMC/Microbiology

The CMC review was completed by Ravindra K. Kasliwal Ph.D., and cosigned by Ravi Harapanhalli on 2/27/2008. Their recommendation is as below:

"The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided trademark and labeling acceptability has been determined by Office of Drug Safety (DMETS) and provided the manufacturing sites are deemed acceptable for cGMP compliance. The product quality microbiology has recommended approval on 06-Feb-2008. The recommendation for Office of Compliance regarding the acceptability of the manufacturing facilities is pending as of the date of this review."

3.1 General product quality considerations

According to the microbiology reviewer, Anastasia G. Lolas, M.S., and co-signed by Stephen Langille Ph.D., this NDA is recommended for approval (Date archived: 2/6/2008) from microbiology point of view.

3.2 Facilities review/inspection

Information is pending.

3.3Other notable issues

Per CMC review, the company has not provided data showing compatibility of the constitution solution, Sterile Water for Injection, USP, with other commonly available diluents such as . The data (assay and impurity profile) should be provided as part of the phase 4 commitment within 6 months of approval of the application (comment for company is provided at the end of this review).

It is recommended in the CMC review that the following be included in the action letter:

"We remind you of your agreement in an amendment dated 12-Feb-2008 to initiate change controls for all the documents impacted by the revision to the maximum hold time not to exceed and to submit appropriate post-approval correspondence reflecting this change."

4. Nonclinical Pharmacology/Toxicology

Pharmacology/Toxicology Review and Evaluation was signed by Anwar Goheer Ph.D. and cosigned by team leader John Leighton Ph.D. on 2/27/2008. According to the review, the nonclinical studies are sufficient to support the approval of this NDA. Excerpt from his review states:

"A. Recommendation on approvability: The non-clinical studies submitted to this NDA provide sufficient information to support the use of Treanda ® (bendamustine hydrochloride) for the treatment of patients with chronic lymphocytic leukemia (CLL)."
"B. Recommendation for nonclinical studies: No additional non-clinical studies are required."
"C. Recommendations on labeling: A separate review will be conducted."

4.1 General nonclinical pharmacology/toxicology considerations

According to Dr Goheer's review, "Bendamustine hydrochloride [Treanda®, Cytostasan® (Germany), and Ribomustine® (Germany)] belongs to bifunctional nitrogen mustards. Nitrogen mustard and its derivatives are alkylating agents which dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage produced can lead to cell death via several pathways. The precise mechanism of action of bendamustine has not been fully characterized."

4.2 Carcinogenicity

As observed in Dr. Goheer's review, bendamustine is a genotoxic alkylating agent. Oral administration for four days induced mammary carcinoma and pulmonary adenomas in mice."

4.3 Reproductive toxicology

Dr. Goheer's review also stated that embryo-fetal developmental studies were not conducted by the sponsor. During embryo-fetal developmental toxicity study, intraperitoneal administration of bendamustine produced embryotoxic and teratogenic effects in mice.

4.4 Other notable issues

Per Dr. Goheer's review, nonclinical safety issues relevant to clinical use were reduction in WBC and lymphocytes were observed in a dose related manner during pivotal repeat dose toxicity studies in rats and dogs. Treatment related microscopic changes were seen in kidneys (tubular degeneration/necrosis) in both species. Cardiomyopathy (focal/multifocal) was observed in male rats only. Heart rates of dogs at 6.6 mg/kg/day were reduced during cycle 2 (2 males & 1 female, 3/6 animals). A vigilant monitoring of QT prolongation is warranted until more clinical experience is gained. Bendamustine is mutagenic, carcinogenic, and teratogenic like other nitrogen mustard alkylating agents. There are no outstanding issues noted in Dr Goheer's review.

5 Clinical Pharmacology/Biopharmaceutics

Julie Bullock, Ph.D. was the clinical pharmacology reviewer for this NDA. Her recommendations were as follows:

"This NDA is considered to be deficient from a clinical pharmacology perspective due to the lack of data available regarding pharmacokinetics at the proposed dose, dose proportionality, human excretion and metabolism, effect on QT prolongation, in-vivo drug-drug interactions, and in-vitro p-glycoprotein screens." She recommended that the NDA will be considered acceptable pending the sponsor's agreement to four Phase 4 commitments. "No pharmacokinetic data was obtained at the proposed dose (100 mg/m2 IV over 30-mins) in the proposed CLL patient population. In addition, there were no formal PK dose ranging studies, and no multiple dose pharmacokinetic assessments. A mass-balance study in humans was initiated in 2008. Completion of the mass balance study, assessment of QT prolongation, [redacted] in-vitro p-gp substrate and inhibition screens, and in-vivo interaction studies with a CYP1A2 inhibitor and inducer will be phase 4 commitments. The completion of renal and/or hepatic studies will depend on the outcome of the mass balance evaluation." Dr. Bullock's review was cosigned by Brian Booth Ph.D. on 2/22/2008.

5.1 General clinical pharmacology/biopharmaceutics considerations:

The Clinical pharmacology assessments were mostly based on Studies conducted in patients with Non-Hodgkin's Lymphoma (NHL). As noted by Dr. Booth, Team Leader/Deputy Director, Clinical Pharmacology, "the dose in this patient population is 20% higher than the dose used for CLL patients (100 mg/m^2). In the NHL patients, the higher dose was infused for 1 hour (twice as long as CLL patients) and had an elimination half-life of about 5 hours. The Cmax was approximately 5600 ng/ml, and the AUC was approximately 6600 ng·hr/ml. No information is available from these studies regarding the dose proportionality of bendamustine. Bendamustine generates two active metabolites, named M3 and M4. However, concentrations of these metabolites in vivo appear to be 1/10 (M3) and

1/100th (M4) of the concentrations of the parent, and are not likely to contribute significantly to the activity of the drug."

5.2 Drug-drug interactions

Per Dr Booth, "Based on in vitro studies, cytochrome P-450 1A2 (CYP 1A2) appears to mediate the metabolism of bendamustine. No in vivo drug-drug interactions were conducted to assess the impact of co-administering medications that induce CYP 1A2 (e.g. smoking, omeprazole) which could reduce bendamustine plasma concentrations to sub-therapeutic levels. Also, no in vivo studies were conducted to assess the effect of CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin), which might be expected to cause toxicity via increased plasma levels of bendamustine. The role of P-glycoprotein and other transporters in the fate of bendamustine was not assessed."

5.3 Pathway of Elimination

No "mass balance" study was conducted, and the routes of elimination and the extent that these routes play in the elimination of the drug were not determined. Therefore, although metabolism plays some role in the elimination of the drug, extent of renal elimination remains unknown. Therefore, the need for studies to assess the effect of organ dysfunction on drug elimination has not yet been assessed."

5.4 Demographic interactions/special populations

According to Dr. Booth, a pharmacokinetic study of bendamustine in Japanese patients was also undertaken. This study revealed a similar disposition of bendamustine, but Japanese patients had a mean clearance that was 20% lower than the North American population. The clinical significance of this finding is unclear.

5.5 Thorough QT study or other QT assessment

QT assessment has not been conducted and will be a post-marketing commitment

5.6 Other notable issues

See post-marketing commitments.

6 Clinical Microbiology

Not Applicable.

7 Clinical/Statistical

7.1 Efficacy

7.1.1 Dose identification/selection and limitations

Per applicant, two dose finding studies were conducted in previously treated patients with refractory or progressive Binet stage B or C CLL with 15 and 16 patients respectively. In one study in which bendamustine was administered every 21 days, MTD was 70 mg/m^2/day administered on day 1 and 2. Based on these results, it was recommended that the treatment cycle be prolonged to 28 days. In the

second study with younger and less heavily treated patients, the MTD was 100 mg/m^2 on day 1 and 2, when given every 21 days. A recommendation was made in this study as well, to prolong the treatment cycle to 28. Later, in a Scientific Protocol Review Board Meeting, experts recommended that 100 mg/m^2 be administered on days 1 and 2 and repeated every 28 days.

7.1.2 Randomized, Phase 3 clinical study

The applicant submitted a single randomized study titled "*Title of Study: Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naïve Patients With (Binet Stage B/C) B-CLL Requiring Therapy*". This study was conducted from 5th November 2002 through 26th March 2006. The safety and efficacy of bendamustine were evaluated in trial comparing bendamustine to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

Table: Dose and schedule of bendamustine and chlorambucil

Treatment Arms	Dose and Schedule
Treanda N=153	100 mg/m^2 on days 1 and 2 during each 28-day cycle.
Chlorambucil N=148	0.8 mg/kg (Broca's normal weight) orally on days 1 and 15 or, if necessary, divided doses on days 1 and 2 and on days 15 and 16 during each 28-day cycle.

Co-primary endpoints:
- Overall response rate (ORR) based on the criteria as defined by the NCI-WG on CLL (original protocol)
- Progression-free survival (PFS)

The primary efficacy endpoints were overall response rate (ORR) and progression-free survival (PFS) assessed for the intent-to-treat (ITT) population. Originally, these were based on the NCI-WG criteria for CLL. In amendment #4, the primary endpoints were to be based on ICRA assessment. Overall response rate (ORR) was defined as the proportion of patients in each treatment group with a best response of complete response (CR), nodular partial response (nPR), or partial response (PR) to treatment. Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death for any cause, whichever occurred first.

Analysis of the co-primary endpoints will be described using three different major analyses, i.e., as assessed by Independent Response Assessment Committee (ICRA), investigator's assessment and "calculated assessment". The "calculated assessment" was the applicant's efficacy assessment that used a computer programmed algorithm based on NCI-WG criteria for CLL with elements obtained from the source documents.

Secondary endpoints were:

- time to progression (TTP)
- duration of response
- overall survival (OS)
- infection rate
- quality of life
- toxicities

The secondary endpoints will not be discussed further in this review. Please see MOR for details.

Results:

The demographics were unremarkable except that all but one patient were Caucasians. Seventy percent had Binet Stage B disease and 30% had stage C disease. Ninety percent patients had co-expression of CD5, CD23 and either CD19 or CD20 or both. Two of the largest enrolling centers were found by the applicant to have several major deviations from the protocol. These sites enrolled 54 patients.

Efficacy

Applicant's table

Primary Efficacy Variable	**TREANDA (N=153)**	**Chlorambucil (N=148)**	**p-value**
Response Rate by Independent Review, n (%)			
Overall response rate	95 (62)	49 (33)	<0.0001
(95%CI)	(54.40, 69.78)	(25.53, 40.69)	
Complete response (CR)	42 (27)	3 (2)	
Nodular partial response (nPR)	15 (10)	4 (3)	
Partial response (PR)	38 (25)	42 (28)	
Response Rate by Calculated Analysis, n (%)			
Overall response rate	90 (59)	38 (26)	<0.0001
(95%CI)	(51.03, 66.62)	(18.64, 32.71)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)	4 (3)	0	
Partial response (PR)	73 (48)	37 (25)	
Progression-Free Survival by Independent Review			
Median, months	21	9	
Hazard ratio (95% CI)	0.23 (0.13 – 0.39)		<0.0001
Progression-Free Survival by Calculated Analysis			
Median, months	18	6	
Hazard ratio (95% CI)	0.27 (0.17 – 0.43)		<0.0001

CI=confidence interval

*CR only assigned in patients with requisite bone marrow sample for confirmation.

Table: Efficacy Data based on Calculated Algorithm based on NCI-WG Criteria for CLL
FDA Statistical Reviewer's table

	TREANDA (N=153)	Chlorambucil (N=148)	p-value
Response Rate n(%)			
Overall response rate	90 (59)	38 (26)	**<0.0001**
(95% CI)	(51.03, 66.62)	(18.64, 32.71)	
Complete response (CR)*	13 (8)	1 (<1)	
Nodular partial response (nPR)	4 (3)	0	
Partial response (PR)	73 (48)	37 (25)	
Progression-Free Survival			
Median, months (95% CI)	18 (11.7, 23.5)	6 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		**<0.0001**

*CR was defined as peripheral lymphocyte count $\leq 4.0 \times 10^9$/L, neutrophils $\geq 1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L, hemoglobin > 110g/L, , absence of palpable hepatosplenomegaly, lymph nodes ≤ 1.5 cm, < 30% lymphocytes without nodularity in at least a normocellular bone marrow and absence of "B" symptoms

Response Rate (RR):

The overall response rate was approximately 60% in the bendamustine arm and 26% -33% in the chlorambucil arm as assessed by ICRA or by the calculated algorithm based on NCI-WG CLL criteria respectively (see tables above). The CRs were 27% according to ICRA assessment and 8% according to the calculated algorithm. For RR according to investigator's assessment, please see MOR. The clinical and statistical teams recommend that the efficacy findings be based on the calculated algorithm that used NCI-WG criteria for CLL for the labeling for reasons discussed below.

ICRA assessed versus calculated algorithm-based analysis:

According to applicant, the original sponsor supplied the ICRA with the tumor evaluations from all patients blinded for patient name, center, treatment arm and overall response assessment. Each ICRA member evaluated all patients separately. The assessments were provided to the sponsor who compared the assessment of the ICRA members. Patients with identical assessments were to have analysis entered directly. Responses assessed differently underwent a discussion and consensus process between the ICRA members. The analysis with the consolidated overall response was used. However, no records on the decision making were kept, and therefore, the results based on the ICRA assessment can not be verified.

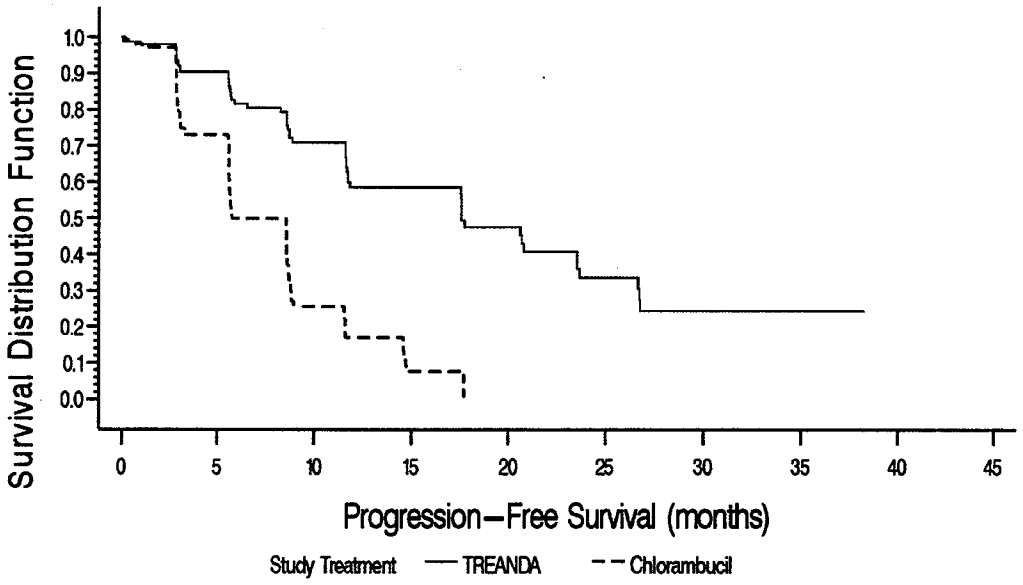
the ICRA-assessed analyses . The RR by this assessment has a markedly higher number of CRs, although the ORR is similar to that obtained by the calculated algorithm. However, the results according to ICRA assessment are not verifiable.

ICRA did not adhere to the NCI-WG criteria as specified in the original protocol. The reasons for deviation from NCI-WG criteria for individual patients were not captured. The results based on ICRA assessment are not verifiable.

Progression-free Survival:

The median PFS based on the ICRA assessment was 21 months in the bendamustine arm and 9 months in the chlorambucil treatment group; the difference between treatment groups in PFS was statistically significant in favor of bendamustine treatment. Hazard ratio for this difference was 0.23. For the NCI-WG criteria based calculated analysis, the median PFS was 18 months on the Bendamustine arm and 6 months on the chlorambucil arm with a hazard ratio of 0.27. The difference in median PFS was 12 months between the two groups in both analyses.

Figure: PFS based on prespecified algorithm based on NCI-WG criteria



7.1.3 Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical efficacy reviewer Dr. Qin Ryan and clinical safety reviewer Ms. Virginia Kwitkowski M.S., R.N., C.R.N.P., both recommend approval of bendamustine for CLL pending completion of financial disclosure by the applicant.

The efficacy analyses of the primary endpoint were statistically significant in favor of bendamustine and these included the following

- RR and PFS based on prespecified NCI-WG criteria,
- RR and PFS based on ICRA,
- RR and PFS based on analyses excluding of the 2 sites with major violations.

As noted by Ms Kwitkowski, the requirements for blood transfusions (20% on Treanda arm), decreased with increasing number of treatments. This improvement in anemia was most likely due to disease response. Patients with Patients with complete responses (CRs) had more improvement in hemoglobin than those with partial responses (PRs).

Overall survival was immature at the time of data cut-off.

7.1.4 Pediatric use/PREA waivers/deferrals

CLL is a disease that generally affects older individuals. A pediatric waiver was given to Treanda for this indication.

7.1.5 Discussion of notable efficacy issues

The efficacy of bendamustine has been demonstrated by a clinically and statistically significant improvement in response rate and progression-free survival. The response rate improved to 59% with an 8% CR rate. A twelve month improvement in median progression-free survival was observed. No drug has demonstrated an unequivocal improvement in overall survival to date.

7.2 Safety

7.2.1 General safety considerations

The safety population included 153 patients treated on the Treanda arm. The population was 45-77 years of age, 63% male, 100% white, and had treatment naïve CLL. Adverse reactions were reported according to NCI CTC v.2.0.

According to the safety reviewer Virginia Kwitkowski, "Non-hematologic adverse reactions were mostly of low grade (1-2). Eighty-eight (58%) patients in the bendamustine treatment group and 44 (31%) patients in the chlorambucil treatment group reported at least one grade 3 or 4 adverse reaction. Both grade 3 and 4 adverse reactions occurred more frequently in the bendamustine treatment group than in the chlorambucil treatment group. Grade 3 events were reported in 33% of the bendamustine patients as compared to 22% in the chlorambucil patients. Grade 4 events were reported in 25% of patients in the bendamustine group as compared to 8% of patients in the chlorambucil group"

7.2.2 Safety findings from submitted clinical trials

In the randomized CLL clinical study, hematologic adverse reactions (any grade) in the Treanda group that occurred with a frequency greater than 15% were neutropenia (28%), thrombocytopenia (23%), anemia (19%), and leukopenia (18%). Non-hematologic adverse reactions (any grade) in the Treanda group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%). Grade 3 or greater hematology laboratory test abnormalities were anemia (13%),

thrombocytopenia (11%), and decreased neutrophils (43%). The incidence of febrile neutropenia was 6% and 20% of the patients were transfused with RBCs. The most frequent adverse reactions leading to study withdrawal for patients receiving Treanda were hypersensitivity (2%) and pyrexia (1%).

"Grade 3/ 4 hematologic adverse reactions with a frequency greater than 10% in the bendamustine treatment group were neutropenia (24%), leukopenia (15%), and thrombocytopenia (13%). Grade 3/4 non-hematologic adverse reactions were reported by 52 (34%) patients in the bendamustine treatment group and 25 (17%) patients in the chlorambucil treatment group. Grade 3/ 4 non-hematologic adverse reactions with a frequency greater than 1% in the bendamustine treatment group were pyrexia (4%), pneumonia (3%), rash (3%), hypertension (3%), hypertensive crisis (2%), hyperuricemia (2%), and infection (2%). Five patients (3%) in the bendamustine treatment group experienced febrile neutropenia compared with none in the chlorambucil group. Neutropenic infection occurred in 10 bendamustine patients compared with 1 in the chlorambucil group. There were 2 events of grade 3 sepsis, both in patients in the bendamustine treatment group. Both patients recovered. Grade 3/4 hematologic adverse reactions with a frequency greater than 5% in the chlorambucil treatment group were neutropenia (9%) and thrombocytopenia (8%)".

Myelosuppression, infections related to myelosuppression, tumor lysis syndrome, hypersensitivity reactions, hypertension and other cardiac events and secondary malignancies were identified as significant adverse reactions in the safety review.

"Thirty-four deaths occurred during the conduct of study 02CLLIII. An equal number (17) of deaths occurred in each treatment group" and "The most common attribution for death was progression of disease (41% of patients in each group). Four patients died during the treatment phase of the study or within 30 days of the last study drug dose, one patient in the bendamustine group and three patients in the chlorambucil group."

According to Ms Kwitkowski, "Twenty-two patients were withdrawn from the study because of adverse reactions; 17 (11%) patients who received bendamustine and 5 (3%) patients who received chlorambucil. The most frequent adverse reactions causing withdrawal were hypersensitivity (occurring in 3 bendamustine patients and 1 chlorambucil patient) and pyrexia (occurring in 2 bendamustine patients and 1 chlorambucil patient)."

She also comments: "Non-clinical studies described dose-related cardiac toxicity in animals. The clinical dose-escalation studies demonstrated dose-related cardiac toxicities. Though the overall incidence of cardiac toxicity in the bendamustine arm was low (and similar to the chlorambucil arm); bendamustine may have cardiac toxicities, particularly at higher doses than those utilized in the pivotal trials for CLL and NHL. The large variety of cardiac events reported in these smaller studies make it difficult to provide firm attribution to bendamustine. ECG monitoring in this study was not adequate to evaluate the potential for QT prolongation because ECGs were only obtained at baseline and end of study; and interval measurements were not obtained."

7.2.3 Safety update

Per Ms Kwitkowski: "The postmarketing data provided by the Applicant does not provide new safety concerns that would affect the regulatory decision to approve bendamustine for CLL."

7.2.4 Discussion of primary reviewer's comments and conclusions

I concur with the primary reviewer's conclusions.

7.2.5 Pre-Approval Safety Conference

A Pre-Approval Safety Conference was conducted on 2/27/2008. The findings of the safety reviewer were discussed and are included in this review above and in Ms. Kwitkowski's review of safety.

7.2.5 Discussion of notable safety issues

See section 7.2.1.

Statistics Review Team's comments:

According to Shenghui Tang, Ph.D., primary statistics reviewer, "A total of 302 patients were screened and 301 were randomly assigned to treatment (1 patient was not assigned to a treatment group due to refusal) at 45 centers throughout 8 countries. The sponsor reported that the proportion of patients with ORR was 62% in the bendamustine treatment group compared with 33% in the chlorambucil treatment group ($p<0.0001$) as determined by the Independent Committee for Response Assessment (ICRA). The primary PFS analysis showed that the bendamustine treatment was superior to chlorambucil treatment (median 21 vs. 9 months, hazard ratio (HR) 0.23, $p<0.0001$). Based on the data submitted by the sponsor these results were confirmed by this reviewer and the data support the efficacy claim."

"Whether the endpoints and the sizes of the effects on these two endpoints in this phase III study are adequate for approval is a clinical decision." (Review dated 2/19/2008, concurrence signatures provided by Dr. Sridhara and Dr. Chakravarty on the same dates).

According to Rajeshwari Sridhara Ph.D., Team Leader and Deputy Director for Biometrics, "I concur with the primary reviewer, Dr. Tang's conclusion that the data submitted supports the claim that bendamustine has demonstrated superior overall response rate (ORR) and progression-free survival (PFS) compared to chlorambucil (ORR of 59% vs. 26% and PFS HR = 0.52, p-value < 0.0001)."

"Progression-free survival was assessed by a panel of three independent expert hematologic oncologists and also objectively calculated using an algorithm based on NCI working group criteria. According to the sponsor, in performing the review the members of the independent panel were allowed to exercise clinical judgment in determining response." and "The FDA reviewers were able to verify the calculated response rates and PFS, but could not verify the same as determined by the independent panel due the subjective nature of the independent evaluation. Therefore, it is recommended that the calculated response rates and PFS estimates be included in the product label." Her review is dated 2/25/2008 and was cosigned on the same day by Aloka Chakravarty Ph.D.

8 Advisory Committee Meeting

None held.

9 Other Relevant Regulatory Issues

None.

10 Financial Disclosure

Per applicant, many of the studies contained in this NDA, including the pivotal trial Study 02CLLLIII were conducted by another sponsor, Astellas, at clinical sites in Europe only; they were not conducted under an IND. Therefore, the sponsor of these studies did not prospectively request financial disclosure information from any investigator. The applicant asked representatives from Astellas if it were possible to obtain information from the investigators in support of this application. Astellas responded that they would be unable to obtain the required information for this randomized study.

The applicant is making efforts to obtain financial disclosure from the investigators on FDA's request.

11 Labeling

Labeling has not been completed and will be addressed in an amendment to the CDTL's review.

11.1. Proprietary name

DDMAC and DMETS reviews are pending.

11.2. Physician labeling

Labeling has not been completed and will be addressed in an amendment to the CDTL's review.

11.3. Carton and immediate container labels

To be addressed in an amendment to the CDTL's review.

11.4 Patient labeling/Medication guide

This is an intravenous formulation that will not be self-administered by the patient. Patient labeling is not required.

12. DSI Audits

In the DSI review dated 2/29/2008, Lauren Iacono-Connors, Ph.D. concludes that the study data collected at the 4 sites inspected appear reliable. The inspection of Cephalon Inc., did not identify any critical issues. Only the sponsor inspection has completed the EIR and provided that to DSI for support of the CIS. The 4 CIs final reports (EIRs) have not been completed to date. While 2 of the of the 4 clinical investigators inspected were issued Form FDA 483 inspection observations, it does not appear that the compliance deviations would significantly alter overall study outcome.

Dr. O'Connor stated that "DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits".

13. Conclusions and Recommendations

13.1. Recommended regulatory action

Pending reviews of DMETS and DDMAC, all disciplines recommend approval of Treanda for CLL. A statistically significant improvement in response rate, and progression free survival was observed. The adverse event profile is acceptable.

13.2. Safety concerns to be followed Postmarketing

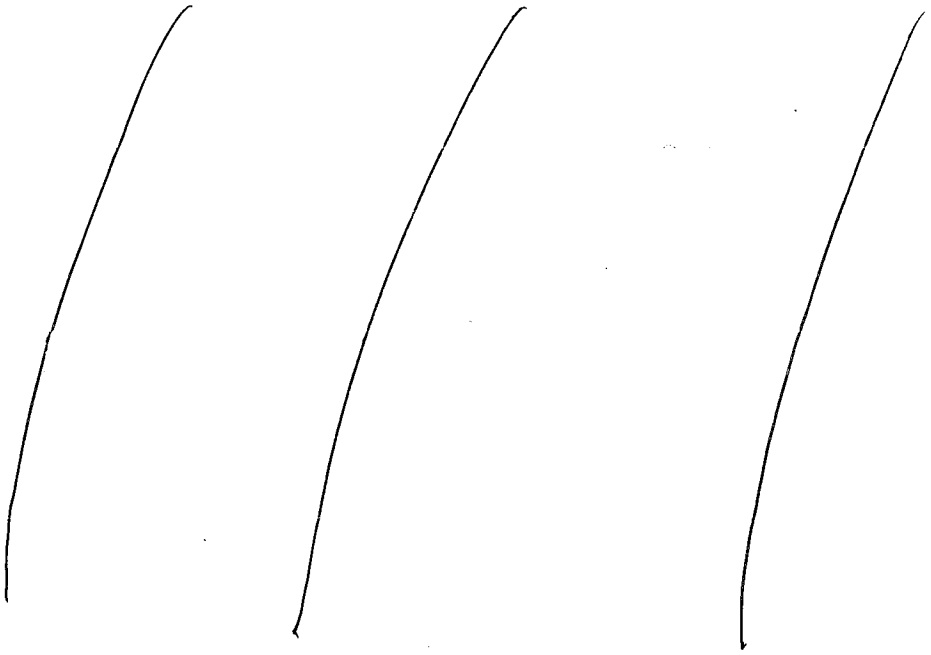
As noted in Ms. Kwitkowski's review, a risk management program does not appear to be necessary for bendamustine, above and beyond labeling recommendations.

13.3. Risk Minimization Action Plan, if any

None.

13.4. Postmarketing studies

Please see the action letter for the finalized PMCs. PMC under discussion at this time are:



Bibliography

1. Cheson BD, Bennett JM, Kay N et al. National Cancer Institute-Sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;12,4990-4997
2. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Annals of Oncology* 13:1285-1289, 2002

Note: An amendment to this review will be archived when more information is available.

Amna Ibrahim MD
Clinical Team Leader
Cross-Disciplinary Team Leader

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/s/

Amna Ibrahim
3/5/2008 05:21:23 PM
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