CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA (505(b)(2))
Application Number	208194 Supporting Document 1
Priority or Standard	Standard
Submit Date	February 13, 2015
Received Date	February 13, 2015
PDUFA Goal Date	December 13, 2015
Division	Division of Hematology Products
Reviewer Name	Andrew Dmytrijuk M.D.
Review Completion Date	November 17, 2015
Established Name	Bendamustine Hydrochloride Injection
Trade Name	Bendeka®
Therapeutic Class	Alkylating Drug
Applicant	Eagle Pharmaceuticals Inc. 50 Tice Blvd. Suite 315 Woodcliff Lake, NJ 07677
Formulation	Injection
Dosing Regimen	100mg/4mL (25mg/mL)
Indication	Treatment Of Patients With Chronic Lymphocytic Leukemia (CLL). Treatment Of Patients With Indolent B-Cell Non-Hodgkin Lymphoma (NHL) That Has Progressed During Or Within Six Months Of Treatment With Rituximab Or A Rituximab-Containing Regimen.
Intended Population	Patients With Chronic Lymphocytic Leukemia and Indolent B-Cell Non-Hodgkin Lymphoma

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 208194 supporting document 1 letter date February 13, 2015 is a 505(b)(2) application for Bendeka® (bendamustine hydrochloride injection) 100mg/4mL (25mg/mL) in a 50 mL admixture, a new formulation of bendamustine hydrochloride. From a clinical perspective NDA 208194 should be granted approval for the following indications which are the same indications as the reference drug.

- Bendamustine hydrochloride is an alkylating drug indicated for treatment of patients with:
    - Chronic lymphocytic leukemia (CLL).
    - Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

The reference drug is bendamustine hydrochloride (Treanda®) manufactured by Teva Pharmaceuticals. Treanda (NDA 22303 and NDA 22249) manufactured as a lyophilized powder for injection, was approved for marketing on March 20, 2008 (for the CLL indication) and on October 31, 2008 (for the NHL indication) and is the reference listed drug for this new application. An injectable solution formulation of Treanda was approved for marketing on September 13, 2013 as a Chemistry, Manufacturing and Controls (CMC) Manufacturing Supplement (NDA 22249 Supplement-015). Both of the approved bendamustine hydrochloride formulations (lyophilized powder and injectable solution) have the same indications as those proposed for Bendeka. The sponsor asserts that the new formulation of bendamustine hydrochloride (Bendeka) is compatible with closed system transfer devices (CSTDs), adaptors, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS) because it does not contain N, N-dimethylacetamide (DMA) compared to the reference drug. The CMC reviewer should also comment on the compatibility of the new formulation. Also, the Bendeka product may be administered intravenously over 10 minutes compared to the reference bendamustine product (Treanda) intravenous administration of 60 minutes because of the higher concentration, i.e., 100mg/4mL (25mg/mL) in a 50 mL admixture, of the Bendeka product than is required for the Treanda lyophilized powder product, i.e., 25mg/vial or 100mg/vial reconstituted to 5mg/mL. From a clinical perspective the pharmacokinetic results, the proportion of patients with adverse events and severity of adverse events in the bioequivalence study EGL-BDM-C-1301 were similar for Bendeka infusion over 10 minutes compared to Treanda infusion over 60 minutes.

The Bendeka product label along with my labeling recommendations in section 9.3 Labeling Recommendations in this review should be forwarded to the sponsor.

1.2 Risk Benefit Assessment

The clinical recommendation for the approval of Bendeka is based on the safety and efficacy of the marketed bendamustine (Treanda) lyophilized powder for injection product (NDA 22249), supportive safety and efficacy information from the marketed bendamustine (Treanda) products and the available Bendeka supportive safety information from the bioequivalence study EGL-BDM-C-1301.

Study EGL-BDM-C-1301 titled, "Phase 1, Open-Label, Crossover, Randomized, Bioequivalence Study To Evaluate Two Formulations Of Bendamustine (Bdm) Hydrochloride (Hcl) Administered To Cancer Patients" was conducted in a total of 83 patients with a histologically confirmed diagnosis of any malignant disease, i.e., solid tumors and hematologic malignancies, for which no curative or standard therapy is appropriate. In this study the extent (AUC) of drug exposure was within 80-125% of the acceptance range for bioequivalence according to the sponsor's analysis. From a clinical perspective the results of these studies demonstrated that the new bendamustine product (Bendeka) and the reference bendamustine product (Treanda) had similar bioequivalence. The Clinical Pharmacology reviewer should also comment on the acceptability of the results of study EGL-BDM-C-1301 to support approval of the drug. A summary of the key clinical pharmacology results from the clinical perspective is shown in section 4.4 Clinical Pharmacology in this review.

No new or additional safety concerns were identified in this Clinical Review of NDA 208194 for the new bendamustine hydrochloride formulation (Bendeka). Overall, the risk benefit assessment favors the approval of the Bendeka formulation for the same indications as that of the Treanda formulation. Bendeka offers patients a more rapid intravenous infusion of bendamustine hydrochloride (10 minutes for Bendeka compared to 60 minutes for Treanda) and does contain DMA which is compatible with closed system transfer devices (CSTDs), adaptors, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS). Overall the proportion of patients with adverse events and severity of adverse events were similar for Bendeka infusion over 10 minutes compared to Treanda infusion over 60 minutes in study EGL-BDM-C-1301. For example, a similar proportion of patients reported serious adverse events (SAEs) after treatment with Treanda (12/81, 15%) or Bendeka (12/73, 16%). It does not appear that the more rapid infusion of Bendeka compared to Treanda increases the risk or severity of adverse reactions for the intended populations, i.e., patients with CLL or indolent B-cell NHL.

The sponsor is requesting a Waiver for Pediatric Studies for Bendeka (NDA 208194) for patients (b) (4). The sponsor requests that a Waiver of Pediatric Studies be granted because Bendeka does not differ from Treanda except for dosage form. The Treanda label states in section 8.4 Pediatric Use that the effectiveness of Treanda in pediatric patients has not been established. Treanda was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The Treanda label also states that the

safety profile for Treanda in pediatric patients was consistent with that seen in adults, and no new safety signals were identified. Bendeka contains the same active ingredient as Treanda but may be infused more rapidly, i.e., over 10 minutes compared to Treanda which is infused over 60 minutes. The indications for Bendeka are the same as that for Treanda and patients will be treated with the same total drug dose as that for Treanda. There are no new active ingredients, no new indications, no change in the route of administration and no significant differences in the safety profiles of Bendeka compared to Treanda even though Bendeka is more rapidly infused compared to Treanda. The difference in the dosage form pertains to the final administration of the product, i.e., rate of infusion of drug. The sponsor's request is reasonable and I recommend that the sponsor's Pediatric Waiver Request be granted. Also, the bendamustine 50mL admixture was granted Orphan Designation for both indications on July 2, 2014 and is not subject to PREA (see Orange Book (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No post-marketing risk evaluation and mitigation strategy (REMS) is recommended for the Bendeka formulation.

1.4 Recommendations for Postmarket Requirements and Commitments

No Postmarketing Requirements (PMRs) or Postmarketing Commitments (PMCs) for this application for Bendeka (NDA 208194 supporting document 1) are recommended. There are no outstanding PMRs or PMCs for the reference bendamustine product Treanda.

2 Introduction and Regulatory Background

2.1 Product Information

The sponsor submits NDA 208194 for Bendeka which is a new injectable bendamustine hydrochloride formulation. The sponsor cross-references NDA 22303 for Treanda (bendamustine hydrochloride) lyophilized powder formulation to support the safety and efficacy of the Bendeka formulation. The sponsor proposes the same indications for Bendeka as for Treanda as follows.

- Bendamustine hydrochloride is an alkylating drug indicated for treatment of patients with:
    - Chronic lymphocytic leukemia (CLL). The efficacy relative to first line therapies other than chlorambucil has not been established.

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

A Dear Health Care Provider (DHCP) Letter regarding important safety and incompatibility information for Treanda injection (45 mg/0.5 mL or 180 mg/2 mL solution) was issued on March 09, 2015. The DHCP letter states that Treanda Injection (45 mg/0.5 mL or 180 mg/2 mL solution) is not compatible with closed system transfer devices (CSTDs), adaptors, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS) due to contact with N,N-dimethylacetamide (DMA). This incompatibility leads to device failure, e.g., leaking, breaking, or operational failure of CSTD components, possible product contamination, and potential serious adverse health consequences to the practitioner including skin reactions, or to the patient, including but not limited to the risk of small blood vessel blockage if they receive product contaminated with dissolved ABS or polycarbonate.

In NDA 208194 supporting document 4 letter date March 13, 2015 the sponsor (Eagle Pharmaceuticals) states that their bendamustine hydrochloride injection product, i.e., Bendeka 100 mg/4 mL (25 mg/mL) in a 50 mL admixture, is DMA free and does not have the same incompatibility safety concerns as the Teva Pharmaceuticals bendamustine product (Treanda). The CMC reviewer should also comment on the compatibility of the new formulation. The sponsor's table below shows a comparison of the currently available bendamustine hydrochloride formulations. Also, Bendeka may be administered intravenously over 10 minutes compared to the reference bendamustine product (Treanda) intravenous administration of 60 minutes because of the higher concentration, i.e., 100mg/4mL (25mg/mL) in a 50 mL admixture, of the Bendeka product than is required for the Treanda lyophilized powder product, i.e., 25mg/vial or 100mg/vial reconstituted to 5mg/mL.

Table 1. Available Bendamustine (BDM) Hydrochloride Formulations

Product	Treanda (bendamustine HCl) for Injection (100 mg vial[a])		Treanda (bendamustine HCl) Injection, 90 mg/mL (180 mg/2 mL[b])		Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)	
Dosage Form	Lyophilized Powder		Sterile Solution		Sterile Solution	
How Supplied	Single use vial		Single use vial		Multi-use vial (up to 28 days)	
Composition	Ingredients	Amount per vial	Ingredients	Amount per vial	Ingredients	Amount per vial
	BDM HCl	100 mg	BDM HCl	180 mg	BDM HCl	100 mg
	Mannitol, USP	170 mg	Propylene Glycol, USP	648 mg	Monothioglycerol, NF	20 mg
			N,N-Dimethylacetamide (DMA), EP	1172 mg	Propylene Glycol, USP	(b) (4)
					Polyethylene Glycol 400 (PEG 400), NF[c]	

DMA = N,N-Dimethylacetamide; EP = European Pharmacopeia; HCl = hydrochloride; NF = National Formulary; PEG = polyethylene glycol; USP = United States Pharmacopeia

[a] Treanda (bendamustine HCl) for Injection (Lyophilized) is also available in a 25 mg vial which has the same product composition.

[b] Treanda (bendamustine HCl) Injection (Sterile Solution) is also available in a 45 mg/0.5 mL vial, which has the same product composition.

[c] PEG 400 acidity may be modified using sodium hydroxide (NaOH) in water-for-injection solution.

Sponsor's table NDA 208194 Module 2 Introduction page 2

2.2 Tables of Currently Available Treatments for Proposed Indications

The reviewer's table below shows the currently available treatments and their indications.

Table 2. Bendamustine Hydrochloride NDA Applications

Generic Name	**Bendamustine Hydrochloride**	**Bendamustine Hydrochloride**	**Bendamustine Hydrochloride**
Trade Name	Treanda	Treanda	None
NDA Number	22249	22303	205580
Sponsor	Teva Pharmaceuticals	Teva Pharmaceuticals	Eagle Pharmaceuticals
Dosage Form	Injectable solution	Lyophilized powder for injection	Injectable (b) (4)
Original Approval Date	March 20, 2008	October 31, 2008	July 2, 2014 (Tentative Approval Granted)
Indications	Bendamustine hydrochloride is an alkylating drug indicated for treatment of patients with: • Chronic lymphocytic leukemia (CLL). The efficacy relative to first line therapies other than chlorambucil has not been established. • Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.	Same as for NDA 22249	Bendamustine hydrochloride injection (b) (4) • Indolent B-cell non-Hodgkin lymphoma (NHL (b) (4)

Reviewer's table.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient for Bendeka is the same as that for Treanda, i.e., bendamustine hydrochloride.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety concerns for Bendeka are similar to those of Treanda. The Treanda product label contains the following wording in the Warnings and Precautions section.

- Myelosuppression: (b) (4)
- Infections: (b) (4)
- Anaphylaxis and Infusion Reactions: (b) (4) Monitor clinically and discontinue drug for severe reactions. (b) (4)
- Tumor Lysis Syndrome: May lead to acute renal failure and death; (b) (4)
- Skin Reactions: (b) (4) Cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), some fatal, have been reported when bendamustine hydrochloride was administered concomitantly with allopurinol and other medications known to cause these syndromes.
- Other Malignancies: Pre-malignant and malignant diseases have been reported.
- Extravasation: (b) (4) during and after administration.
- Embryo-fetal toxicity: (b) (4)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- On July 2, 2014 the sponsor (Eagle Pharmaceuticals Inc.) received Tentative Marketing Approval for NDA 205580 which was a 505(b)(2) application for (b) (4) (b) (4) bendamustine hydrochloride (b) (4) Only a Tentative Marketing Approval was granted because Cephalon Inc.'s product, Treanda (bendamustine hydrochloride), had orphan drug exclusivity that blocked regular approval of Eagle Pharmaceutical's NDA 205580 application.
- The Filing Meeting for NDA 208194 was held on April 13, 2015.

Reviewer comment for section 2. The sponsor proposes the same indications and labeling information for Bendeka as for Treanda.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

An Office of Study Integrity and Surveillance (OSIS) review was conducted for the analytical portion of the bioequivalence study EGL-BDM-C-1301 by Dr. Hansong Chen (Pharmacologist, Division of New Drug Bioequivalence Evaluation (DNDBE), final signature date August 4, 2015). In his review Dr. Chen states that the data from the audited study were found to be reliable. Therefore, this reviewer recommends that the data be accepted for further Agency review.

3.2 Compliance with Good Clinical Practices

EGL-BDM-C-1301 was conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. The protocol was approved by an Institutional Review Board prior to initiation and implementation of the study. Written informed consent provided by the patient was required in order to enroll into the study EGL-BDM-C-1301. The informed consent, protocol violations and site-specific issues were reviewed and found to be within accepted standards.

3.3 Financial Disclosures

No investigators participating in the trials supporting NDA 208194 reported a financial interest.

Reviewer comment for section 3: All studies were conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practices and local regulatory requirements. No investigators in the studies supporting NDA 208194 reported an equity interest. The ethics and good clinical practices considerations for this application are acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review of NDA 208194 supporting document 1 is ongoing. No review issues were noted by CMC reviewers for the Filing Communication – No Filing Review Issues Identified letter which was sent to the sponsor on April 13, 2015.

4.2 Clinical Microbiology

No Clinical Microbiology issues were identified in the Filing Communication – No Filing Review Issues Identified letter which was sent to the sponsor on April 13, 2015. The Clinical Microbiology review of NDA 208194 supporting document 1 is ongoing.

4.3 Preclinical Pharmacology/Toxicology

In his review of NDA 208194 supporting document 1 Dr. Michael Manning (Division of Hematology Oncology Toxicology Reviewer, final signature date October 1, 2015) states that the sponsor's nonclinical testing strategy was designed in accordance with FDA/CDER Draft Guidance for Industry and Review Staff: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route (March 2008). The review by Dr. Manning states that the sponsor submitted reports to assess the hemolytic and irritant potential of bendamustine hydrochloride at a concentration of up to 5.6 mg/mL, the highest final admixture concentration covering the clinical dose range. Dr. Manning states in his review that from the Pharmacology/Toxicology perspective, bendamustine hydrochloride, administered as a 50mL admixture over an infusion time of 10 minutes may be approved for the proposed indications.

4.4 Clinical Pharmacology

Clinical Pharmacology review of NDA 208194 supporting document 1 is ongoing. No Clinical Pharmacology issues were identified in the Filing Communication – No Filing Review Issues Identified letter which was sent to the sponsor on April 13, 2015. Support for the approval of this application for Bendeka comes from one bioequivalence study EGL-BDM-C-1301. Additional details regarding this study can be found in section 5.1 Table of Studies in this review. A summary of study EGL-BDM-C-1301 can be found below in section 5.3 Discussion of Individual Studies. Key efficacy results (from a clinical perspective) and safety results from study EGL-BDM-C-1301 are summarized in section 6 Review of Clinical Efficacy and section 7 Review of Safety, respectively, in this review.

Reviewer comment for section 4. CMC, Clinical Microbiology and Clinical Pharmacology reviews of NDA 208194 are ongoing. These reviewers should comment on the approvability of NDA 208194. No CMC, Clinical Microbiology or Clinical Pharmacology concerns for NDA 208030 have been identified from a Clinical perspective.

5 Sources of Clinical Data

5.1 Table of Studies

The table below shows the study included to support NDA application 208194 for Bendeka.

Table 3. Table of Studies

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	EGL-BDM-C-1301	Section 5.3.3.2	Primary To demonstrate the BE of BDM $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ between 2 formulations of BDM HCl: (1) Eagle brand low volume (50 mL admixture) BDM HCl (Eagle-BDM [T]; 120 mg/m^2) given IV over 10 minutes, and (2) Teva brand standard volume (500 mL admixture) BDM HCl (Teva-BDM [R]; 120 mg/m^2) given IV over 60 minutes. Secondary To evaluate the infusion-related safety and tolerability profile of Eagle-BDM. To characterize additional PK parameters of Eagle-BDM (T) and Teva BDM (R) as well as PK parameters for metabolite M3 [after Eagle-BDM and Teva-BDM infusion].	Open-label, randomized, crossover, Phase 1	Eagle-BDM (BDM HCl liquid formulation) diluted into a 50-mL infusion bag (0.9% NaCl Injection, USP normal saline). Teva-BDM (TREANDA® BDM HCl lyophilized powder) reconstituted and diluted into a 500-mL infusion bag (0.9% NaCl Injection, USP normal saline) Study Treatments (Eagle-BDM or Teva-BDM) were administered on Cycle 1, Day 1; Cycle 1, Day 2; and Cycle 2, Day 1. On Cycle 2, Day 2, all patients received a dose of Eagle-BDM. Eagle-BDM was administered as a 120 mg/m^2 IV infusion over 10 minutes or a calculated maximum infusion rate of 12 mg/m^2/min. Teva-BDM was administered as a 120 mg/m^2 IV infusion over 60 minutes or a calculated maximum infusion rate of 2.0 mg/m^2/min.	83 patients randomized 81 patients received either Eagle-BDM or Teva-BDM 59 (71.1%) patients completed 24 (28.9%) patients discontinued early.	Cancer patients	56 day treatment period (2 study cycles of 28 days [± 2 days])	Study Complete; Full CSR

BDM = bendamustine; Eagle-BDM = Bendeka; Teva-BDM = Treanda
Sponsor's table NDA 208194 section 5.2 Tabular list of Clinical Studies

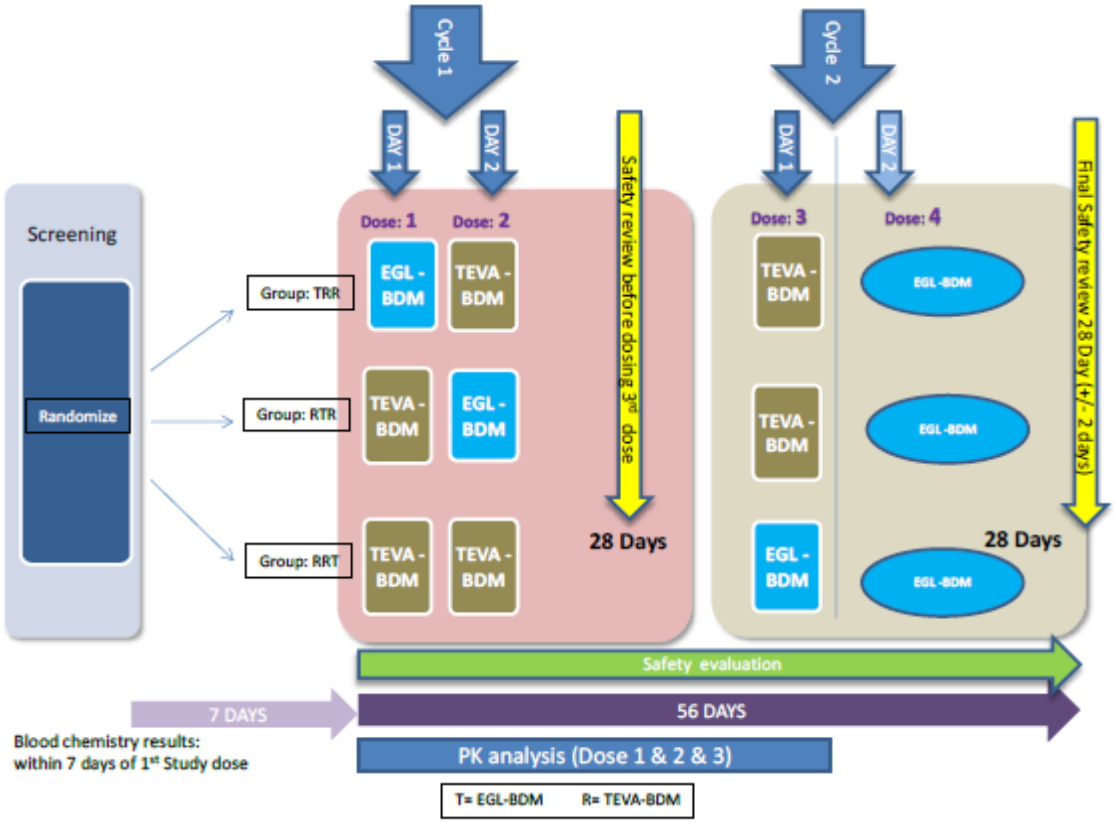
5.2 Review Strategy

NDA 208194 supporting document 1 is a 505b(2) application for Bendeka that cross-references the safety and efficacy data of the marketed bendamustine product Treanda in NDA 22249. Clinical review of the study shown in section 5.1 Tables of Studies is in this review. This Clinical Review for Bendeka (NDA 208194) focuses on the available safety information from study EGL-BDM-C-1301.

5.3 Discussion of Individual Studies

The study supporting the Bendeka application NDA 208194 is described in section 5.1 Table of Studies in this review, i.e., study EGL-BDM-C-1301. Briefly, study EGL-BDM-C-1301 was an open-label, randomized, crossover (3-period, partially replicated) Phase 1 study to demonstrate the bioequivalence (BE), safety and tolerability profile of 2 formulations of bendamustine hydrochloride (120 mg/m^2) administered to cancer patients with histologically confirmed diagnosis of cancer (solid tumors and hematologic malignancies excluding CLL) who had progressed or relapsed on standard therapy, or for whom no curative or standard therapy was appropriate. The formulations of bendamustine administered were Eagle-Bendamustine (Eagle-BDM, Bendeka) given intravenously (IV) over 10 minutes and Teva-Bendamustine (Teva-BDM, Treanda) given IV over 60 minutes. The study was a partially replicated design where the reference product was replicated across 2 periods. Each patient participated in a Screening Visit and a 56-day treatment period (2 Study Treatment cycles of 28 days [± 2 days]). Two single doses of Study Treatment were administered during each 28-day cycle. The End-of-Study (EOS) Visit occurred on Cycle 2, Day 28 (or 28 days [± 2 days] from administration of the last Study Treatment) for the purpose of assessing safety and tolerability. A total of 81 subjects (34 male and 47 female) adult (age 40-82 years) were enrolled in the study. The EGL-BDM-C-1301 Study Schema is shown in the sponsor's figure below.

Figure 1. EGL-BDM-C-1301 Study Schema



EGL-BDM = Eagle bendamustine hydrochloride injection (Eagle-BDM); N = number of patients; PK = pharmacokinetic; R = reference product (Teva-BDM); T = test product (Eagle-BDM); Teva-BDM = Teva bendamustine hydrochloride Injection.

Sponsor's figure EGL-BDM-C-1301 study report page 40

Patients were monitored and evaluated according to the study schedule shown in the sponsor's table below.

Table 4. EGL-BDM-C-1301 Study Schedule

Visit:	Screening Visit[a]	Cycle 1				Cycle 2		End of Study
		Treatment Administration		Follow-up		Treatment Administration		Follow-up
Study Days: Assessments	Day -14 to Day -1	Cycle 1, Day 1 Dose 1	Cycle 1, Day 2 Dose 2	Cycle 1, Day 21 (± 2 days)	Cycle 1, Day 28[b] (± 2 days)	Cycle 2, Day 1[b] Dose 3	Cycle 2, Day 2 Dose 4 (Eagle-BDM)	EOS Visit[c,d,e] Cycle 2, Day 28 (± 2 days)
Informed consent[f]	X							
Inclusion and exclusion criteria	X	X						
Demographics[g]	X							
Medical history[h]	X							
Prior anticancer treatment	X							
Relevant prior non-cancer treatments	X							
Tumor assessment[i]	X							
Concomitant medications[j]	X	X	X	X	X	X	X	X
ECOG Performance Status	X			X		X		X
Physical examination[k]	X			X		X		X
Weight	X	X		X		X		X
Height	X							
Pregnancy test	X[l]					X[l,m]		
Vital signs (HR, RR, BP, temp) [n]	X	X	X	X	X	X	X	X
Hematology [o,p,q]	X[r]	X[s]		X	X[t]	X[t]		X
Blood chemistry [o,u]	X	X[s]		X	X[t]	X[t]		X
Adverse events [v]	X[w]	X	X	X	X	X	X	X

Visit	Screening Visit[a]	Cycle 1				Cycle 2		End of Study
		Treatment Administration		Follow-up		Treatment Administration		Follow-up
Study Days: Assessments	Day -14 to Day -1	Cycle 1, Day 1 Dose 1	Cycle 1, Day 2 Dose 2	Cycle 1, Day 21 (± 2 days)	Cycle 1, Day 28[b] (± 2 days)	Cycle 2, Day 1[b] Dose 3	Cycle 2, Day 2 Dose 4 (Eagle-BDM)	EOS Visit[c,d,e] Cycle 2, Day 28 (± 2 days)
Treatment assignment	X							
Administration of Study Treatment[x]		X[y]	X[y]			X[y]	X[y,z]	
PK blood draws[aa]		X	X			X		
Smoking status and usage		X	X	X	X	X	X	X
Entry into the OLE protocol EGL-BDM-C-1301-OLE								X

AE = adverse event; ALC = absolute lymphocyte count; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BDM HCl = bendamustine hydrochloride; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; Cl = chloride; Cr = creatinine; CrCl = creatinine clearance; Eagle-BDM = Eagle bendamustine hydrochloride injection; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; HCO_3 = bicarbonate; HR = heart rate; K = potassium; min = minute(s); MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; Na = sodium; OLE = open-label extension; PK = pharmacokinetic; RR = respiratory rate; TBili = total bilirubin; Temp = temperature (°F or °C); ULN = upper limit of normal.

Notes:

[a] The Screening assessments were performed between Days -1 and -14 before administration of randomized Study Treatment in the treatment period.

[b] If the blood test results from the Cycle 1, Day 21 Visit warranted it, and if there was no AE to prevent the patient from receiving Dose 3, then the Cycle 1, Day 28 Visit and Cycle 2, Day 1 Visit could have been performed on the same day and the assessments only needed to be performed once. If an unrelated AE prevented Cycle 2 from starting on schedule, the Study Treatment could have been delayed for a maximum of 2 weeks; otherwise, the patient was to be dropped from the study and replaced.

[c] Patients who completed the study attended a safety follow-up visit (EOS Visit) on Day 56 ± 2 days (Cycle 2, Day 28) unless the ANC level $\geq 1 \times 10^9$ neutrophils/L and platelet count of $\geq 75 \times 10^9$/L had not been reached. In this case, the patient was to be followed up, based on the center's standard of care and presumed to be approximately 3 to 5 days, until their ANC level reached $\geq 1 \times 10^9$ neutrophils/L and platelet count reached $\geq 75 \times 10^9$/L, and the patient was withdrawn from the study. The patient was required to attend their EOS Visit 28 days (± 2 days) after the last Study Treatment administration for safety and tolerability assessments.

[d] Patients withdrawn prematurely had their EOS Visit 28 days (± 2 days) from administration of the last Study Treatment to assess safety and tolerability.

[e] Patients could have been included in an OLE study at the discretion of the Investigator at the end of the study.

[f] Before any protocol procedures or tests.

[g] Including date of birth, gender, race, ethnicity, and smoking history.

[h] Including oncology history (eg, date of diagnosis) and details regarding surgical procedures, non-surgical (medical), and radiotherapy treatment received.
[i] Tumor assessment was performed during the Baseline period if not performed within 56 days of planned start of treatment. Imaging relevant to primary tumor and known spread was performed. Patients with tumor types that often metastasize to brain (eg, breast and lung cancers) must have undergone brain imaging within 56 days before the start of Study Treatment, even if asymptomatic. Patients with tumor types that did not often metastasize to brain (eg, colon carcinoma) were to undergo brain imaging only if there was a clinical suspicion of metastasis.
[j] Before Study Treatment administration.
[k] Full body physical examination at the Screening Visit; brief examinations of pertinent systems at other times.
[l] Serum pregnancy test.
[m] Urine pregnancy test.
[n] Vital signs (HR, RR, sitting BP, and temp) were measured and recorded within 1 hour before each injection administration, at the end of infusion (+ 1 min), 30 minutes (± 1 min), 1 hour (± 2 min), and 2 hours (± 5 min) postinfusion, and before discharge from the infusion center. In addition, if the patient experienced an AE, then additional vital sign measurements were taken as required.
[o] Samples were taken before Study Treatment administration.
[p] CBC (ANC, ALC, red blood cells, white blood cells, hemoglobin, hematocrit, platelets, MCV, MCH, MCHC, monocytes [absolute], eosinophils [absolute], basophils [absolute]).
[q] For ANC and ALC, a machine CBC with machine differential was to be used, however, a manual ANC and ALC was performed if the machine ANC result was < 2,000 neutrophils.
[r] If serum Cr was > 1.5 × ULN, the patient was eligible if CrCl was > 40 mL/min.
[s] No need to repeat if Screening values were normal.
[t] If Cycle 1, Day 28 and Cycle 2, Day 1 fell within 24 hours, the safety blood sample may have only been drawn once.
[u] ALP, ALT, AST, TBili, BUN, Cl, Cr, K, Na, and HCO_3 blood sampling for safety laboratory determination were performed within 2 weeks before the first Study Treatment administration. The results of the safety laboratory had to be available at time of randomization/treatment assignment.
[v] All AEs experienced from the time informed consent was signed were collected; those occurring from the start of Study Treatment were considered treatment-emergent AEs.
[w] Any conditions present on entry to the study were recorded.
[x] Study Treatments were administered on Cycle 1, Days 1 and 2; and Cycle 2, Day 1 for PK evaluation.
[y] ANC level had to be $\geq 1 \times 10^9$ neutrophils/L and platelets had to be $\geq 75 \times 10^9$/L before Study Treatment administration. If ANC and platelet levels had not reached $\geq 1 \times 10^9$ neutrophils/L and $\geq 75 \times 10^9$/L respectively, within 2 weeks of the planned date of treatment, the patient was withdrawn from the study and replaced.
[z] On Cycle 2, Day 2, all patients were to receive a dose of Eagle – BDM (Dose 4) without PK sampling being performed. All subsequent therapeutic treatment was administered exclusively off protocol.
[aa] PK blood draws for both BDM HCl drug products: Cycle 1, Days 1 and 2 and Cycle 2, Day 1, PK draws were performed at:
- 15 to 30 minutes before the start of infusion
- half-way through the infusion period (5 minutes after start of infusion for 10-minute infusion, 30 minutes after start of infusion for 60-minute infusion) (± 1 min)
- immediately following the end of infusion (within 1 minute)
- at the following times post end of the infusion: 5 (± 1 min), 15 (± 1 min), 30 (± 2 min), 45 minutes (± 3 min), and 1 (± 5 min), 1.5 (± 5 min), 2 (± 5 min), 3 (± 10 min), 4 (± 10 min), 5 (± 10 min), and 8 (± 30 min) hours
- 24 hours from the start of the infusion (± 30 min) – Dose 1 and Dose 3 (Day 1 of both cycles) only.

Sponsor's table Study Report EGL-BDM-C-1301 pages 42-44

The key inclusion criteria were as follows.

- Histologically confirmed diagnosis of any malignant disease for which no curative or standard therapy is appropriate. Patients with chronic lymphocytic leukemia (CLL) were excluded.
- Hemoglobin > 9g/dL.
- Absolute neutrophil count ≥ 1500/µL.
- Platelet count ≥ 100,000/µL.
- Liver transaminases < 2.5 x upper limit of normal (ULN) and total bilirubin < 1.5 x ULN.
- Serum creatinine ≤ 1.5 x ULN and urine creatinine clearance by Cockroft-Gault ≥ 40mL/min.

The key exclusion criteria were as follows.

- Surgery or radiation therapy within 4 weeks of enrollment.
- Presence of brain metastases.

- Body mass index (BMI) ≥ 35kg/m^2.
- Pregnant or nursing mothers.
- History of HIV infection or other ongoing infection.

The 90% confidence intervals of the ratio of least-squares means for AUC_{0-t} and $AUC_{0-\infty}$ of the test formulation to reference formulation were to be within the 80% to 125% range. Safety was assessed by monitoring adverse events throughout the study. Key efficacy results (from a clinical perspective) and safety results from study EGL-BDM-C-1301 are summarized in section 6 Review of Clinical Efficacy and section 7 Review of Safety, respectively, in this review.

In this study 83 patients were enrolled. Two patients were randomized but did not receive study drug. 81 patients received at least 1 dose of bendamustine. Fifty seven patients completed the study. There were 24 patients who were discontinued from the study prematurely. Early discontinuations from the study were for the following reasons: adverse events (n=4 consisting of grade 3 fatigue, grade 3 pneumonia, grade 2 edema, grade 2 nausea in one patient each), death (n = 3 consisting of disease progression in 2 patients and disease progression with edema in 1 patient), insufficient therapeutic response (n =4), patients lost to follow-up (n =1), sponsor/ investigator request (n = 5), patient withdrew consent (n = 5) and other reason not specified (n = 2). Protocol violations consisted almost entirely of violations in the pharmacokinetic (PK) sampling guideline (26/28 patients). The other protocol violations were infusion related protocol deviations. The range of infusion time for Bendeka was 9-17 minutes and the infusion time for Treanda was 58-95 minutes. The key demographics of patients enrolled in study EGL-BDM-C-1301 are summarized in the sponsor's tables below. The median age of patients enrolled was 64 years (range 40-82 years). Most patients (47/81, 58%) were females. Patients in this study were most frequently diagnosed with breast cancer (11/81, 14%) or other cancers (19/81, 23%). In this study 38/81 (47%) patients had stage IV cancer at enrollment.

Table 5. Key Patient Demographics

Demographic	TRR (N=26)	RTR (N=26)	RRT (N=29)	Total (N=81)
Age (years)				
N	26	26	29	81
Mean	61.2	63.3	65.3	63.3
Median	59.5	67.5	65.0	64.0
Standard Deviation	10.41	12.28	10.04	10.92
Min, Max	43, 81	40, 78	43, 82	40, 82
Gender, n (%)				
Male	9 (34.6)	14 (53.8)	11 (37.9)	34 (42.0)
Female	17 (65.4)	12 (46.2)	18 (62.1)	47 (58.0)
Race, n (%)				
White	23 (88.5)	23 (88.5)	22 (75.9)	68 (84.0)
Black/African American	3 (11.5)	2 (7.7)	5 (17.2)	10 (12.3)
Asian	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian/Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown/Not reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (3.8)	1 (3.4)	2 (2.5)
Ethnicity, n (%)				
Hispanic or Latino	2 (7.7)	2 (7.7)	7 (24.1)	11 (13.6)
Not Hispanic or Latino	24 (92.3)	24 (92.3)	22 (75.9)	70 (86.4)
Unknown/Not reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline Parameter	TRR (N=26)	RTR (N=26)	RRT (N=29)	Total (N=81)
BSA (m^2)				
N	25	26	29	80
Mean	1.84	1.91	1.76	1.83
Median	1.78	1.86	1.74	1.78
Standard Deviation	0.25	0.30	0.26	0.27
Min, Max	1.48, 2.39	1.32, 2.48	1.33, 2.32	1.32, 2.48
ECOG performance status, n (%)				
0	6 (23.1)	5 (19.2)	8 (27.6)	19 (23.5)
1	16 (61.5)	21 (80.8)	19 (65.5)	56 (69.1)
2	4 (15.4)	0 (0.0)	2 (6.9)	6 (7.4)
Primary cancer diagnosis, n (%)				
Head and neck localized lesion	1 (3.8)	0 (0.0)	1 (3.4)	2 (2.5)
Esophagus/Oesophagus	2 (7.7)	0 (0.0)	1 (3.4)	3 (3.7)
Lung	1 (3.8)	3 (11.5)	3 (10.3)	7 (8.6)
Breast	4 (15.4)	3 (11.5)	4 (13.8)	11 (13.6)
Colon/Large intestine	4 (15.4)	3 (11.5)	3 (10.3)	10 (12.3)
Rectum	2 (7.7)	1 (3.8)	3 (10.3)	6 (7.4)
Gall bladder/Bile duct	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.2)
Pancreas	1 (3.8)	1 (3.8)	1 (3.4)	3 (3.7)
Kidney	1 (3.8)	0 (0.0)	2 (6.9)	3 (3.7)
Urinary bladder	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.2)
Ovary	1 (3.8)	1 (3.8)	2 (6.9)	4 (4.9)
Uterus	2 (7.7)	0 (0.0)	0 (0.0)	2 (2.5)
Cervix	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.2)
Prostate	0 (0.0)	3 (11.5)	0 (0.0)	3 (3.7)
Soft tissue	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.2)
Lymphoma	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.2)
Myeloma	1 (3.8)	1 (3.8)	1 (3.4)	3 (3.7)
Other	4 (15.4)	9 (34.6)	6 (20.7)	19 (23.5)

Baseline Parameter	TRR (N=26)	RTR (N=26)	RRT (N=29)	Total (N=81)
Cancer stage at diagnosis, n (%)				
Stage I	1 (3.8)	1 (3.8)	3 (10.3)	5 (6.2)
Stage IA	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.2)
Stage IB	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.2)
Stage II	2 (7.7)	1 (3.8)	2 (6.9)	5 (6.2)
Stage IIA	1 (3.8)	2 (7.7)	1 (3.4)	4 (4.9)
Stage IIB	1 (3.8)	1 (3.8)	0 (0.0)	2 (2.5)
Stage III	3 (11.5)	1 (3.8)	5 (17.2)	9 (11.1)
Stage IIIA	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.2)
Stage IIIB	3 (11.5)	3 (11.5)	1 (3.4)	7 (8.6)
Stage IV	12 (46.2)	13 (50.0)	13 (44.8)	38 (46.9)
Other	2 (7.7)	3 (11.5)	3 (10.3)	8 (9.9)

Source: Table 14.1.4.1
BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; R = reference product (Teva-BDM), T = test product (Eagle-BDM).

Sponsor's tables EGL-BDM-C-1301 study report page 89 and 91-93

Reviewer comment for section 5. From a clinical perspective the study supporting the Jadenu application NDA 208194, i.e., EGL-BDM-C-1301, appears to be reasonably well designed to support a bioequivalence comparison of Bendeka to the reference Treanda product. The Clinical Pharmacology review of NDA 208194 is ongoing. The safety assessment considerations for these studies are acceptable. Routine physical examinations, evaluations for laboratory adverse reactions and clinical adverse reactions such as electrocardiographic (ECG) changes were performed. From a clinical perspective the protocol violations appear to be minor and did not appear to significantly confound the safety or efficacy results for study EGL-BDM-C-1301. In this study 81 patients received at least 1 dose of study drug. Most patients enrolled in this study were diagnosed with breast or other cancers. Patients enrolled in this study were primarily diagnosed with stage IV disease which carries with it a poor prognosis. Exclusion of patients from study EGL-BDM-C-1301 is acceptable from a clinical perspective because FDA stated in a Type B Meeting on January 15, 2013 that the sponsor should evaluate the Bendeka 120mg/m^2 IV administered over 10 minutes dose in this bridging study, i.e., EGL-BDM-C-1301 (see FDA Meeting Minutes final signature date January 16, 2015). However, the bendamustine hydrochloride approved dose for the indolent NHL indication is 120 mg/m^2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. The bendamustine hydrochloride approved dose for the CLL indication is 100 mg/m^2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. Therefore, patients with CLL were excluded from study EGL-BDM-C-1301. In addition, clinical practice for the treatment of aggressive CLL has expanded to include chemo-immunotherapy and the

new tyrosine kinase inhibitor, ibrutinib, which may limit the clinical utility of bendamustine for the CLL indication.

6 Review of Clinical Efficacy

In NDA 208194 supporting document 1 the sponsor proposes that Bendeka is indicated for the same indications as the Treanda reference drug product, i.e.,

- Bendamustine hydrochloride is an alkylating drug indicated for treatment of patients with:
    - Chronic lymphocytic leukemia (CLL).
    - Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

The approval of this indication for Bendeka is supported by the pharmacokinetic results from study EGL-BDM-C-1301 which is described in section 5.3 Discussion of Individual Studies in this review. The sponsor's table below summarizes the key pharmacology results of study EGL-BDM-C-1301 from a clinical perspective. The sponsor's table shows that pharmacokinetic parameters are similar between the Bendeka product and the Treanda product.

Table 6. Pharmacokinetic Results Study EGL-BDM-C-1301

BDM AUC_{0-t} (ng.h/mL)	**FDA Requested**	
PKE Population	**Primary PKE (N=60)**	**Secondary Sensitivity PKE (N=57)**
Eagle-BDM (Test)[a]	9546.49	9855.58
Teva-BDM (Reference)[a]	9450.25	9618.32
Test/Reference[a]	**1.01**	**1.02**
90% Confidence Interval	**0.914 – 1.114**	**0.925 – 1.135**
Upper Critical Bound	-0.09	-0.09
S_{WR}	0.392	0.391
S^2_{WR}	0.154	0.153
BE Method	RSABE	RSABE
BE Result	**Passed**	**Passed**
BDM $AUC_{0-\infty}$ (ng.h/mL)	**FDA Requested**	
PKE Population	**Primary PKE (N=60)**	**Secondary Sensitivity PKE (N=57)**
Eagle-BDM (Test)[a]	9547.23	9884.32
Teva-BDM (Reference)[a]	9464.6	9632.81
Test/Reference[a]	**1.01**	**1.03**
90% Confidence Interval	**0.915 -1.115**	**0.926 -1.137**
Upper Critical Bound	-0.09	-0.09
S_{WR}	0.391	0.391
S^2_{WR}	0.153	0.153
BE Method	RSABE	RSABE
BE Result	**Passed**	**Passed**

Source: Tables 14.2.1.1.10.1 and 14.2.2.3 (n=60); Tables 14.2.1.1.11.1 and 14.2.2.4 (n=57); Tables 14.2.1.1.1.1 and 14.2.2.1 (n=44); Tables 14.2.1.1.4.1 and 14.2.2.2 (n=38).
ANOVA = analysis of variance; AUC = area under the time-BDM concentration curve; $AUC_{0-\infty}$ = AUC from zero to infinity; AUC_{0-t} = AUC from zero to the time of the last quantifiable concentration; BE = bioequivalence; Eagle-BDM = Eagle bendamustine hydrochloride injection; FDA = Food and Drug Administration; N = number of patients in the population; PKE = pharmacokinetic evaluable; RSABE = reference-scaled average bioequivalence; S_{WR} = within-patient standard deviation of the reference product; S^2_{WR} = within-patient variability; Teva-BDM = Teva bendamustine hydrochloride injection (Treanda)
[a] Geometric Means Values

Sponsor's table EGL-BDM-C-1301 study report page 103

Reviewer comment for section 6. The sponsor cross references the efficacy and safety of Treanda lyophilized powder formulation to support the current application for Bendeka in NDA 208194. Bendeka may be administered intravenously over 10 minutes

compared to the reference bendamustine product (Treanda) intravenous administration of 60 minutes because of the higher concentration, i.e., 100mg/4mL (25mg/mL) in a 50 mL admixture, of the Bendeka product than is required for the Treanda lyophilized powder product, i.e., 25mg/vial or 100mg/vial reconstituted to 5mg/mL. From a clinical perspective based on the sponsor's analysis the bioequivalence appears to be similar for Bendeka compared to Treanda as demonstrated in the comparative bioequivalence study EGL-BDM-C-1301 submitted in NDA 208194 supporting document 1. The Clinical Pharmacology review of NDA 208194 is ongoing. The Clinical Pharmacology reviewer should comment on the acceptability of the results of study EGL-BDM-C-1301 to support approval of the Bendeka formulation.

7 Review of Safety

7.1.1 Methods

The sponsor cross references the efficacy and safety of Treanda lyophilized powder to support the current application for Bendeka NDA 208194. Study EGL-BDM-C-1301 discussed in section 5 Sources of Clinical Data was reviewed to evaluate the safety of Bendeka in the application NDA 208194.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were characterized according to National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) v. 4 criteria.

7.2 Adequacy of Safety Assessments

Overall 81adult patients with histologically confirmed diagnosis of cancer (solid tumors and hematologic malignancies excluding chronic lymphocytic leukemia [CLL]) who had progressed or relapsed on standard therapy, or for whom no curative or standard therapy was appropriate received at least 1 dose of bendamustine. Patients in this study were most frequently diagnosed with breast cancer (11/81, 14%) or other cancers (19/81, 23%). There were 5 patients enrolled with hematologic malignancies including one patient with NHL, one patient with Waldenstrom Macroglobulinemia and three patients with multiple myeloma. In this study 38/81 (47%) patients had stage IV cancer at enrollment.

7.3 Major Safety Results

7.3.1 Deaths

In this study 6 deaths were reported (patient #101009, 104005, 104012, 108001, 108013 and 101001). The deaths occurred between 18 and 46 days after administering

the last dose of study drug. The primary cause of death for all 6 patients was attributed to disease progression and included endometrial cancer (n =2), fibrosarcoma (n=1), lung cancer brain metastases (n=1), leiomyosarcoma (n=1) and esophageal cancer (n=2). These cases are briefly summarized as follows.

- Patient 101009 – Male age 40 years with a history of fibrosarcoma stage IV. The patient received 2 doses of study drug (Bendeka then Treanda). The patient died 25 days after the last dose of study drug.
- Patient 104005 – Male age 69 years with a history of bladder cancer stage IV. The patient had bilateral lower extremity edema considered to be related to venous thromboembolic disease. The patient received 2 doses of study drug (Bendeka then Treanda). The patient died 46 days after the last dose of study drug.
- Patient 104012 – Female age 72 years with a history of endometrial cancer stage IV. The subject received 2 doses of study drug (Treanda then Bendeka). The patient died 23 days after the last dose of study drug.
- Patient 108001 – Male age 60 years with a history of spindle cell sarcoma stage IV. The patient received 2 doses of study drug (Treanda then Bendeka). The patient died 18 days after the last dose of study drug.
- Patient 108013 – Female age 53 years with a history of endometrial cancer stage IV. The patient received 2 doses of study drug (Treanda then Bendeka). The patient died 24 days after the last dose of study drug.
- Patient 101001 – Male age 73 years with a history of esophageal cancer stage IV. The patient completed the study but died 34 days after the last dose of study drug due to disease progression.

7.3.2 Nonfatal Serious Adverse Events

The reviewer's table below summarizes the frequency of SAEs and treatment related adverse events. A similar proportion of patients reported SAEs after treatment with Treanda (12/81, 15%) or Bendeka (12/73, 16%). SAEs reported in ≥ 3 patients was abdominal pain (n = 3 Treanda, n = 1 Bendeka). No other SAEs were reported in ≥ 3 patients.

Table 7. Frequency of Serious Adverse Events And Treatment Related Adverse Events*

n, %	Treanda (n = 81)	Bendeka (n=73)
SAEs	12, 15	12, 16
Grade ≥ 3	10, 12	12, 16
AEs Definitely Related to Study Drug	10, 12	7, 10
AEs Possibly/Probably Related to Study Drug	27, 33	25, 34

*Proximal to most recent study drug administration. SAEs = Serious adverse events; AEs = Adverse events. Reviewer's table derived from sponsor's tables EGL-BDM-C-1301 page 115

7.3.3 Dropouts and/or Discontinuations

There were 24 patients who were discontinued from the study prematurely as discussed in section 5.3 Discussion of Individual Studies in this review. Early discontinuations from the study were for the following reasons: adverse events (n=4 consisting of grade 3 fatigue, grade 3 pneumonia, grade 2 edema, grade 2 nausea in one patient each), death (n = 3 consisting of disease progression in 2 patients and disease progression with edema in 1 patient), insufficient therapeutic response (n =4), patients lost to follow-up (n =1), sponsor/ investigator request (n = 5), patient withdrew consent (n = 5) and other reason not specified (n = 2).

7.3.4 Significant Adverse Events

A total of 40 (49.4%) patients experienced a total of 78 adverse events (AEs) either during infusion or within 1 hour after the end of infusion. A similar proportion of patients treated with either study drug (26/81, 32% for Treanda compared to 21/73, 29% for Bendeka) had AEs within 1 hour after the end of infusion of either study drug.

In this study 38/81 (47%) of patients reported CTCAE grade ≥ 3 AEs. There were 20/81(25%) of patients most recently treated with Treanda compared to 25/73 (34%) of patients most recently treated with Bendeka who reported CTCAE grade ≥ 3 AEs. CTCAE Grade 4 AEs were reported in 3 patients who had 6 events including pericardial effusion, gastric ulcer hemorrhage, hyperkalemia, respiratory distress, respiratory failure and pleural effusion after treatment with Treanda and 1 patient had one CTCAE Grade 4 event of acute pancreatitis after treatment with Bendeka.

7.4.1 Supportive Safety Results

The most common adverse events reported in ≥ 15% of patients in study EGL-BDM-C-1301 overall are shown in the reviewers table below. The table shows that nausea, fatigue, pyrexia, dehydration, decreased appetite and anemia were the most common AEs reported for after recent treatment with either study during.

Table 8. Most Common Adverse Events in Study EGL-BDM-C-1301

Adverse Event (n, %)	Treanda (n = 81)	Bendeka (n = 73)
Nausea	20, 25	14, 19
Fatigue	17, 21	16, 22
Pyrexia	5, 6	12, 16
Dehydration	10, 12	11, 15
Decreased appetite	9, 11	11, 15
Anemia	10, 12	11, 15

Reviewer's table derived from sponsor's table EGL-BDM-C-1301 study report page 127

7.4.2 Laboratory Findings

Clinical laboratories that were evaluated with each period included hematologic, hepatic and renal function tests. Overall, no significant laboratory changes were reported for subjects during study EGL-BDM-C-1301 and between treatments.

7.4.3 Vital Signs and Electrocardiograms (ECGs)

No significant changes in vital signs or ECGs were reported during any treatment period in study EGL-BDM-C-1301.

7.4.4 Immunogenicity

No immunogenicity concerns are expected with the small molecule bendamustine hydrochloride. No immunogenicity assays were performed.

7.5 Additional Safety Evaluations

Dr. Manning (Pharmacology/Toxicology Reviewer in the Division of Hematology Products) states in his review of NDA 208194 (final signature date October 1, 2015) that the sponsor submitted reports to assess the hemolytic and irritant potential of bendamustine hydrochloride at a concentration of up to 5.6 mg/mL, i.e., the highest final admixture concentration covering the clinical dose range. (b) (4) In his review Dr. Manning states that the sponsor conducted a GLP-compliant local tolerance study in rabbits evaluating the irritation potential of bendamustine hydrochloride administered by intended IV and unintended perivascular (PV) routes of administration. Dr. Manning states that administration of either bendamustine hydrochloride formulation intravenously or placebo was associated with a similar degree

of minor trauma and do not represent a toxicologically significant concern. Perivascular administration of the new bendamustine hydrochloride formulation was associated with local macroscopic and microscopic irritation that was not observed with Treanda or placebo. The irritation extended up to 2 cm from the injection site and was followed by epidermal hyperplasia, consistent with normal tissue repair processes.

Toxicities generally associated with administration of a hyperosmotic intravenous solution are hemolysis, phlebitis, and/or infusion site reactions if there is drug extravasation. (Al-Benna, et al.: Extravasation injuries in adults. Dermatology. 2013; 1-8) In NDA 208194 (study EGL-BDM-C-1301) there were no reported adverse events of hemolysis, phlebitis or local drug administration site adverse reactions of the skin reported during the infusion of study drug or within 1 hour after the end of study drug infusion. In this study there were 2 patients who reported skin adverse events during or within 1 hour after the end of study drug administration. One patient most recently treated with Bendeka developed mild urticaria and one patient most recently treated with Treanda developed a mild macular rash.

Reviewer comment for section 7. Review of safety in study EGL-BDM-C-1301 supporting the Bendeka application NDA 208194 does not raise new or additional safety concerns for the Bendeka formulation and faster infusion rate compared to the marketed Treanda lyophilized powder product. This study was conducted in patients with a histologically confirmed diagnosis of any malignant disease for which no curative or standard therapy is appropriate. Most patients 38/81 (47%) in this study had stage IV solid tumor malignancies at the time of enrollment in which disease progression and a high mortality rate is expected. In this study 6 patients died. All 6 patients had stage IV disease and a poor prognosis (AJCC Cancer Staging Handbook, 2002). There was no clear difference between Bendeka and Treanda in the proportion of patients with CTCAE grade ≥ 3 AEs or SAEs. Exclusion of patients with CLL from study EGL-BDM-1301-C is acceptable, as is also stated in the Reviewer Comment for section 5 in this review, because the recommended dose of Treanda for patients with CLL is lower than the recommended dose of Treanda for patients with indolent NHL which would make it difficult to compare pharmacokinetic results for patients with CLL to those with solid tumor malignancies or NHL.

(b) (4)

that the increased osmolality of the Eagle formulation of bendamustine will not result in a clinically meaningful increase in toxicities associated with administration of a hyperosmotic intravenous solution, i.e., phlebitis and/or infusion site reactions. In clinical practice chemotherapy is typically administered to patients via central venous access, e.g., peripherally inserted central catheter or Hickman catheter. Administration of chemotherapeutic agents through central venous access minimizes the risks of phlebitis associated with drugs that are hyperosmolar due the increased venous blood flow with central venous access. (b) (4)

(b) (4) assessment of the potential for these adverse reactions and his conclusion. In NDA 208194 there were no reported adverse reactions of phlebitis or hemolysis. Skin adverse events were generally reported infrequently and were considered to be to be of mild severity. There were two patients who developed adverse skin reactions (mild macular rash and mild urticaria) during the study drug administration or within 1 hour after the end of study drug administration. The faster infusion rate of Bendeka, i.e., 10minutes, compared to the infusion rate of Treanda, i.e., 60 minutes, does not appear to increase the risk for hemolysis, phlebitis or infusion site reactions. Also, the current proposed Warnings and Precautions section labeling for Bendeka is the same as that of Treanda and states that there is a potential risk for skin reactions including SJS and TEN and extravasation.

The sponsor is requesting a Waiver for Pediatric Studies for Bendeka (NDA 208194) for patients age (b) (4). The Treanda label states in section 8.4 Pediatric Use that the effectiveness of Treanda in pediatric patients has not been established. Treanda was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The Treanda label also states that the safety profile for Treanda in pediatric patients was consistent with that seen in adults, and no new safety signals were identified. Bendeka is a ready-to-dilute concentrated solution that will be administered as an intravenous infusion over 10 minutes after dilution with normal saline, 2.5% dextrose/0.45% saline or 5% dextrose injection. Treanda is a lyophilized powder in a single-use vial that requires reconstitution with sterile water for injection and additional dilution prior to administration as an intravenous infusion over 60 minutes. The indications for Bendeka are the same as that for Treanda and patients will be treated with the same total drug dose as that for Treanda. There are no new active ingredients, no new indications, there is no new route of administration and no significant difference in the safety profile of Bendeka compared to the Treanda lyophilized powder formulation even though Bendeka is infused more rapidly compared to Treanda. The difference in the dosage form pertains to the final administration of the product, i.e., rate of infusion of drug. The sponsor's request is reasonable and I recommend that the sponsor's Pediatric Waiver Request be granted. Also, it should be noted that the bendamustine 50mL admixture was granted Orphan Designation for both indications on July 2, 2014 and is not subject to PREA (see Orange Book (b) (4)

8 Postmarket Experience

Clinical reviews of the annual reports for the Treanda products (submitted under NDA 22249) have not identified new concerns for this drug. There are no outstanding Postmarketing Requirements (PMRs) or Postmarketing Commitments (PMCs) for either Treanda formulation at this time. There are no recommended PMRs or PMCs for Bendeka at this time.

Reviewer comment for section 8: There are no recommended PMRs or PMCs for Bendeka (NDA 208194) at this time.

9 Appendices

9.1 Literature Review/References

No new safety concerns were identified after a brief literature search for bendamustine hydrochloride.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting is planned.

9.3 Labeling Recommendations

The Bendeka product label attached below incorporates the labeling recommendations from the FDA review team. Key clinical labeling recommendations for the Bendeka product label and rationale for these changes are shown in the attached FDA comments in the draft product label (FDA proposed wording additions in underline and highlighted format and my proposed wording deletions in strikethrough and highlighted format). The key labeling changes in the Bendeka product label are as follows:

- Section 3 Dosage Forms and Strengths
  Injection: 100 mg/4 mL (25 mg/mL), (b) (4) a clear and colorless to yellow solution (b) (4) a multiple dose vial. (b) (4)

- Section 6.1 Adverse Events in Clinical Trials
  The safety of bendamustine hydrochloride administered IV as a 50 mL admixture over a 10- minute infusion is supported by clinical trials using bendamustine hydrochloride administered IV as a 500 mL admixture over 30-60 minutes infusion time, as well as an open-label, crossover study in 81 'end-of-life' cancer patients treated with bendamustine hydrochloride. In total, safety data from clinical studies are available from over 400 cancer patients exposed to bendamustine hydrochloride at doses in the range used in the treatment of CLL and NHL. No clinically significant differences in the adverse event profile were noted among (b) (4) bendamustine hydrochloride as a 500 mL admixture over standard infusion time (30-60 minutes) and (b) (4) administered bendamustine hydrochloride as a 50 mL admixture in a 'short-time' infusion over

10 minutes. The safety and tolerability of bendamustine hydrochloride was evaluated in an 8-week clinical study of bendamustine hydrochloride in 81 'end-of-life' cancer patients, diagnosed with solid tumors and hematologic malignancies (excluding CLL). The population was 40-82 years of age, 58% females, 84% white, 12.3% Black, 1.2% Asian and 2.5% were classified as 'other'. Bendamustine hydrochloride was administered IV at a 120 mg/m2 dose as a 50 mL admixture over 10 minutes. Patients in the study received bendamustine hydrochloride (50 mL IV, over 10 minutes) or bendamustine hydrochloride (500 mL IV, over 60 minutes) on Days 1 and 2 every 28 days for two consecutive 2-day cycles.

(b) (4)

Adverse reactions (any grade) that occurred with a frequency greater than 5% during bendamustine hydrochloride infusion and within one hour post-infusion were nausea (8.2%) and fatigue (5.5%).

Reviewer comment for section 9: I agree with the proposed FDA labeling recommendations. The attached Bendeka product label should be forwarded to the sponsor.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

ANDREW DMYTRIJUK
11/19/2015

KATHY M ROBIE SUH
11/19/2015
Final wording of label is being negotiated with the sponsor.