CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205580Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 205580
Supporting document/s:	1 (original) and 8 (resubmission after refuse to file)
Applicant's letter date:	September 6, 2013
CDER stamp date:	September 6, 2013
Product:	Bendamustine HCl
Indication:	Chronic Lymphocytic Leukemia (CLL) Non-Hodgkin's lymphoma (NHL)
Applicant:	Eagle Pharmaceuticals, Inc. (EPI)
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Christopher M. Sheth, Ph.D. (DHOT)
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1 Executive Summary

1.1 Introduction

Treanda® (bendamustine HCl) is an alkylating drug that was approved in 2008 (NDA 022249) for the treatment of CLL and Indolent NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. Bendamustine HCl is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage produced can lead to cell death via several pathways (including DNA, RNA and protein synthesis inhibition, leading to subsequent apoptosis).

The Applicant, EPI, has submitted this 505(b)(2) NDA for a bendamustine HCl product that is intended to be used via the same (IV) route, at the same dose levels and for the same indications as the listed drug (LD), Treanda. EPI's to-be-marketed formulation that is the subject of this NDA is different from the Treanda® formulation, in that it will be supplied as a ready-to-dilute concentrated sterile solution containing bendamustine HCl (100 mg), monothioglycerol (20 mg), propylene glycol (0.4 mL), and polyethylene glycol 400 (QS to 4 mL), rather than a lyophilized powder of bendamustine HCl (100 mg) and mannitol (170 mg). Prior to IV administration, both reconstituted Treanda (5 mg/mL in sterile water) and EPI's ready-to-dilute (25 mg/mL) formulation of bendamustine HCl require further dilution into 500 mL of 0.9% Sodium Chloride Injection or, alternatively, 500 mL of 2.5% Dextrose / 0.45% Sodium Chloride Injection. The final concentrations of both Treanda- and EPI-bendamustine HCl will be 0.2-(b) (4) mg/mL.

EPI has included in this NDA a request for waiver for pharmacokinetic bioequivalency studies (Supporting Document #1, eCTD Module 1, Section 1.12.15) for bendamustine HCl. Inclusion of the biowaiver request was based on End-of-Phase 2 meeting discussions (December 12, 2012), in which the Agency indicated that such a waiver may be granted provided EPI submit a side-by-side comparison of the physiochemical properties of the LD and EPI's product, including comparative characterizations of the product in the vial and the final solution to be administered to patients after dilution. EPI submitted GLP-compliant nonclinical "special toxicology" studies (i.e., single dose local tolerance in rabbits and hemolytic potential in human whole blood) of their product compared with Treanda. No additional toxicology, pharmacology or PK/PD study results were submitted by EPI for this NDA.

1.2 Brief Discussion of Nonclinical Findings

EPI relies upon the FDA's previous findings of safety and effectiveness for Treanda®, as described in the drug's approved labeling. The Applicant has not performed any animal pharmacology studies in support of the NDA approval for bendamustine HCl. EPI conducted GLP-compliant local tolerance studies in rabbits, in addition to in vitro hemolytic potential studies in human whole blood, comparing their bendamustine HCl

product with the LD (Treanda®). There was no indication of hemolysis in human blood exposed to EPI's bendamustine HCl. Intravenous administration of EPI's bendamustine HCl was well tolerated in the rabbit local tolerance study, as exemplified by results typical of minor trauma associated with injection procedures. Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for EPI's bendamustine HCl at the defined levels.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, bendamustine HCl may be approved for the proposed indications.

1.3.2 Additional Non Clinical Recommendations

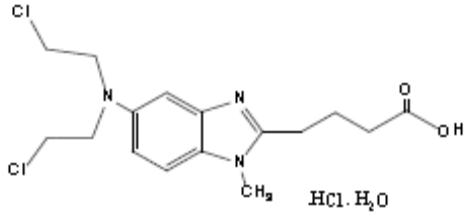
None

1.3.3 Labeling

The nonclinical sections of the label will be comparable to the label of the LD.

2 Drug Information

2.1 Drug

CAS Registry Number:	3543-75-7
Generic Name:	Bendamustine HCl
Code Name:	Not Applicable
Chemical Name:	1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-methyl-,hydrochloride (1:1)
Molecular Formula:	$C_{16}H_{21}Cl_2N_3O_2 \cdot HCl \cdot H_2O$
Molecular Weight:	412.72
Structure or Biochemical Description:	
Pharmacologic Class:	Alkylating drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 022249 (Treanda); IND 109789 (bendamustine HCl injection concentrate); DMF (b) (4) (bendamustine HCl)

2.3 Drug Formulation

Table 1 Comparison of Treanda 100 mg Vial and EPI's Bendamustine HCl

(Excerpted from Applicant's Submission)

Product	Treanda (bendamustine HCl) for Injection (100 mg vial)		Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)	
Dosage Form	Lyophilized powder		Sterile Solution	
Composition	*Ingredients*	*Amount per vial*	*Ingredient*	*Amount per vial*
	Bendamustine HCl	100 mg	Bendamustine HCl	100 mg
	Mannitol, USP	170 mg	Monothioglycerol, NF	20 mg
			Propylene Glycol, USP	0.4 mL
			Polyethylene Glycol 400 (PEG 400), NF*	QS to 4 mL

(b) (4)

Table 2 Comparison of Preparation and Final Solution for Infusion

(Excerpted from Applicant's Submission)

Product		Treanda (bendamustine HCl) for Injection (100 mg vial)		Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)	
Reconstitution		Reconstituted with sterile water for injection to yield a solution of 5 mg/mL		No reconstitution is needed (A ready to dilute solution of 25 mg/mL)	
Further Dilution prior to Infusion		Withdraw require dose and dilute into 500 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride/2.5% Dextrose Injection, USP.		Withdraw require dose and dilute into 500 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride/2.5% Dextrose Injection, USP.	
Final Solution for Infusion*	Admixture Concentration Covering Dose Range	0.2 mg/mL	0.6 mg/mL	0.2 mg/mL	(b) (4) mg/mL
	pH	(b) (4)			
	Osmolarity (mOsm/kg)				

Table 3 Proposed Specifications for EPI's Drug Product

(Excerpted from Applicant's Submission)

Test	Proposed Specification		Justification
Description	Release: Clear colorless to slight yellow solution, essentially free from visible particulates		Based on the appearance of newly manufactured product.
	Shelf: Clear colorless to yellow solution, essentially free from visible particulates		Based on the appearance of development batches over time
Identification: HPLC	By HPLC: The retention time of the major peak in the sample solution corresponds to that in the standard solution as obtained in the Assay.		Based on the retention time of the reference standard.
Identification: HPLC/UV	By HPLC: In the HPLC assay, the UV spectrum of the analyte peak in the sample solution exhibits the same maxima as those in the UV spectrum of the standard..		Based on the UV spectrum of the reference standard.
Bendamustine HCl Assay (By HPLC)	Release (b) (4) %		Based on typical USP drug product assay limits.
	Shelf: (b) (4) %		
Related Substances:	Release:	Shelf:	Based on the ICH Q3B(R2) guidance for impurity limits, literature evidence that some impurities (b) (4) and the data obtained for the RLD. Please see Section 3.2.P.5.6.2 for further details
(b) (4)	NMT (b) (4) %	NMT (b) (4) %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	NMT %	
	NMT %	NMT %	
Total impurities:	NMT 2.0 %	NMT %	
(b) (4)			
Particulate Matter	≥ 10 µm: NMT (b) (4) particles ≥ 25 µm: NMT (b) (4) particles		Based on the *Particulate Matter in Injections* USP <788> requirements for small volume parenteral products tested by the microscopic particle count test, Method II.
Volume in Container	Release only: NLT (b) (4) mL		Based on *Injections* USP <1> requirements for container content.
Sterility	Sterile		Based on *Sterility Test* USP <71>
Bacterial Endotoxin	NMT (b) (4) EU/mg		Based on *Bacterial Endotoxins Test* USP <85>. Please see Section 3.2.P.5.6.4 for further details.
(b) (4)			

2.4 Comments on Novel Excipients

EPI developed their [redacted] (b) (4) solution of bendamustine HCl as an alternative formulation to the lyophilized listed drug; by substituting polyethylene glycol 400 [redacted] (b) (4), propylene glycol [redacted] (b) (4), and monothioglycerol [redacted] (b) (4) for mannitol. The components, their respective strengths in the vial, concentrations as IV administered, and maximum daily doses are presented below (Table 4).

Table 4 Administered Concentration and Maximum Daily Dose of Excipients in Eagle's Bendamustine HCl Product

(Excerpted from Applicant's Submission)

Components	Strength	Concentration as Administered	Maximum Daily Dose	Maximum Daily Dose for 2.0 m^2 BSA
Bendamustine HCl	25 mg/mL	0.2-[redacted] (b) (4) mg/mL	120 mg/m^2	[redacted] (b) (4) mg
Polyethylene glycol 400, NF	[redacted] (b) (4)			
Propylene glycol, USP				
Monothioglycerol, NF	5 mg/mL			

According to the Agency's database of inactive ingredients (IIG), there are several FDA approved IV products containing one or more of the excipients used in EPI's product. The maximum daily doses of the excipients (and concentrations as administered) are higher in the previously approved drugs when compared to the maximum daily doses associated with EPI's bendamustine HCl. Some examples are provided below:

Busulfex® contains polyethylene glycol 400 at 67% (v/v):
Dose = 0.8 mg/kg Busulfex × 70 kg (adult body weight) = 56 mg
Vials are 6 mg/mL
56 mg ÷ 6 mg/mL = 9.3 mL (every six hours for 4 days)
9.3 mL × 4 (# of doses in 24 hours) = 37.3 mL Busulfex/day
37.3 mL × 67% polyethylene glycol 400 = 25 mL polyethylene glycol 400/day

Ativan® for injection contains propylene glycol at ≈82%:
Dose (maximum for status epilepticus in adults) = 4 mg + 4 mg (10 to 15 minutes later)
Each mL contains 2 mg or 4 mg Ativan
8 mg (max dose) ÷ 2 mg/mL = 4 mL
4 mL × 82% propylene glycol = 3.2 mL propylene glycol

Methyldopate HCl Injection contains monothioglycerol at 2 mg/mL:
Dose (maximum in adults) = 1000 mg every 6 hours = 4000 mg/day
Each mL contains 50 mg methyldopate HCl
4000 mg (max dose) ÷ 50 mg/mL = 80 mL
80 mL × 2 mg monothioglycerol/mL = 160 mg monothioglycerol/day

2.5 Comments on Impurities/Degradants of Concern

The specifications for impurities in the drug substance are acceptable from a Pharmacology/Toxicology perspective as they comply with the qualification threshold in ICH Q3A. The impurities in this product do not need to be controlled to lower levels due to any genotoxic potential based on the genotoxic activity of the active pharmaceutical ingredient (API) and the indication.

The impurities identified in EPI's bendamustine HCl drug product include (b) (4) (Table 3). The specifications for (b) (4) are qualified as per ICH Q3B(R2) (b) (4). The specification for any single unidentified impurity (NMT %) is also acceptable as it complies with the Q3B qualification threshold based on the maximum daily dose of EPI's bendamustine HCl injection being (b) (4) mg/day. The Applicant provided a justification for the proposed specifications for (b) (4) and (b) (4). This justification was based on a side-by-side comparison of the stability of reconstituted solutions of EPI's bendamustine HCl and the listed drug (LD) at pre-defined temperatures using 0.9% Sodium Chloride Injection and 0.45% Sodium Chloride/2.5 % Dextrose Injection. This stability comparison showed that higher levels of (b) (4) and (b) (4) were detected in the LD reconstituted solutions, as compared to the respective reconstituted solutions of EPI's product (admixture study report (b) (4)-P1268-13-R001-0).

The amounts of the classified (class 2 and 3) residual solvents in the drug substance and the excipients comprising EPI's product are acceptable based on ICH Q3C limits for solvents under option 1; for doses that do not exceed 10 g/day. (b) (4) is an unclassified residual solvent detectable in the (b) (4) however the levels are acceptable based on the Applicant's calculation that the daily exposure from their product ((b) (4) mg/day) will be lower than the permitted daily exposure ((b) (4) mg/day).

2.6 Proposed Clinical Population and Dosing Regimen

EPI proposed dosing recommendations consistent with current Treanda® labeling for the treatment of CLL and NHL. The recommended dose for treatment of CLL is 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle (up to 8 cycles). The recommended dose for treatment of NHL is 120 mg/m^2 infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle (up to 8 cycles).

2.7 Regulatory Background

The Applicant submitted NDA 205580 on July 1, 2013, and resubmitted on September 6, 2013 after addressing items cited in a refuse to file letter dated August 28, 2013. The listed drug is Treanda (NDA 022249). A pre-IND meeting was held with EPI on November 9, 2010 to obtain agreement with the Agency on the proposed type of NDA

(b) (4)

filing and development program. An End-of-Phase 2 meeting was held with EPI on December 12, 2012, to discuss their plans to submit a 505(b)(2) NDA for bendamustine HCl.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	eCTD Module
Hemolytic Properties of Test and Reference Formulations of Bendamustine Hydrochloride in Human Whole Blood (# 8280095)	4.2.3.7
Single Dose Intravenous and Perivascular Tolerance Study of Bendamustine Containing Formulations in Male Rabbits (# 13-2342)	4.2.3.6

3.2 Studies Not Reviewed

Study Title	eCTD Module
Hemolytic Properties of Test and Reference Formulations of Bendamustine Hydrochloride in Human Whole Blood (# 8264313)	4.2.3.7
Single Dose Intravenous and Perivascular Tolerance of Bendamustine-Containing Formulations in Male Rabbits (# 12-2298)	4.2.3.6
Single Dose Perivascular Tolerance of Bendamustine-Containing Formulations in Male Rabbits with a 21-Day Recovery Period (# 12-2311)	4.2.3.6

3.3 Previous Reviews Referenced

None

4 Pharmacology

No new pharmacology studies were submitted.

5 Pharmacokinetics/ADME

No PK or ADME study reports were submitted. EPI submitted a request for waiver for pharmacokinetic bioequivalency studies (Module 1.12.15) of bendamustine HCl based on discussions with the Agency at the December 12, 2013 End-of-Phase 2 meeting. EPI submitted a side-by-side comparison of their product and the listed drug (Treanda for Injection), including comparative characterizations of the products in the vial and the final reconstituted solutions (Tables 1 and 2, and admixture study repor (b) (4) -P1268-13-R001-0).

6 General Toxicology

Not submitted

7 Genetic Toxicology

Not submitted

8 Carcinogenicity

Not submitted

9 Reproductive and Developmental Toxicology

Not submitted

10 Special Toxicology Studies

The Applicant submitted data from nonclinical studies designed to comply with Agency 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). As EPI's bendamustine HCl is a reformulation of an approved drug substance and is to be administered in an identical manner (IV) to the listed drug, EPI submitted reports for studies of local toxic effects in addition to studies evaluating the compatibility of their product with blood.

Hemolysis study:

The hemolytic potential of EPI's bendamustine HCl was tested in human whole blood in comparison with the listed drug, Treanda. Human whole blood (1mL) was incubated at 37°C for 30 minutes with 10 different solutions, including: EPI's bendamustine HCl injection placebo [5 mg/mL monothioglycerol and (b) (4) propylene glycol in polyethylene glycol 400] diluted with saline (1:34 v/v) and (4.32:15 v/v); EPI's bendamustine HCl at 0.47, 1.1, 2.0, or 2.8 mg/mL; listed drug (Treanda) placebo (b) (4) mg/mL mannitol in sterile water); listed drug (Treanda) at 0.41 mg/mL; negative control (human plasma); and positive control (1% Saponin). Human plasma (1 mL) was also incubated at 37°C for 30 minutes with EPI's bendamustine HCl injection placebo [5 mg/mL monothioglycerol and (b) (4) propylene glycol in polyethylene glycol 400] diluted with saline (4.32:15 v/v) and EPI's bendamustine HCl at 2.8 mg/mL. Following incubation and centrifugation, plasma was harvested and hemolysis was evaluated by spectrophotometric analysis for hemoglobin in the supernatant. The results from the evaluation are presented below (Table 5). No hemolysis was observed in any of the samples tested, except for the positive control.

Table 5 Test and Comparator Article Preparations in Diluent, and Placebos, Combined with Human Whole Blood and Plasma

Tube Numbers	Dilution of Article or Placebo to Saline (volume)	Calculated Bendamustine HCl Concentration after Dilution (mg/mL)	Volume of Plasma, Diluted Solution, or Saponin added to 1 mL Whole Blood (mL)	Ratio of Plasma, Diluted Solution, or Saponin:Whole Blood	Total Sample Volume [solution + whole blood (mL)]	Calculated Bendamustine HCl Concentration in Total Sample Volume (mg/mL)	Hemoglobin Index[a] (mg/dL)	Test Result	Supernatant Color[b]
Solution 1: EPI bendamustine HCl Placebo (diluted with saline), pH = 3.23									
1-4	1:34	NA	2	20:10	3	NA	1 to 4	Negative	Clear
Solution 2: EPI bendamustine HCl (25 mg/mL, diluted to 0.7 mg/mL with saline), pH = 3.20									
5-8	1:34	0.7	2	20:10	3	0.47	3 to 5	Negative	Clear
Solution 3: Treanda Placebo (dilutes with saline), pH = 3.27									
9-12	14.0:100	NA	2	20:10	3	NA	3 to 4	Negative	Clear
Solution 4: Treanda (5 mg/mL, diluted to 0.6 mg/mL with saline), pH = 3.21									
13-16	14.0:100	0.61	2	20:10	3	0.41	2 to 9	Negative	Clear
Solution 5: EPI bendamustine HCl Placebo (diluted with saline), pH = 3.18									
17-20	4.32:15	NA	1	10:10	2	NA	0 to 9	Negative	Clear
21-24	4.32:15	NA	1[c]	10:10	2	NA	0 to 1	Negative	Yellow, Slightly Cloudy
Solution 6: EPI bendamustine HCl (25 mg/mL, diluted to 2.2 mg/mL with saline), pH = 2.94									
25-28	1.44:15	2.2	1	10:10	2	1.1	2 to 7	Negative	Clear
Solution 7: EPI bendamustine HCl (25 mg/mL, diluted to 4.0 mg/mL with saline), pH = 3.05									
29-32	2.88:15	4.0	1	10:10	2	2.0	3 to 5	Negative	Clear
Solution 8: EPI bendamustine HCl (25 mg/mL, diluted to 5.6 mg/mL with saline), pH = 3.09									
33-36	4.32:15	5.6	1	10:10	2	2.8	6 to 26	Negative	Clear

Tube Numbers	Dilution of Article or Placebo to Saline (volume)	Calculated Bendamustine HCl Concentration after Dilution (mg/mL)	Volume of Plasma, Diluted Solution, or Saponin added to 1 mL Whole Blood (mL)	Ratio of Plasma, Diluted Solution, or Saponin:Whole Blood	Total Sample Volume [solution + whole blood (mL)]	Calculated Bendamustine HCl Concentration in Total Sample Volume (mg/mL)	Hemoglobin Index[a] (mg/dL)	Test Result	Supernatant Color[b]
37-40	4.32:15	5.6	1[c]	10:10	2	2.8	0 to 1	Negative	Yellow, Slightly Cloudy
Negative Control									
41-44	NA	NA	1[c]	1:1	2	NA	3 to 4	Negative	Clear
Positive Control									
45-48	NA	NA	1[d]	1:1	2	NA	5571 to 5934	Positive	Red

NA = Not applicable
Negative = No hemolysis (relative to negative control)
Positive = Hemolysis (concentration of hemoglobin is greater than or equal to 500 mg/dL more than that of the negative control).
a = Hemoglobin concentration of the mixture supernatants.
b = A description of clear indicates no change from the color of plasma alone.
c = Plasma separated from whole blood sample.
d = 1% Saponin added to 1 mL whole blood. Saponin is a hemolytic agent used to lyse erythrocytes.

Local tolerance study:

A stand-alone single-dose IV and perivascular (PV) tolerance study of bendamustine containing formulations (EPI's bendamustine HCl compared with the listed drug, Treanda) was conducted in male albino New Zealand White rabbits to assess for potential local toxic effects. The rabbits were approximately 4.5 to 5.5 months of age and weighed 2.8 to 3.2 kg at the initiation of dosing. Three males/group (IV) and 3 males/group (PV) received a single dose of bendamustine formulation and corresponding placebo in the left and right ear, respectively; according to the outline below. Animals were held for a 96-hour (post-dose) observation period. Following the observation period, all animals were sacrificed and a macroscopic and microscopic examination of both ears was performed.

Experimental outline

(Excerpted from Applicant's Submission)

Group	Dose					Number of Male Animals			
	Route	Dose[a] (mg/kg IV or mg PV)	Volume (mL per dose)	Bendamustine Concentration[a] (mg/mL)	Infusion Duration minute/rate (mL/min)	Total	Left Ear[a]	Right Ear[a]	96-hour Necropsy
1 = Treanda®/Treanda® Placebo	IV	5	25	0.6	30/0.83[b, c]	3	3	3	3
2 = BDM1 in saline/BDM1 Placebo	IV	5	2.7	5.6	10/0.27[b, c]	3	3	3	3
3 = Treanda®/Treanda® Placebo	PV	0.15	0.25	0.6	NA	3	3	3	3
4 = BDM1 in saline/BDM1 Placebo	PV	1.4	0.25	5.6	NA	3	3	3	3

[a]Doses represent active pharmaceutical ingredient as administered to the left ear. Placebo formulations (0 mg; 0 mg/mL) were administered to the right ear. For the IV groups the dose was presented as mg/kg, for the PV groups the dose was presented as mg administered.

[b]These rates assumed a rabbit body weight of 3 kg. The rate/minute was adjusted in accordance with the actual body weight to reach the 5 mg/kg target in the specified infusion duration (of either 10 or 30 minutes)

[c]As the volumes and infusion rates changed based on the body weights, the following dose volumes were used: 8.3 mL/kg (5 mg/kg ÷ 0.6 mg/mL) for Group 1; 0.89 mL/kg (5 mg/kg ÷ 5.6 mg/mL) for Group 2. For consistency, the same dose volumes were used for the placebos.
The first day of dosing was defined as Day 1 of the study.

IV administration (the intended clinical route of EPI's bendamustine HCl and the listed drug) of both bendamustine formulations and their respective placebos (i.e., vehicle controls) were well tolerated under the conditions of this study. The results of the dermal evaluations, gross pathology, and histopathology were typical of the minor trauma associated with injection procedures and do not represent a toxicologically significant concern (Table 6).

Table 6 Dermal, Macroscopic, and Microscopic Findings in Local Tolerance Study of Test and Comparator Article Preparations

(Excerpted from Applicant's Submission)

	Treanda® in saline (0.6 mg/mL)	Treanda® Placebo in saline	BDM1 in saline (5.6 mg/mL)	BDM1 Placebo in saline	Treanda® in saline (0.6 mg/mL)	Treanda® Placebo in saline	BDM1 in saline (5.6 mg/mL)	BDM1 Placebo in saline
	5 (mg/kg IV) M		5 (mg/kg IV) M		0.15 (mg PV) M		1.4 (mg PV) M	
Number of Animals	3 3				3		3	
Noteworthy Findings								
Died or Euthanized Moribund	0 0				0		0	
Body Weight (%)	- -				-		-	
Dermal Evaluations[a]								
Erythema Slight	1	-	1	1	-	-	1	2
Erythema Moderate	1	1	1	-	-	-	1	-
Bruising	-	-	-	-	-	-	1	-
Eschar	-	-	-	-	-	-	-	1
Clinical Observations	- -				-		-	

- No noteworthy findings.

[a] Incidence represents numbers of animals affected with greatest severity noted. IV = intravenous; PV = perivascular (Continued)

	Treanda® in saline (0.6 mg/mL)	Treanda® Placebo in saline	BDM1 in saline (5.6 mg/mL)	BDM1 Placebo in saline	Treanda® in saline (0.6 mg/mL)	Treanda® Placebo in saline	BDM1 in saline (5.6 mg/mL)	BDM1 Placebo in saline
	5 (mg/kg IV) M		5 (mg/kg IV) M		0.15 (mg PV) M		1.4 (mg/PV) M	
Number of Animals	3 3				3		3	
Gross Pathology								
Discolored	0	0	2	1	0	0	2	2
Scab	2	1	0	0	0	0	1	2
Histopathology								
Injection Site								
Edema/Collagen Degeneration	1	2	0	0	1	1	3	2
Mixed Inflammation	0	0	0	1	0	1	2	0
Hemorrhage	1	1	1	0	0	1	2	1
Hyperplasia, epithelial	0	0	0	0	0	0	2	0
Epidermal Pustule, Erosion/ Ulceration	0 0 0			0	0 0 2 0			
Scab	0	0	1	0	0	0	2	0
Thrombus	0 0 0			1	0 0 0 0			
2 cm Distal to Injection Site								
Edema/Collagen Degeneration	1	1	0	0	0	0	3	0
Mixed Inflammation	0	0	0	0	0	0	2	0
Hemorrhage	0	0	0	0	0	0	2	0
Hyperplasia, epithelial	0	0	0	0	0	0	2	0
Epidermal Pustule, Erosion/ Ulceration	0 0 0			0	0 0 1 0			
Scab	0	0	0	0	0	0	1	0
4 cm Distal to Injection Site								
Edema/Collagen Degeneration	0	0	0	0	0	0	2	1
Mixed Inflammation	0	0	0	0	0	0	1	0
Hemorrhage	0	2	1	0	1	0	1	0

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

None

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

/s/

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12/20/2013

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12/20/2013