CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-203

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM TO STATISTICAL REVIEW AND EVALUATION OF NDA 22-303

NDA/Serial Number:	22-303/N000
Drug Name:	Treanda® (bendamustine hydrochloride) for injection
Indication(s):	Indolent B-cell non-Hodgkin's lymphoma (NHL)
Applicant:	Cephalon, Inc.
Date(s):	Submission Date: December 28, 2007
	PDUFA Date: October 31, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 5
Statistical Reviewer:	P. Chris Holland, MS
Concurring Reviewers:	Deputy Division Director: Rajeshwari Sridhara, PhD
	Division Director: Aloka Chakravarty, PhD
Medical Division:	Division of Drug Oncology Products
Clinical Team:	Medical Reviewer: Virginia Kwitkowski, MS, RN, CRNP
	Medical Team Leader: Amna Ibrahim, MD
Project Manager:	Milinda Vialpando

Keywords: open-label, response rate, duration of response, Kaplan-Meier curve, censoring, subgroup analyses, historical control, progression-free survival

This is an addendum to the statistical review and evaluation of NDA 22-303/N000 for Treanda (bendamustine hydrochloride) that was filed into DFS on September 26, 2008.

Correction:

The lower bound to the 95% confidence interval around the duration of response based on IRC assessments from study SDX-105-03 is incorrect in 9 places in the document. In these places, the lower bound appears as (b) (4) The correct value is 31.0.

Where the correction should be made:

(b) (4)

Note Regarding Study SDX-105-01:

During the course of labeling discussions, it was decided that the Phase II study SDX-105-01 would not be used as a supportive study in the labeling because it could not be confirmed which patients enrolled in this trial meet the definition of being refractory to rituximab or a rituximab-containing regimen (progression within 6 months). Results from this study should therefore be interpreted with this limitation in mind.

P. Chris Holland, MS
Mathematical Statistician
Date: 10/29/2008

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/s/

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Addendum to statistical review

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

This is an NDA submission for the approval of bendamustine hydrochloride (HCL) for injection for the treatment of indolent B-cell Non-Hodgkin's Lymphoma (NHL) for patients who have progressed during or following treatment with rituximab or a rituximab-containing regimen. A previous NDA for bendamustine was submitted on September 19, 2007 for the indication of CLL (NDA #22-249). It was approved on March 20, 2008, during the review of this NDA.

The primary study being used to support the proposed indication is study SDX-105-03, a single-arm, multi-center study in approximately 100 patients with indolent B-cell NHL who are refractory to rituximab. A Phase II study (SDX-105-01) with a similar design is being used to support this NDA. Both trials enrolled patients in the US and Canada.

The sponsor is claiming that the effectiveness of bendamustine in the proposed indication has been demonstrated by these two trials. Because these are single-arm studies, no statistical inferences are being drawn from them in this review. Rather, the emphasis is on the response rate and duration of responses.

1.1 Conclusions and Recommendations

Based on this reviewer's analysis of the assessments made by the independent review committee (IRC) in study SDX-105-03, 74 out of 100 patients (74%) achieved a best response of PR, CRu, or CR (95% CI: 64.3%, 82.3%). These results differ slightly from those of the sponsor due to a correction to the status of Patient 24093 whose best response was changed from a PR to a SD since the PR response occurred 2 days after the data cut-off date of July 15, 2007. The recalculated median duration of response (DR) is 40 weeks (95% CI: 30.3, 46.9). These results are consistent with those based on investigator assessments and with those from the subset of patients in study SDX-105-01 who had indolent NHL. Subgroup analyses mostly revealed consistent results between subgroups based on demographic and baseline characteristics, although effectiveness was somewhat diminished among patients who were refractory to prior alkylator therapies and prior chemotherapies.

Whether the effectiveness is adequate for approval of bendamustine for the proposed indication will be determined by clinical judgment and an assessment of the product's overall risk/benefit profile.

1.2 Brief Overview of Clinical Studies

Study SDX-105-03 is a single-arm study conducted in approximately 100 patients across 28 centers in the US and Canada with indolent B-cell NHL who had progressed during or following treatment with rituximab or a rituximab-containing regimen. Patients were to be treated with bendamustine HCL at 120 mg/m^2 administered by IV infusion over 60 minutes at single doses, repeated every 3 weeks on days 1 and 2. Treatment was to include at least six and at most eight 3-week cycles followed by an end-of-treatment evaluation within 28 days of the last dose of

study drug. Patient accrual started in October, 2005 and the data cutoff date for the final report was July 16, 2007.

The primary objective of the study was to describe the overall response rate (ORR) and duration of response (DR) to a regimen of bendamustine in patients with rituximab-refractory indolent NHL. The secondary efficacy objective was to assess the duration of progression-free survival (PFS). Primary results are based on assessments by an independent review committee (IRC). Other secondary objectives of the study relate to assessments of safety and pharmacokinetic parameters.

This study underwent a special protocol assessment (SPA) by the FDA.

Study SDX-105-01 is a Phase II single-arm study with a similar design and patient population to that of study SDX-105-03. The dose and treatment regimens were identical between the two studies, as were the rules for dose reductions, although patients in Study SDX-105-01 were allowed to stay on treatment for a maximum of 12 cycles, compared to 8 in study SDX-105-03. The primary difference with respect to the patient population is that study SDX-105-01 allowed patients with transformed B-cell NHL to enroll in the trial whereas study SDX-105-03 did not. Another notable difference is that response was not assessed by an IRC in study SDX-105-01.

1.3 Statistical Issues and Findings

1. Although double-blind, randomized trials are generally preferred, objective endpoints in single-arm trials may be considered for approval in an oncology setting where treatment options are limited and placebo controls are unethical. In treating NHL patients who are refractory to rituximab or a rituximab-containing regimen, major tumor regressions in a single-arm trial can be presumed to be attributable to the test drug. Evidence of sufficiently high objective response rates along with durable response durations can be considered as the basis for regulatory approval in this clinical setting.

2. Statistical inferences involving historical controls or arbitrary cut-points are not meaningful or reliable in single-arm trials. Results from inferential analyses are therefore not reported in this review, although 95% confidence intervals are.

3. During the review of study SDX-105-03 by the clinical reviewer, two discrepancies with the IRC response assessments were noted between the data sets, data listings, and the study report results. After confirmation from the sponsor (via an e-mail sent on July 28, 2008), the following changes were made for this reviewer's analyses:
    - The best response for Patient 65036 was changed from a CR to a CRu in order to reflect the final decision by the IRC's oncologist adjudicator
    - The best response for Patient 24093 was changed from a PR to an SD since the PR response occurred 2 days after the data cut-off date of July 15, 2007

As a result of these changes, the ORR based on the IRC assessments (the primary endpoint) comes to 74% (95% CI: 64.3%, 82.3%). The median duration of response is 40 weeks (95% CI: 30.3, 46.9). The CR rate was reduced from 14% as reported by the applicant to 13%.

4. The IRC results in study SDX-105-03 are similar to those obtained from the investigator assessments of response. Using the investigator assessments, the ORR is 80% (95% CI: 70.8, 87.3) and the median duration of response is 39 weeks (95% CI: 33.7, 60.1).

5. The data are further supported by results from Study SDX-105-01, a Phase II study with a similar design and patient population to that of SDX-105-03. When considering only those patients in SDX-105-01 who had indolent NHL, the ORR is 79% (95% CI: 66.3, 88.1) and the median duration of response is 39 weeks (95% CI: 26.6, 72.6). In all, there was 88% concurrence with respect to response between the IRC and investigator assessments

6. Results are generally similar across various subgroups defined by demographic and baseline characteristics. A possible exception is with regards to subgroups based on prior alkylator and chemotherapy response status. Response rates are lower among patients who are refractory to prior alkylator therapies (60% ORR) and refractory to prior chemotherapies (61% ORR), compared to those who are sensitive to prior alkylator therapies (86% ORR) and sensitive to prior chemotherapies (88% ORR). In both groups, refractory patients experienced shorter DRs compared to sensitive patients (33 weeks *vs.* 42 weeks, respectively, for prior alkylator therapy patients and 27 weeks *vs.* 43 weeks, respectively, for prior chemotherapy patients).

Table A provides point estimates and 95% CIs for ORRs and median DRs for studies SDX-105-03 and SDX-105-01.

Table A: Summary of Overall Response Rates and Response Durations (Studies SDX-105-03 and SDX-105-01)

		CR+CRu+PR			Response Duration	
Study	**Assessor**	**N**	**Events**	**95% CI**	**Median (weeks)**	**95% CI**
SDX-105-03	IRC	100	74 (74%)	(64.3, 82.3)	40.1	(30.3, 46.9)
	Investigator	100	80 (80%)	(70.8, 87.3)	39.4	(33.7, 60.1)
SDX-105-01[1]	Investigator	61	48 (79%)	(66.3, 88.1)	39.3	(26.6, 72.6)

[1] Includes patients with indolent NHL only.