

## **4. Appendices**

### **4.1 PHARMACOMETRIC REVIEW:**

#### **PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES FOR THE SAFETY AND EFFICACY OF TREANDA**

##### **SUMMARY:**

In the current submission, the sponsor submitted a data analyses report titled "*Pharmacokinetic/Pharmacodynamic Analyses Of The Safety And Efficacy Of Treanda® (Bendamustine HCl) In Patients With Indolent Non-Hodgkin's Lymphoma (NHL) Who Are Refractory To Rituximab*". This report has been reviewed by FDA reviewer. No exposure measures were found to be significant predictors of responder status, duration of response (DR), or progression-free survival (PFS) within the studied exposure range. Among the safety endpoints evaluated in the PK/PD analyses, nausea was the only safety endpoint that was found to be statistically significantly related to bendamustine exposure.

##### **DATA USED FOR ANALYSES:**

Data for this analysis were obtained from study SDX-105-03, which was a phase 3, multicenter, open label, 6-treatment cycle, single-agent study in patients with indolent NHL refractory to rituximab.

In this study, bendamustine was administered as a 60-minute *iv* infusion at a dose of 120 mg/m<sup>2</sup> on day 1 and day 2 of 6 consecutive 21-day treatment cycles. If a patient was continuing to experience clinical benefit at cycle 6, the patient received up to 2 additional cycles of bendamustine.

The primary efficacy variables were overall response rate (ORR) and duration of response (DR). ORR was defined as the proportion of patients who achieved a best response of complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during the study.

The secondary efficacy variable was progression-free survival (PFS). PFS for each patient was defined as the time interval from the date of first study drug dose to the first documentation of disease progression, change of therapy, or death regardless of cause, whichever occurred first. Patients without disease progression, change of therapy, or death were censored at the date of last known progression-free assessment.

Safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, physical examination findings, electrocardiogram (ECG) findings, and concomitant medication usage.

##### **POPULATION PHARMACOKINETICS:**

The population pharmacokinetic analyses report for study SDX-105-03 was submitted with the original NDA 22-249 and has been reviewed by FDA. The following is a brief summary about the population pharmacokinetics of bendamustine and its active metabolites:

Plasma samples for SDX-105-03 were assayed for bendamustine, and its active metabolites (N-desmethyl-bendamustine (M4) and  $\gamma$ -hydroxy-bendamustine (M3)). Patients in the General Clinical Research Center (GCRC) group had a full PK profile on day 1 of cycle 1. In addition, sparse PK samples were collected from the non-GCRC patients, up to 4 samples per patient. Sparse PK samples were collected on day 1 of cycle 2 at the following times: predose, between 0.25 and 0.5 h after the start of the infusion, and between 1 and 3 hr after the start of the infusion from 88 patients. Nonlinear mixed effects modeling was used to develop separate population PK models for bendamustine, M3 and M4. The models are summarized below:

- bendamustine: 3-compartment model with 0-order input and 1st-order elimination
- M4: 1-compartment model with 0-order input and 1st-order elimination
- M3: 2-compartment model with 0-order input, 1st-order elimination and a metabolite-formation lag time

These population PK models were used to compute individual PK exposures (AUC and C<sub>max</sub>) for bendamustine, M4 and M3.

For details on the population PK model, see the clinical pharmacology review of the original NDA 22-249.

## **POPULATION PHARMACOKINETICS/PHARMACODYNAMICS:**

### **METHOD:**

The exploration of potential PK/PD relationships for bendamustine included evaluation of 3 efficacy endpoints (responder status, DR, and PFS) and 3 safety adverse events (fatigue, nausea, and vomiting) and 1 laboratory abnormality (neutropenia). The adverse events/laboratory abnormality were selected due to the fact that they are known to be frequently associated with bendamustine treatment.

Exposure measures used in the exposure-response analyses include:

- cycle 1 maximum plasma concentration (C<sub>max</sub>) for bendamustine,
- cycle 1 area under the concentration-time curve (AUC) for bendamustine,
- cumulative bendamustine AUC,
- cycle 1 composite C<sub>max</sub>,
- cycle 1 composite AUC,
- cumulative composite AUC.

Composite measures of exposure were weighted sums of exposures based on the relative potency of bendamustine and its two active metabolites, M3 and M4. Cumulative AUC values were calculated as the sum of the AUCs calculated for all treatment cycles.

Only patients in the defined primary analysis set (all enrolled patients who were treated with any amount of bendamustine) and who had at least 1 bendamustine exposure measure were included in the PK/PD analyses.

For responder status, logistic regression was used to characterize the exposure-response relationship. Kaplan-Meier plots of DR and PFS were constructed by categorizing each exposure into 2 groups using the median cycle 1 exposure measure.

The safety profile of bendamustine was evaluated by logistic regression for the relationship between bendamustine exposure and the occurrence of the adverse events (fatigue, nausea, and vomiting). The relationship between neutropenia and exposure to bendamustine was graphically evaluated across cycles. No formal statistical modeling of neutropenia was performed.

The population PK/PD analysis was completed using both SAS software and NONMEM® software, Version 6, Level 1.0, with NM-TRAN, Version IV, Level 1.0, PREDPP, Version V, Level 1.0.

## **RESULTS:**

### **PK/PD for efficacy:**

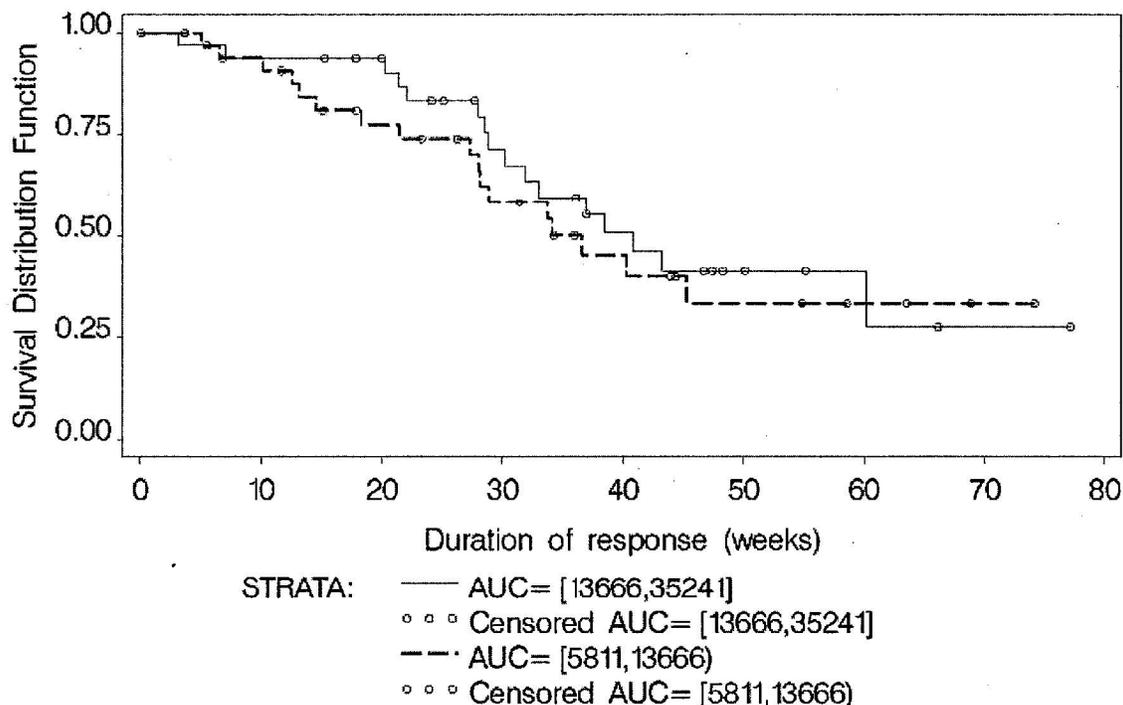
**Responder status:** Of the 80 patients in the PK/PD efficacy analysis, 68 patients (85%) were responders after treatment with bendamustine. Exploratory graphical analyses demonstrated that responders and non-responders had similar cycle 1 bendamustine and composite exposure values. The logistic regression analysis of responder status included the evaluation of cycle 1 bendamustine AUC and Cmax, cycle 1 composite AUC and Cmax, cumulative bendamustine AUC, and cumulative composite AUC. Cumulative bendamustine AUC and cumulative composite AUC were statistically significant predictors of responder status (change in the minimum value of the objective function (MVOF) of greater than 12, p-value <0.0004). Because no cycle 1 exposure measure was a significant predictor of responder status, the number of cycles completed was also analyzed to determine if the significance of the cumulative AUC measures was related to time alone. The number of completed cycles was more significant than cumulative exposure (p-value <0.0001) and there was no additional benefit to the inclusion of cycle 1 exposure once number of cycles was in the model; therefore, the significance of the cumulative exposures was deemed related more to time than exposure. No exposure measures were significant predictors of responder status within the studied exposure range.

**Reviewer's Comments:** The results from the sponsor's logistic regression analyses were confirmed the FDA reviewer using SAS software. The results

were generally consistent. In addition to the sponsor's models, the FDA reviewer also tested using the logarithm of AUC and Cmax in the logistic regression, and none of them turned out to be significant predictors of the responder status. The FDA reviewer agrees with the sponsor's conclusion that no exposure measures were significant predictors of responder status within the studied exposure range.

**DR:** The mean (SD) DR was 31.60 (18.27) weeks and ranged from 0.1 to 77 weeks. Exploratory graphical analyses demonstrated no relationship between DR and exposure. Kaplan-Meier analysis resulted in no statistically significant relationship between DR and cycle 1 bendamustine AUC, composite AUC, cycle 1 bendamustine Cmax, or composite Cmax (p-value=0.5246, 0.9712, 0.5572, and 0.8748, respectively). As an example, the Kaplan-Meier Plot of Duration of Response, Stratified by Median Cycle 1 Bendamustine AUC is shown in Figure 1.

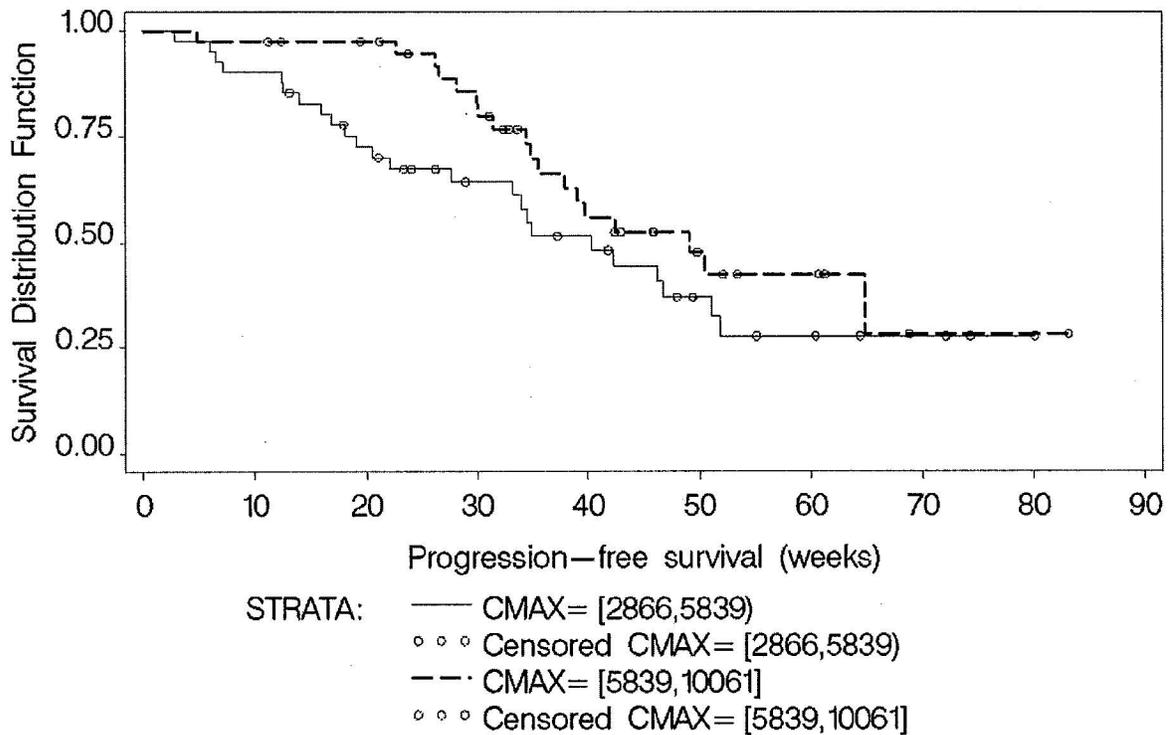
**Figure 1. Kaplan-Meier Plot of Duration of Response, Stratified by Median Cycle 1 Bendamustine AUC**



**PFS:** The mean (SD) PFS was 35.79 (18.42) weeks and ranged from 2.9 to 83 weeks. Exploratory graphical analyses demonstrated an initial trend for a relationship between PFS and cycle 1 bendamustine Cmax up to 60 weeks, followed by no

difference in PFS after 60 weeks of treatment with bendamustine (Figure 2). The relationship between PFS and cycle 1 bendamustine AUC, cycle 1 composite AUC, and cycle 1 composite Cmax demonstrated an initial trend up to 30 weeks followed by no difference in PFS by exposure after 30 weeks of treatment with bendamustine. Kaplan-Meier analysis resulted in no statistically significant relationship between PFS and cycle 1 bendamustine AUC, cycle 1 composite AUC, cycle 1 bendamustine Cmax, or cycle 1 composite Cmax (p-value=0.3025, 0.2870, 0.1563, and 0.5135, respectively).

**Figure 2. Kaplan-Meier Plot of Progression-Free Survival, Stratified by Median Cycle 1 Bendamustine Cmax**



**PK/PD for Safety:**

**Fatigue:** Of the 80 patients in the PK/PD safety analyses, 45 patients (56%) had at least 1 occurrence of fatigue during the treatment period. Exploratory graphical analyses of the data demonstrated no relationships between the occurrence of fatigue and measures of bendamustine exposure. The ranges of exposures were similar in patients who experienced and in those who did not experience fatigue. Logistic regression analysis confirmed that no exposure measures were statistically significant predictors of the probability of fatigue.

**Nausea:** A total of 59 patients (74%) had at least 1 occurrence of nausea during the

treatment period. Exploratory graphical analyses of the data indicated potential relationships between the occurrence of nausea and both cycle 1 bendamustine C<sub>max</sub> and cycle 1 composite C<sub>max</sub>. Logistic regression analysis showed that cycle 1 bendamustine C<sub>max</sub> and cycle 1 composite C<sub>max</sub> were both statistically significant predictors (p-value=0.013 and p-value=0.013) of the probability of the nausea. Since both exposures were equally significant, cycle 1 bendamustine C<sub>max</sub> was deemed the more appropriate exposure measure, given that cycle 1 composite C<sub>max</sub> is composed mostly of bendamustine, and because the 2 measures were highly correlated (r>0.99). No covariates were found to be statistically significant predictors of the probability of nausea. The final exposure-response model for nausea includes a statistically significant relationship between cycle 1 bendamustine C<sub>max</sub> and probability of nausea. The table of parameter estimates from the nausea model is shown in Table 2.

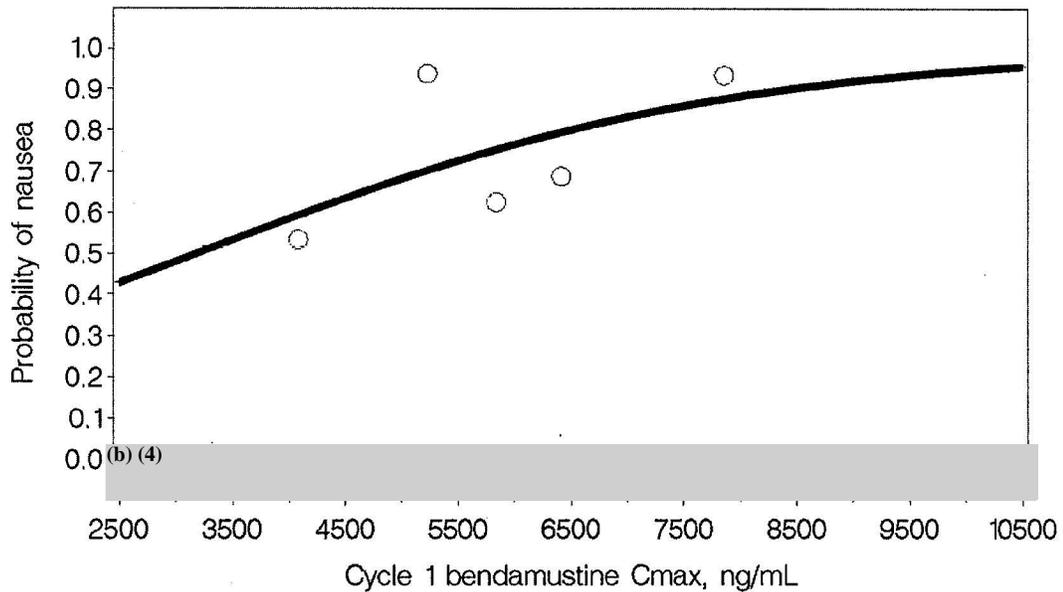
**Table 1. Parameter Estimates and Standard Errors from the Model for the Occurrence of Nausea (N=78)**

Parameter	Final parameter estimate		Odds ratio	95% confidence interval for odds ratio		p-value
	Population mean	SE		Lower bound	Upper bound	
Intercept	1.1329	0.2760	NA	NA	NA	NA
Slope for bendamustine C <sub>max</sub> ng/mL	0.000420	0.000216	1.00043	1.00	1.00088	0.0389
Hosmer-Lemeshow Goodness-of-Fit Test=13.01 with 8 Degrees of Freedom (p-value=0.1115)			Area Under the ROC Curve=0.63			
Minimum value of the objective function = 84.541						

SE= standard error, ROC=area under the receiver operating characteristic curve, NA=not applicable, C<sub>max</sub>=maximum plasma concentration.

At the median cycle 1 bendamustine C<sub>max</sub> value of 5839 ng/mL for the 120 mg/m<sup>2</sup> dose of bendamustine, the model-predicted probability of nausea is 0.753. As cycle 1 bendamustine C<sub>max</sub> increases, the model-predicted probability of nausea increases. The odds ratio of 1.00043 indicates that for a 100-unit (ng/mL) increase in cycle 1 bendamustine C<sub>max</sub>, the probability of a nausea adverse event is 1.043 times more likely. The model-based predicted probability of nausea versus cycle 1 bendamustine C<sub>max</sub> with observed probabilities from cycle 1 bendamustine C<sub>max</sub> values in bins of equal sample size is shown in Figure 8-5. The observed probability of nausea in each bin generally corresponds well with the model-based predicted probabilities.

**Figure 3. Observed and Model-Predicted Probability of the Occurrence of Nausea Versus Cycle 1 Bendamustine C<sub>max</sub>**



The line represents the model-based predicted probability of nausea. The circles represent the median Cmax values and their associated observed probabilities. The hash marks near the x-axis represent the individual Cmax values.

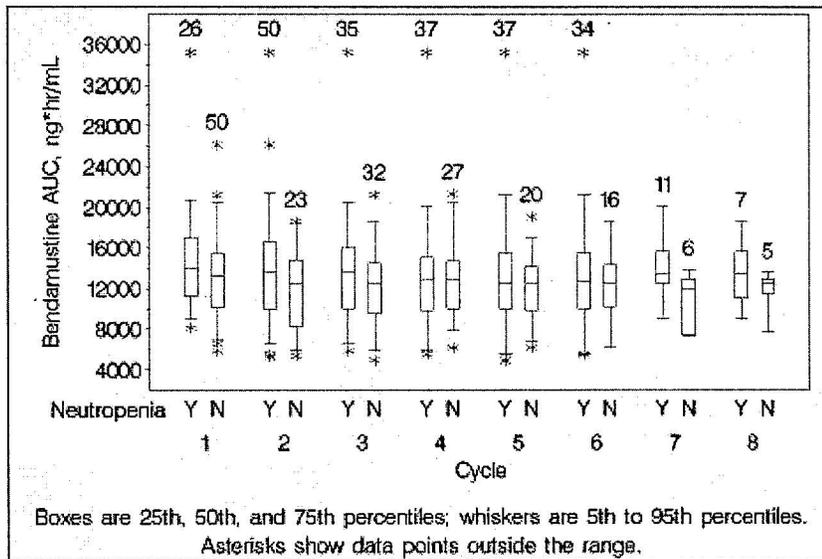
**Vomiting:** A total of 25 patients (31%) had at least 1 occurrence of vomiting during the treatment period. Exploratory graphical analyses of the data demonstrated no relationship between the occurrence of vomiting and measures of bendamustine exposure. Logistical regression analysis confirmed that no exposure measures were statistically significant predictors of the probability of the vomiting.

Reviewer's Comments: The sponsor's logistic regression analyses for fatigue, nausea, and vomiting were conducted using NONMEM software. The results from the sponsor's analyses were confirmed by the FDA reviewer using SAS software. The results were generally consistent. In addition to the sponsor's models, the FDA reviewer also tested using the logarithm of AUC and Cmax in the logistic regression. None of exposure measures turned out to be significant predictors of the occurrence of fatigue and vomiting within the studied exposure range. Cycle 1 bendamustine Cmax and cycle 1 composite Cmax were both statistically significant predictors of the probability of nausea.

**Neutropenia:** Neutropenia was determined based on laboratory measurements. Weekly hematology measurements were conducted in this study. For each patient cycle, the lowest laboratory Absolute Neutrophil Count (ANC) measurement was

taken and graded based on NCI toxicity criteria. Boxplots of bendamustine AUC measures at each cycle demonstrated that patients with neutropenia had slightly higher bendamustine AUC measures during cycles 1 through 3. During cycles 4 through 6, similar bendamustine AUC measures were observed in patients with and without neutropenia.

**Figure 4. Boxplots of Bendamustine AUC Versus Cycle, Stratified by Neutropenia**



**CONCLUSIONS:**

- In the Phase 3 study SDX-105-03, where patients with indolent NHL refractory to rituximab were treated with bendamustine as a 60-minute *iv* infusion at a dose of 120 mg/m<sup>2</sup> on day 1 and day 2 of 6 consecutive 21-day treatment cycles, bendamustine exposure was not a significant predictor of responder status, duration of response or progression-free survival, within the studied exposure range.
- Bendamustine exposure was not a predictor of the occurrence of fatigue or vomiting within the studied exposure range. However, cycle 1 bendamustine Cmax was a statistically significant predictor of the occurrence of nausea.

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