Clinical Pharmacology Review

NDA	22-249/SDN252
Submission Date:	12/27/11
Brand Name:	TREANDA®
Generic Name:	Bendamustine hydrochloride
Formulation:	Injection
OCP Reviewer:	Young Jin Moon, Ph.D.
Pharmacometrics Reviewer:	Justin Earp, Ph.D.
Pharmacometrics Team Leader:	Christine Garnett, Pharm.D.
OCP Team Leader:	Qi Liu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Hematology Products
Sponsor:	Cephalon
Submission Type; Code:	Prior Approval Labeling Supplement
Dosing regimen:	100 mg/m^2 IV over 30 minutes on Days 1 and 2 every 28 days for chronic lymphocytic leukemia; 120 mg/m^2 IV over 60 minutes on Days 1 and 2 of a 21-day cycle for indolent B-cell non-Hodgkin's lymphoma
Indication:	Chronic lymphocytic leukemia; Non-Hodgkin's lymphoma

1 EXECUTIVE SUMMARY

Bendamustine hydrochloride is currently approved for the treatment of patients with chronic lymphocytic leukemia (CLL) and for patients with indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

This submission includes a phase 1/2 study entitled "An Open-Label Study of Bendamustine Hydrochloride for the Treatment of Pediatric Patients with Relapsed or Refractory Acute Leukemia". This study was conducted to respond to a Written Request by the FDA in July 2009, which was last amended on 7 July 2011. In phase 1, a dose of 120 mg/m^2 administered as a 60-minute intravenous (IV) infusion on days 1 and 2 of a 21-day cycle was determined to be the recommended pediatric dose (RPD). In phase 2, none of the 32 patients met the criteria for response (complete remission (CR) or complete remission without platelet recovery (CRp)), which was the primary endpoint for the study. Two patients achieved a partial response (PR). Both patients had acute lymphocytic leukemia (ALL). In phase 1, there were 2 CRs in the 5 patients treated with bendamustine at 90 mg/m^2. Both patients had ALL. None of the 6 patients treated in phase 1 at 120 mg/m^2 dose responded to bendamustine treatment. Five of 6 patients had acute myeloid leukemia (AML). The sponsor is not seeking the indication of relapsed or refractory acute leukemia in pediatric patients.

The pharmacokinetic profiles of bendamustine and its 2 active circulating metabolites, M3 and M4, were characterized in these pediatric patients. Overall, the results obtained for bendamustine, γ-hydroxy-bendamustine (M3) and N-desmethyl-bendamustine (M4) were generally consistent

with those obtained previously in adult cancer patients. Within the pediatric population evaluated in the present study, there did not appear to be any consistent age-related differences in systemic exposure to bendamustine, M3 or M4.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in sNDA 22-249 (SDN252) and considers this sNDA acceptable from a clinical pharmacology perspective.

Labeling Recommendations

See Section 3. Detailed Labeling Recommendations.

Signatures:

Reviewer: Young Jin Moon, Ph.D. Division of Clinical Pharmacology 5	Team Leader: Qi Liu, Ph.D. Division of Clinical Pharmacology 5
Reviewer: Justin Earp, Ph.D. Division of Pharmacometrics	Team Leader: Christine Garnett, Pharm.D. Division of Pharmacometrics

Cc: DHP: CSO - T Ferrara; MTL - A Deisseroth; MO - P Dinnorf
DCP-5: Reviewer - Y Moon, J Earp ; TL – Q Liu, C Garnett
DDD - B Booth ; DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

Bendamustine (b) (4) is a cytotoxic, bifunctional alkylating agent. Approved dosing regimens are 100 mg/m IV over 30 minutes on Days 1 and 2 every 28 days for chronic lymphocytic leukemia; 120 mg/m^2 IV over 60 minutes on Days 1 and 2 of a 21-day cycle for indolent B-cell non-Hodgkin's lymphoma. The pharmacokinetic profiles of bendamustine and its metabolites, γ-hydroxy-bendamustine (M3, equi-effective with bendamustine) and N-desmethyl-bendamustine (M4, 10-fold less active than bendamustine), were determined in this pediatric population. The relationship between patient age and C_{max} and AUC_{0-t} for bendamustine and its 2 active metabolites was examined for the 120 mg/m^2 dose cohort. The results indicated that there were no consistent age-related differences in systemic exposure to bendamustine, M3 or M4 in these pediatric patients. Also, the exposures of bendamustine and its active metabolite M3 in pediatrics at the 120 mg/m^2 dose were similar to those in adults at the same dose.

2 QUESTION BASED REVIEW

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of clinical studies used to support dosing or claims?

This was a phase 1/phase 2, multicenter, open-label, nonrandomized study in 43 pediatric patients with relapsed/refractory acute leukemia. Part 1 (the Phase 1 portion of the study) determined the RPD and dose-limiting toxicities (DLTs) of bendamustine. Part 2 (the Phase 2 portion of the study) evaluated the efficacy and safety of bendamustine. Each part of the study followed the same basic study design. There was up to a 14-day screening period, 1 cycle of induction therapy, subsequent therapy for up to a maximum of 12 cycles total or until disease progression, and a follow-up period for patients who completed or were withdrawn from treatment without progressive disease.

In the Phase-1 portion, the starting dose was 90 mg/m^2 and was escalated to 120 mg/m^2 using a traditional 3+3 dose escalation design. In the Phase-2 portion, patients were administered bendamustine at 120 mg/m^2, i.e., the dose that was identified as the RPD during part 1 of the study. During both parts of the study, bendamustine was administered as an IV infusion over 60 minutes on days 1 and 2 of each treatment cycle.

The reviewer concluded that the study was conducted as described in the WR from a clinical pharmacology perspective (Table 1).

Table 1 Comparison of Written Request and study report

Written Request	Study Report
Type of study	
A phase 1/2 study of bendamustine HCL for the treatment of pediatric patients with relapsed or refractory acute leukemia	Same as the WR
Indication	
Treatment of pediatric patients with relapsed or refractory acute leukemia	Same as the WR
Objectives	
Primary • Phase 1: To determine the recommended phase 2 dose • Phase 2: To evaluate the safety and efficacy of	Same as the WR

bendamustine. Efficacy assessment will include complete response (CR) and complete remission with inadequate platelet recovery (CRp) *Secondary* • To determine the PK profile of bendamustine in pediatric population • To determine the duration of remission (CR+CRp) to bendamustine therapy	
Age group	
1-21 years. At least 10 patients must be treated within each of the following specific age groups (1-6, 7-11 and 12-21 year-old)	In phase 2, 10 patients in 1-6 year-old, 10 patients in 7-11 year-old, and 12 patients in 12-20 year-old age group
Number of patients	
Phase 1: A minimum of 6 and a maximum of 18. In addition, PK profiles must be obtained from a minimum of 6 patients in the RP2D cohort in Phase 1. Phase 2: Additional 26 patients (not including the patients treated in phase 1)	Phase 1: N=5 (90 mg/m^2) and N=6 (120 mg/m^2). PK profiles were obtained from all 6 patients who received 120 mg/m^2 Phase 2: N=32
PK endpoints	
PK samples must be collected through approaches such as rich sampling or optimal sparse sampling.	Blood samples for PK analysis were obtained from every patient on day 1 before infusion, immediately following infusion, and 3, 6, 10 and 24 hours after the start of infusion.
Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or noncompartmental analysis (NCA).	Data were analyzed using both NCA (**Section 2.2.7**) and nonlinear mixed effects modeling (**Section 2.3.1**).
Data from phase 1 and phase 2 must be combined to develop PK-PD models to explore exposure-response (E-R) relationships for measures of safety and effectiveness.	Data from phase 1 and phase 2 were combined to develop PK/PD model. The sponsor's PK/PD model appears acceptable. E-R for safety was explored. Since no efficacy was shown, E-R for effectiveness was not conducted.
The effect of age on the PK of bendamustine within the overall pediatric population must be assessed.	Relationship between age and the C_{max} and AUC of bendamustine/M3/M4 in pediatric patients are shown in **Figure 1, Section 2.3.1.**
Drug information	
• Dosage form: Bendamustine hydrochloride for injection (100 mg/20 mL) • Route of administration: intravenous infusion (IV) • Regimen: Phase 1: The dose escalation scheme, as tolerated, is 90 mg/m^2, 120 mg/m^2, and 150 mg/m^2 IV infusion over 60 minutes IV on days 1 and 2 of each 21-day cycle, with delays up to 2 weeks for bone marrow recovery. A 150 mg/m^2 dose will be administered only if a 120 mg/m^2 dose is deemed safe and the exposure of bendamustine in pediatric patients is less than that in adult patients following administration of 120 mg/m^2 bendamustine. A dose de-escalation to 60 mg/m^2 may be required if two or more dose limiting toxicities occur at the starting dose. Phase 2: The dose and schedule will depend on the results of the Phase 1 dose escalation study.	Same as the WR Phase 1: PK analysis of samples taken from patients at the 120 mg/m^2 dose level confirmed that the plasma exposure to bendamustine in pediatric patients was similar to that in adult patients. For this reason, escalation to 150 mg/m^2 did not occur.

2.2.7 What are the single dose and multiple dose PK parameters?

There were a total of 30 male and 13 female patients enrolled in this study. The ages of the patients ranged from 1 to 19 years, with a median value of 10 years. The body surface areas of the patients ranged from 0.5 to 1.9 m^2, with a mean value of 1.1 m^2. Blood samples for PK analysis were obtained from every patient on day 1 before infusion, immediately following infusion, and 3, 6, 10 and 24 hours after the start of infusion.

The mean ± SD pharmacokinetic parameters for bendamustine and its M3 and M4 metabolites in pediatric cancer patients following a 60-minute intravenous infusion of bendamustine at 90 (n=5) or 120 (n=37) mg/m^2 on day 1 of cycle 1 are shown in Table 2. The sponsor's analysis was confirmed by the reviewer using raw data.

Table 2. Mean ± SD Pharmacokinetic Parameters for Bendamustine and Its M3 and M4 Metabolites in Pediatric Patients After a 60-Minute Intravenous Infusion of Bendamustine HCl at 90 or 120 mg/m^2 on Day 1 of Cycle 1

		Dose Cohort	
Analyte	**Parameter**	**90 mg/m^2 (N=5)**	**120 mg/m^2 (N=37)[a]**
Bendamustine	C_{max} (ng/mL)	5949 ± 3592	7490 ± 3962
	t_{max} (hr)[b]	1.10 [1.00-1.30]	1.10 [0.80-1.30]
	AUC_{0-t} (ng•hr/mL)	12769 ± 6605	13208 ± 7737
	AUC_{0-24} (ng•hr/mL)	NC	14511 ± 7322[c]
M3 Metabolite	C_{max} (ng/mL)	426 ± 396	483 ± 338
	t_{max} (hr)[b]	1.10 [1.00-1.30]	1.10 [0.80-1.30]
	AUC_{0-t} (ng•hr/mL)	880 ± 778	855 ± 576
	AUC_{0-24} (ng•hr/mL)	NC	1337[d]
M4 Metabolite	C_{max} (ng/mL)	48 ± 40	56 ± 30
	t_{max} (hr)[b]	1.10 [1.00-1.30]	1.10 [0.80-1.30]
	AUC_{0-t} (ng•hr/mL)	84 ± 92	90 ± 51
	AUC_{0-24} (ng•hr/mL)	NC	NC

NC: Not calculable.
[a] Excludes 1 patient from the 120-mg/m^2 dose cohort (ID 611001) whose actual dose was approximately 148 mg/m^2.
[b] Median [range].
[c] n=13.
[d] n=2.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

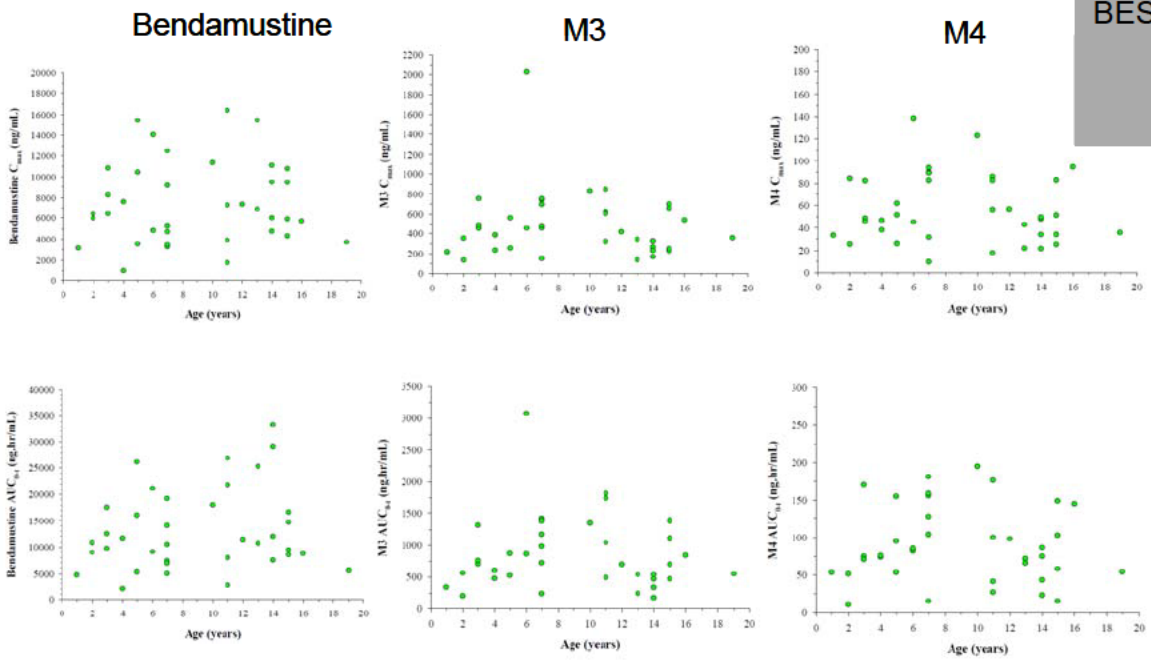
Age

Non-compartmental Analysis

The relationship between patient age and C_{max} and AUC_{0-t} for bendamustine and its 2 active metabolites was examined for the 120-mg/m^2 dose cohort (Figure 1). The results indicated that

there were no consistent age-related differences in systemic exposure to bendamustine, M3 or M4 in these pediatric patients.

Figure 1. Relationship between age and the C_{max} and AUC of bendamustine/M3/M4 in pediatric patients



Population PK

The sponsor conducted separate population pharmacokinetic analyses in pediatric and adult subjects for bendamustine and one of its two active metabolites, M3. The population PK model for adults was developed previously (Study Report CP-07-002) and was previously reviewed by Dr. Qi Liu (See the clinical pharmacology review in DAARTS by Dr. Julie Bullock, 2007). The pediatric model was developed and is provided as part of the current submission (Study Report CP-11-002). Both adult and pediatric analyses include a population PK model for metabolite M3 which has been shown to be equipotent with bendamustine. However, pediatric PK data were inadequate to develop a population PK model for metabolite M4 which is 10-fold less active compared to bendamustine; the majority of the M4 data were below the lower limit of quantification.

The final pediatric population PK model for bendamustine was a 2-compartment open model with zero-order input, first-order elimination, and an inter-individual variability (IIV) term estimated with exponential error structure on central clearance (CL). Residual variability (RV) was expressed as a log error model. All fixed effect model parameters, CL, central volume of distribution (V_c), peripheral volume of distribution (V_p), and inter-compartmental clearance (Q) were scaled to body surface area (BSA). No significant covariates were identified after forward selection and backward elimination. The typical value parameter estimates for bendamustine were: CL (14.2 L/h/m^2), V_c (6.34 L/m^2), V_p (0.132 L/m^2), and Q (0.0626 L/h/m^2). Estimates of half-life for the first and second phases of decline in the concentration-time curve ($t_{1/2\alpha}$, and $t_{1/2\beta}$) for bendamustine were 0.308 hours and 1.47 hours, respectively. The model-predicted median $AUC_{0\text{-}t}$ and C_{max} for bendamustine following administration of 120 mg/m^2 were 7621 ng·h/mL and 6635 ng/mL, respectively. The sponsor's models and methods appear to be acceptable.

Three methods were employed to compare bendamustine and metabolite exposures between pediatrics and adults.

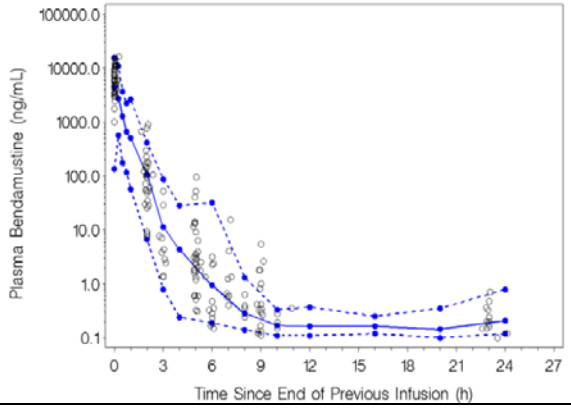
1. The sponsor compared the population PK parameter estimates of CL and V_c between the two populations (Table 3). The sponsor concluded: "The CL and V_c estimates were similar to those of the adult bendamustine and M3 PK models."
2. For bendamustine and metabolites M3 and M4, observed pediatric PK concentration data were plotted with the 2.5, 50, and 97.5 percentiles of the observed concentrations in adults overlaid (Figure 2).
3. The sponsor also provided summary statistics for the model predicted AUC and C_{max} of bendamustine and M3 and the ratio of the values in pediatrics and adults (Table 4).

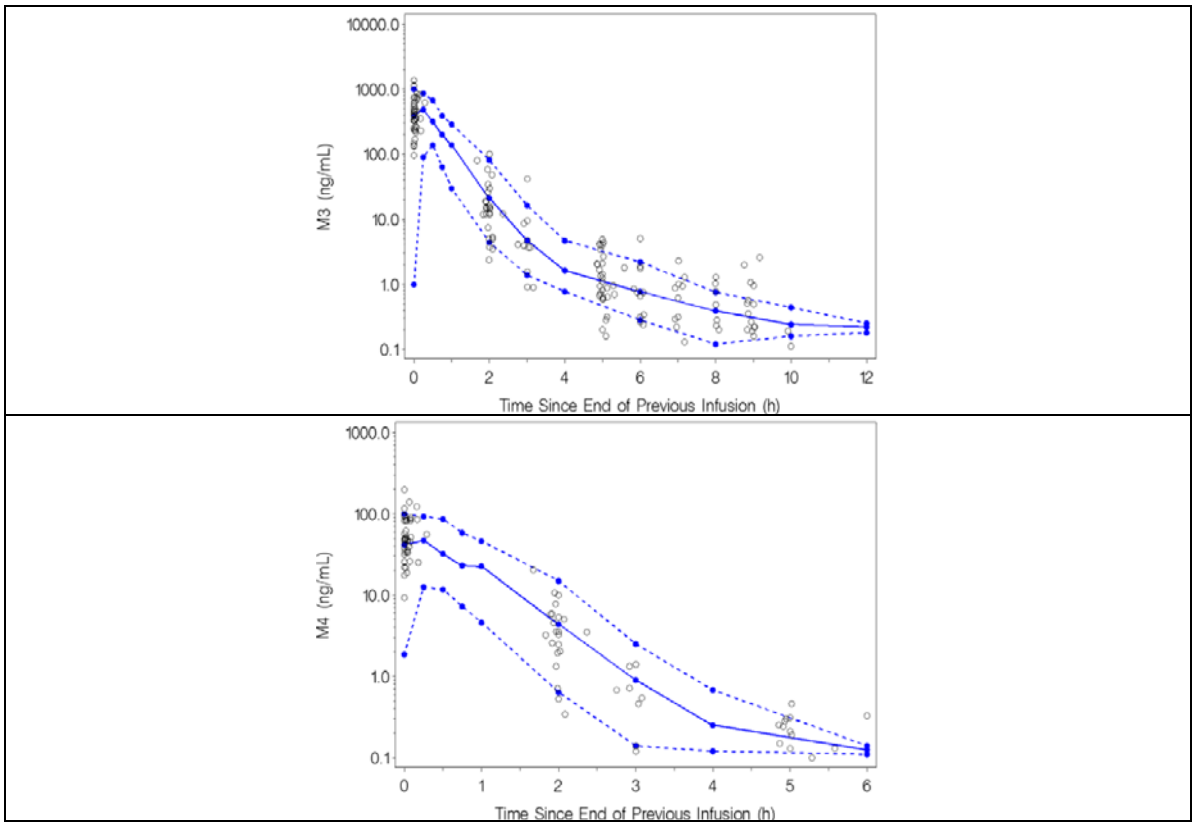
Table 3 Comparison of the population CL and V_c estimates for the pediatric and adult PK models for both bendamustine and M3. To compare CL and V_c values between pediatrics and adults, pediatric CL and V_c values were determined for a person with a BSA of 2.0 m^2, the typical value for the adult population.

	Pediatric Patients	***Adults***
Bendamustine:		
CL (L/hr)	*28.4*	*31.7*
V_c (L)	*12.3*	*14.1*
M3:		
CL (L/hr)	*408*	*347*
V_c (L)	*238*	*209*

(Values are collated from the sponsor's population PK reports no. cp-11-002 and cp-07-002)

Figure 2. Plot of observed pediatric bendamustine (top panel), M3 (middle panel) and M4 (bottom panel) concentration vs. time profiles. The 2.5, 50, and 97.5 percentiles of the observed adult concentrations are indicated by the solid and dashed lines. Pediatric concentration data are shown for both the 90-mg/m^2 and 120-mg/m^2 dose groups.





(Source: Sponsor's Population PK Report No. CP-11-002, Figure 8)

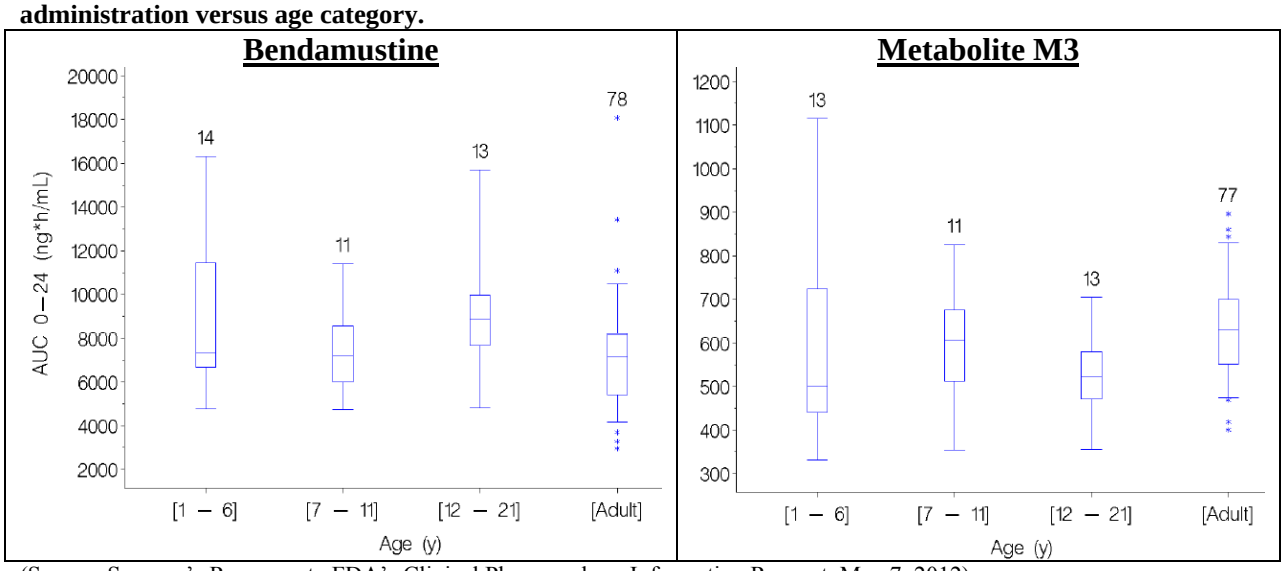
Table 4. Summary Statistics of single-dose bendamustine and M3 body surface area-scaled exposures for the pediatric population and the adult population: 120-mg/m2 dose group.

Exposure	Statistic	Model-predicted adult population study SDX-105-03	Model-predicted pediatric population study C18083/2046 dose = 120 mg/m^2	Model-predicted pediatric:adult ratio
Bendamustine AUC_{0-24}, ng×h/mL	Mean (SD)	7121 (2328.6)	8240 (2782.0)	1.16
	%CV	32.7	33.8	NA
	Median	7142	7621	1.07
	Minimum, Maximum	2959, 18083	4743, 16310	1.60,0.90
	N	78	38	NA
Bendamustine C_{max}, ng/mL	Mean (SD)	5746 (1517.3)	6806 (1534.4)	1.18
	%CV	26.4	22.5	NA
	Median	5701	6635	1.16
	Minimum, Maximum	1539, 10389	4371, 10590	2.84,1.02
	N	78	38	NA
M3 AUC_{0-24}, ng×h/mL	Mean (SD)	633.8 (105.63)	561.5 (163.28)	0.89
	%CV	16.7	29.1	NA
	Median	629.9	523.8	0.83
	Minimum, Maximum	400.5, 896.3	331.8, 1115.0	0.83, 1.24
	N	77	37[b]	NA
M3 C_{max}, ng/mL	Mean (SD)	458.7 (85.76)	425.6 (76.35)	0.93
	%CV	18.7	17.9	NA
	Median	461.8	415.80	0.90
	Minimum, Maximum	136.5, 751.7	296.2, 698.6	2.17, 0.93
	N	77	37[b]	NA

(Source: Sponsor's Study Report Cp-11-002, Table 1)

The exposures of bendamustine and its active metabolite M3 in pediatrics at the 120 mg/m^2 dose were similar to those in adults at the same dose. The cycle 1, day 1 AUC_{0-24} values for both bendamustine are only 16% higher for the pediatric population compared with adults Figure 3, left panel). Whereas, the AUC_{0-24} values for metabolite gamma-OH-bendamustine (M3) are 11% less in pediatric versus adult patients (Figure 3, right panel).

Figure 3. Boxplots of bendamustine and M3 AUC_{0-24} values for single-dose, 120 mg/m^2 administration versus age category.



(Source: Sponsor's Response to FDA's Clinical Pharmacology Information Request, May 7, 2012)

2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess concentrations?

Concentrations of bendamustine, M3 and M4 in human plasma samples were simultaneously determined by [redacted] (b) (4) during November of 2010 through July of 2011 using a validated high-performance liquid chromatography method with tandem mass spectrometric detection (Validation Report DP-2007-031).

Table 5. LC-MS/MS bioassay for Bendamustine, M3, M4 (Report DP-2011-132).

Information Requested	Data
Bioanalytical method validation report location	DP-2007-031
Analytes	Bendamustine, M3, M4
Standard curve concentrations (ng/mL)	Bendamustine: 0.10 to 100.00 ng/mL M3: 0.11 to 106.00 ng/mL M4: 0.10 to 95.00 ng/mL
QC concentrations (ng/mL)	Bendamustine: 0.300, 7.5 and 75 ng/mL M3: 0.318, 7.95 and 79.5 ng/mL M4: 0.285, 7.13 and 71.3 ng/mL
QC intra- and inter-assay accuracy (%)	Bendamustine: 100.8-106.7% M3:100.8-106.9% M4:96.1-98.2%
QC intra- and inter-assay precision (%)	Bendamustine:6.4-15.6% M3:6.5-8.8% M4:5.9-10.7%
Shipment condition	Frozen on dry ice
Storage temperature	-80°C
Number of samples assayed	257
Maximum # of storage days from collection to extraction in this bioanalytical project:	185 days (bendamustine) 212 days (M3 metabolite)* 218 days (M4 metabolite)

Long-term storage stability	At least 233 days at -80°C (bendamustine and M4 metabolite) At least 205 days at -80°C (M3 Metabolite)
Maximum # of freeze/thaw cycles in this bioanalytical project:	4 cycles (bendamustine, M3 metabolite, and M4 metabolite)
Freeze-thaw stability (cycles)	At least 6 cycles at -80°C (bendamustine, M3 metabolite, and M4 metabolite)

* Three samples exceed proven stability: Subject ID332002 3 hr post infusion (5 ng/mL); Subject ID502001 Immediately after infusion (422.83 ng/mL); Subject ID502001 3 hr post infusion (5.66 ng/mL). Those values were within the ranges of other samples' concentration.

3 DETAILED LABELING RECOMMENDATIONS

The sponsor's proposed labeling change is highlighted in yellow. The deletions proposed by the Agency are shown in ~~red strikethrough font~~ and the additions proposed by the Agency are shown in underline blue font.

(b) (4)

[redacted]

In the above mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 and 120 mg/m^2 doses were evaluated in 38 patients aged 1 to 19 years (median age of 10 years). The geometric mean body surface adjusted clearance of bendamustine was 14.2 L/h/m^2. The exposures (AUC_{0-24} and C_{max}) to bendamustine in pediatric patients following a 120-mg/m^2 intravenous infusion over 60-minutes were similar to those in adult patients following the same 120-mg/m^2 dose.

12.3 Pharmacokinetics

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Effect of Age

Bendamustine exposure (as measured by AUC and Cmax) has been studied in adult patients ages 31 through 84 years. The pharmacokinetics of bendamustine (AUC and Cmax) were not significantly different between patients less than or greater than/equal to 65 years of age.

(b) (4)

[redacted]

12.4 Pharmacokinetics/Pharmacodynamics

Based on the pharmacokinetics/pharmacodynamics analyses of data from adult NHL patients, a correlation was observed between nausea and bendamustine Cmax. (b) (4) [redacted]


(b) (4)

4. PHARMACOMETRICS REVIEW

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

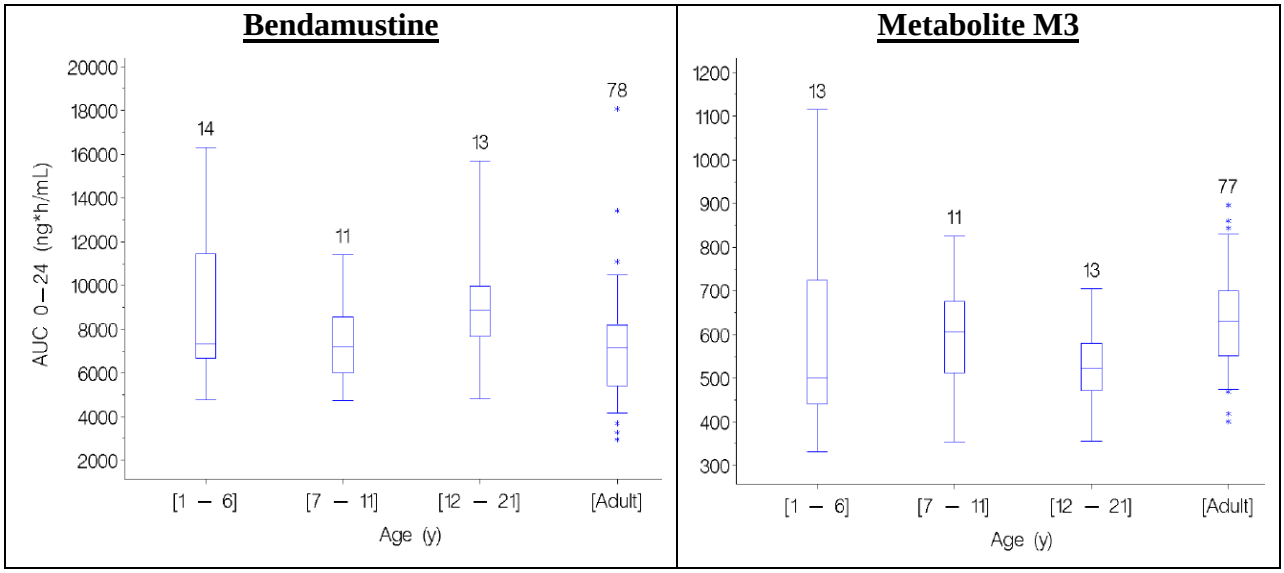
1.1 Key Review Questions

The purpose of this review is to address the following key question.

1.1.1 Are the exposures of bendamustine and its active metabolite M3 in pediatrics at the 120 mg/m^2 dose similar to those in adults at the same dose?

Yes, the cycle 1, day 1 AUC_{0-24} values for both bendamustine are only 16% higher for the pediatric population compared with adults (Figure 1, left panel). Whereas, the AUC_{0-24} values for metabolite gamma-OH-bendamustine (M3) are 11% less in pediatric versus adult patients (Figure 1, right panel).

Figure 1. Boxplots of bendamustine and M3 AUC_{0-24} values for single-dose, 120 mg/m^2 administration versus age category.



(Source: Sponsor's Response to FDA's Clinical Pharmacology Information Request, May 7, 2012)

Additional graphical analyses comparing the exposures (AUC_{0-24} and C_{max} values) between pediatric and adult patients can be found in Section 4.4.2.1.

1.2 Recommendations

Labeling recommendations are made in Section 1.3.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

"8.4 Pediatric Use

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In the above mentioned pediatric trial, the pharmacokinetics of TREANDA at 90 and 120 mg/m^2 doses were evaluated in 38 patients aged 1 to 19 years (median age of 10 years). The geometric mean body surface adjusted clearance of bendamustine was 14.2 L/h/m^2. The exposures (AUC_{0-24} and C_{max}) to bendamustine in pediatric patients following a 120-mg/m^2 intravenous infusion over 60-minutes were similar to those in adult patients following the same 120-mg/m^2 dose.

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(b) (4)

[redacted]

12.4 Pharmacokinetics/Pharmacodynamics

Based on the pharmacokinetics/pharmacodynamics analyses of data from adult NHL patients, a correlation was observed between nausea and bendamustine Cmax. (b) (4)

[redacted]

2 PERTINENT REGULATORY BACKGROUND

Bendamustine was approved in March and October of 2008 for the treatment of Chronic Lymphocytic Leukemia and Non-Hodgkin's Lymphoma, respectively. In January of 2010 the FDA issued a pediatric written request to Cephalon for a pediatric study in patients with relapsed or refractory acute leukemia. In the current submission the sponsor aims to 1) fulfill the requirements of the pediatric written request and 2) update the label with new pediatric related information. The sponsor is not seeking the indication of relapsed or refractory acute leukemia in pediatric patients.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK Analyses

3.1.1 Model Building:

The sponsor conducted separate population pharmacokinetic analyses in pediatric and adult subjects for bendamustine and one of its two active metabolites, M3. The population PK model for adults was developed previously (Study Report CP-07-002) and was previously reviewed by Qi Liu (See the clinical pharmacology review in DAARTS by Dr. Julie Bullock, 2007). The pediatric model was developed and is provided as part of the current submission (Study Report CP-11-002). Both adult and pediatric analyses include a population PK model for metabolite M3 which has been shown to be equipotent with bendamustine. However, pediatric PK data were inadequate to develop a population PK model for metabolite M4 which is 10-fold less active compared to bendamustine; the majority of the M4 data were below the lower limit of quantification.

Final Bendamustine Pediatric Population PK Model:

> "The population pharmacokinetic analysis set included plasma concentration data from 38 pediatric patients at the 120-mg/m^2 dose level and 5 patients at the 90 mg/m^2 dose level. Bendamustine plasma concentrations declined from peak in a triphasic manner. However, the pharmacokinetic sampling scheme did not allow for adequate characterization of the terminal phase. Therefore, the 24-hour samples were excluded from the analysis. The final population PK model for bendamustine was a 2-compartment open model with zero-order input, first-order elimination, and an inter-individual variability (IIV) term estimated with exponential error structure on central clearance (CL). Residual variability (RV) was expressed as a log error model. All fixed effect model parameters, CL, central volume of distribution (V_c), peripheral volume of distribution (V_p), and inter-compartmental clearance (Q) were scaled to body surface area (BSA). No significant covariates were identified after forward selection and backward elimination. The typical value parameter estimates for bendamustine were: CL (14.2 L/h/m^2), Vc (6.34 L/m^2), V_p (0.132 L/m^2), and Q (0.0626 L/h/m^2). Estimates of half-life for the first and second phases of decline in the concentration-time curve ($t_{1/2\alpha}$, and $t_{1/2\beta}$) for bendamustine were 0.308 hours and 1.47 hours, respectively. The model-predicted median AUC_{0-t} and C_{max} for bendamustine following administration of 120 mg/m^2 were 7621 ng h/mL and 6635 ng/mL, respectively."

(Source: Sponsor's Population PK Report No. CP-11-002, Synopsis)

Table 1. Parameter Estimates and Standard Errors from the Bendamustine Final PK Model.

	Final parameter estimate		Magnitude of interindividual variability (%CV)	
Parameter[a,b]	Population mean	%SEM	Final estimate	%SEM
CL (L/h/m^2)	14.2	10.8	31.94	27.7
V_c (L/m^2)	6.34	11.1	NE	NA
V_p (L/m^2)	0.132	23.9	NE	NA
Q (L/h/m^2)	0.0626	30.0	NE	NA
RV (SD): log concentration unit		7.0	NA	NA
Minimum value of the objective function = 125.800				

[a] CL, V_c, V_p, and Q were scaled by BSA. Parameter = coefficient x BSA.
[b] V_p and Q were highly correlated (r^2 = 0.90).

(Source: Sponsor's Population PK Report No. CP-11-002, Table 6)

Metabolite M3 Final Pharmacokinetic Model:

"The PK profile of M3 plasma concentrations declined from peak in a biphasic manner. The final population PK model for M3 was a 2-compartment model with zero-order input set to the rate of bendamustine infusion (representing the rate of M3 formation) and first-order elimination. Interindividual variability terms, described with an exponential error model, were estimated on CL/F and residual variability was expressed with a log error structure. All fixed effect model parameters, CL/F, apparent Q (Q/F), V_c/F, and apparent V_p (V_p/F) were scaled to BSA. Typical value parameter estimates for M3 were CL/F (204 L/h/m^2), Q/F (5.46 L/h/m^2), Vc/F (119 L/m^2), and Vp/F (14.8 L/m^2). These resulted in estimated values of M3 $t_{1/2\alpha}$ and $t_{1/2\beta}$ that were 0.39 hours and 1.94 hours, respectively. The model-predicted median M3 $AUC_{0\text{-}t}$ was 524 ng h/mL and C_{max} was 416 ng/mL, or approximately 1/20th of bendamustine systemic exposure. This represents a significantly lower systemic exposure than the parent compound."

(Source: Sponsor's Population PK Report No. CP-11-002, Synopsis)

Table 2. Parameter Estimates and Standard Errors from the M3 Final PK Model.

	Final parameter estimate		Magnitude of interindividual variability (%CV)	
Parameter[a,b]	Population mean	%SEM	Final estimate	%SEM
CL/F (L/h/m^2)	204	12.0	26.81	19.6
V_c/F (L/m^2)	119	14.2	NE	NA
V_p/F (L/m^2)	14.8	16.7	NE	NA
Q/F (L/h/m^2)	5.46	19.0	NE	NA
RV (SD): log concentration unit	0.462	10.3	NA	NA
Minimum value of the objective function = 125.800				

[a] CL/F, V_c/F V_p/F and Q/F were scaled by BSA. Parameter = coefficient x BSA.
[b] V_p/F and Q/F were highly correlated (r^2 = 0.92) and CL/F and V_c/F were highly correlated (r^2 = 0.87).

(Source: Sponsor's Population PK Report No. CP-11-002, Table 8)

Reviewer's Comments on Bendamustine and M3 Models:

The sponsor's models and methods are acceptable. See the reviewer's analysis for further comments on goodness-of-fit and covariate analyses.

3.1.2 Exposure Comparison Between Pediatrics and Adults:

Three methods were employed to compare bendamustine and metabolite exposures between pediatrics and adults.

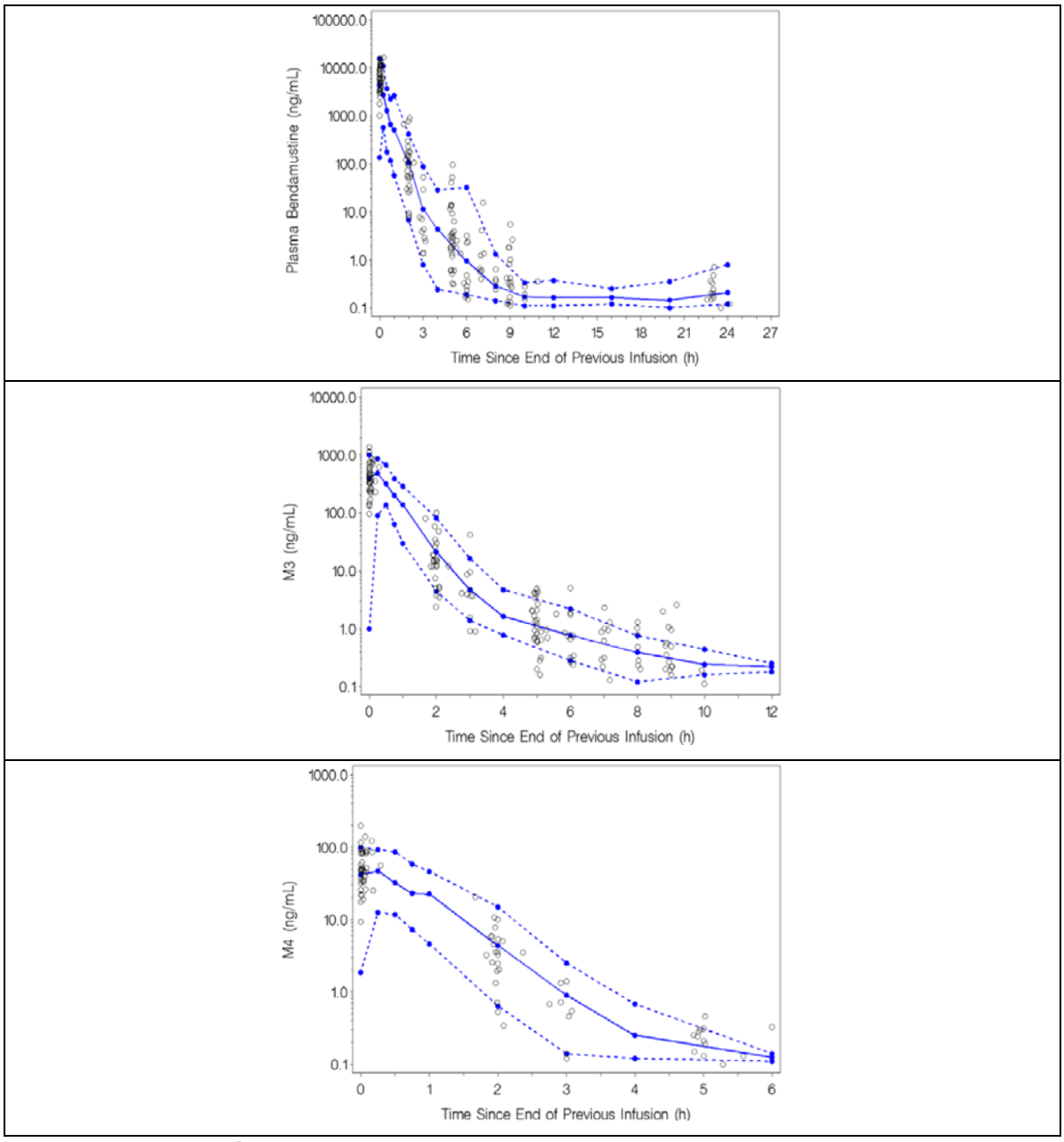
1. The sponsor compared the population PK parameter estimates of CL and V_c between the two populations (Table 3). The sponsor concluded: "The CL and V_c estimates were similar to those of the adult bendamustine and M3 PK models."
2. For bendamustine and metabolites M3 and M4, observed pediatric PK concentration data were plotted with the 2.5, 50, and 97.5 percentiles of the observed concentrations in adults overlaid (Figure 2).
3. The sponsor also provided summary statistics for the model predicted AUC and C_{max} of bendamustine and M3 and the ratio of the values in pediatrics and adults (Table 4).

Table 3. Comparison of the population CL and V_c estimates for the pediatric and adult PK models for both bendamustine and M3. To compare CL and V_c values between pediatrics and adults, pediatric CL and Vc values were determined for a person with a BSA of 2.0 m^2, the typical value for the adult population.

	Pediatric Patients	***Adults***
Bendamustine:		
CL (L/hr)	*28.4*	*31.7*
V_c (L)	*12.3*	*14.1*
M3:		
CL (L/hr)	*408*	*347*
V_c (L)	*238*	*209*

(Values are collated from the sponsor's population PK reports no. cp-11-002 and cp-07-002)

Figure 2. Plot of observed pediatric bendamustine (top panel), M3 (middle panel) and M4 (bottom panel) concentration vs. time profiles. The 2.5, 50, and 97.5 percentiles of the observed adult concentrations are indicated by the solid and dashed lines. Pediatric concentration data are shown for both the 90-mg/m^2 and 120-mg/m^2 dose groups.



(Source: Sponsor's Population PK Report No. CP-11-002, Figures 8)

Table 4. Summary Statistics of single-dose bendamustine and M3 body surface area-scaled exposures for the pediatric population and the adult population: 120-mg/m2 dose group.

Exposure	Statistic	Model-predicted adult population study SDX-105-03	Model-predicted pediatric population study C18083/2046 dose = 120 mg/m^2	Model-predicted pediatric:adult ratio
Bendamustine AUC_{0-24}, ng×h/mL	Mean (SD)	7121 (2328.6)	8240 (2782.0)	1.16
	%CV	32.7	33.8	NA
	Median	7142	7621	1.07
	Minimum, Maximum	2959, 18083	4743, 16310	1.60,0.90
	N	78	38	NA
Bendamustine C_{max}, ng/mL	Mean (SD)	5746 (1517.3)	6806 (1534.4)	1.18
	%CV	26.4	22.5	NA
	Median	5701	6635	1.16
	Minimum, Maximum	1539, 10389	4371, 10590	2.84,1.02
	N	78	38	NA
M3 AUC_{0-24}, ng×h/mL	Mean (SD)	633.8 (105.63)	561.5 (163.28)	0.89
	%CV	16.7	29.1	NA
	Median	629.9	523.8	0.83
	Minimum, Maximum	400.5, 896.3	331.8, 1115.0	0.83, 1.24
	N	77	37[b]	NA
M3 C_{max}, ng/mL	Mean (SD)	458.7 (85.76)	425.6 (76.35)	0.93
	%CV	18.7	17.9	NA
	Median	461.8	415.80	0.90
	Minimum, Maximum	136.5, 751.7	296.2, 698.6	2.17, 0.93
	N	77	37[b]	NA

(Source: Sponsor's Study Report Cp-11-002, Table 1)

Reviewer's Comments:

The sponsor's method is reasonable and shows that the bendamustine's exposure in pediatric patients is 16 percent higher than those in adults, based on the population PK model estimates for AUC_{0-24} and C_{max}.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The reviewer's analysis aims to compare the pediatric bendamustine and metabolite exposures (AUC and Cmax) to those values in adults. The estimates of exposure in pediatrics and adults were determined from the sponsors separate pediatric and adult population PK models. Therefore the pediatric model is reviewed to assess the reliability of the individual estimates of bendamustine and metabolite exposure. The sponsor's adult model was reviewed previously by Qi Liu (See the clinical pharmacology review in DAARTS by Dr. Julie Bullock, 2007).

4.2 Objectives

Analysis objectives are:

1. Evaluate the validity of the sponsor's population PK model with regards to model structure and covariates.
2. Employ additional graphical analyses to compare pediatric and adult bendamustine and metabolite exposures.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR
CP-11-002	refine-bsap1-1eta-logrv-01_ctl.txt	\\cdsesub1\EVSPROD\NDA022249\0040\m5\datasets\cp-11-002\analysis
CP-11-002, CP-11-007	allparm.xpt	\\cdsesub1\EVSPROD\NDA022249\0054\m5\datasets\response-to-request-pediatrics\analysis

4.3.2 Software

NONMEM VI (b) (4) was used to review the sponsor's Population pharmacokinetic analysis. The statistical software R (www.r-project.org) and S-plus (b) (4) were used to generate all plots.

4.3.3 Models

No original model building was conducted for this review.

4.4 Results

4.4.1 Population PK Modeling

The sponsor's population PK model was reviewed to determine if the structural and covariate models for both bendamustine and metabolite M3 were appropriate. The sponsor's final models were run on their datasets. Goodness-of-fit plots were generated to assess the structural models.

Plots of between-subject variability versus covariates were used to determine if certain covariate effects should be included in the model.

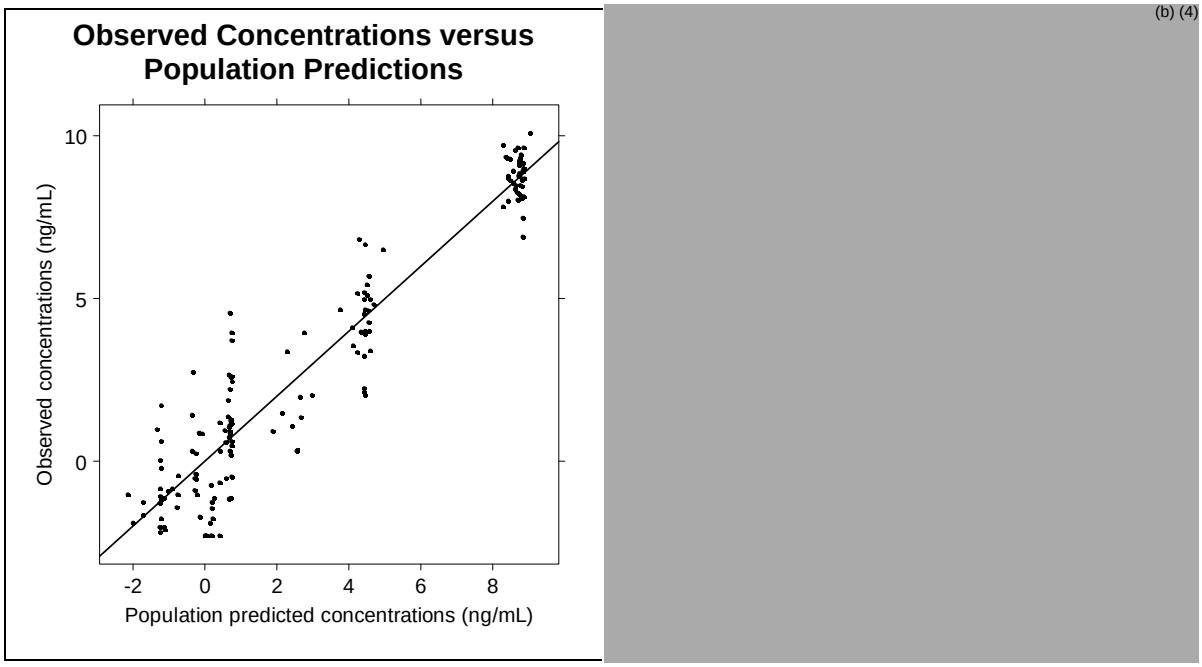
4.4.1.1 Bendamustine

The goodness of fit plots in Figure 3 indicate the sponsor's final PK model reasonably describes the bendamustine data. Shrinkage of the inter-individual variability of CL, in the final model, is 5.3%.

Since dosing was based on body surface area (BSA), BSA was included as a covariate on all CL and V parameters in the base structural model. Figure 4 showed that age, weight, BMI, or Glomular Filtration Rate (GFR) did not meaningfully alter the clearance of bendamustine, after accounting for the effect of BSA.

Figure 5 shows that the most of categorical variables did not impact the CL of bendamustine. However, there appears to be a numerical difference for gender. In general the effect of gender on clearance is often attributed to BW differences, which should be accounted for by BSA. The numerical difference here may be an artifact of model misspecification for the effect of BSA on volume of distribution. Because inter-individual variation in volume of distribution was not estimated, residual effect could be reflected in the eta plots for clearance.

Figure 3. FDA-generated, goodness-of-fit plots for the sponsor's final bendamustine population PK model.



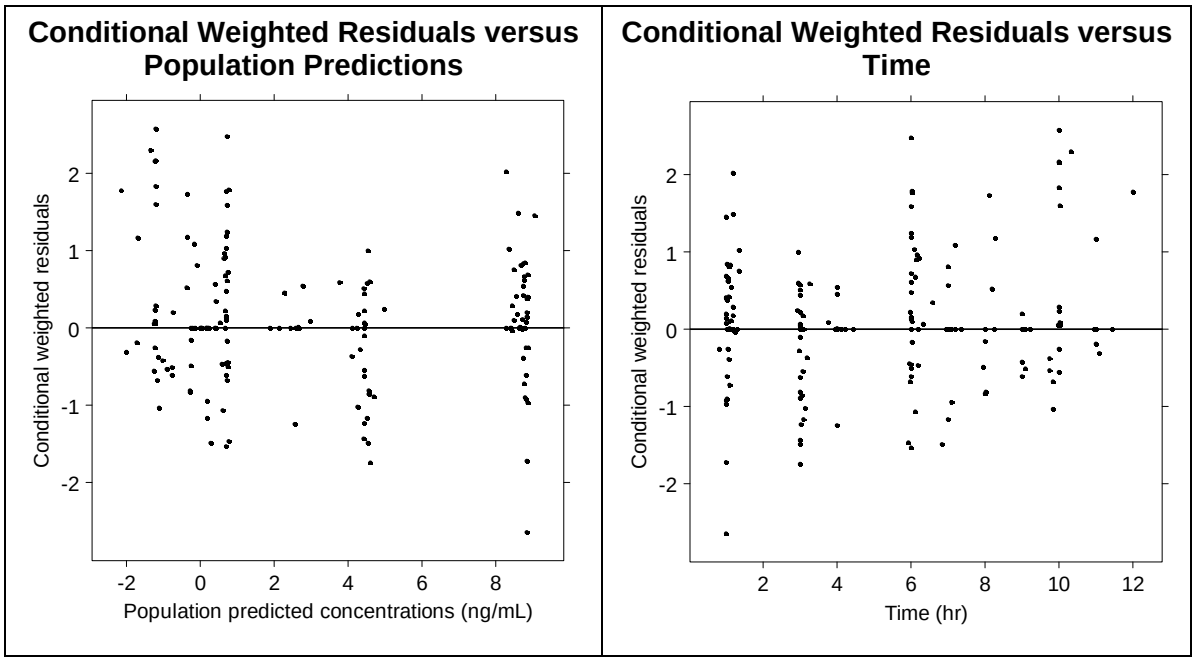
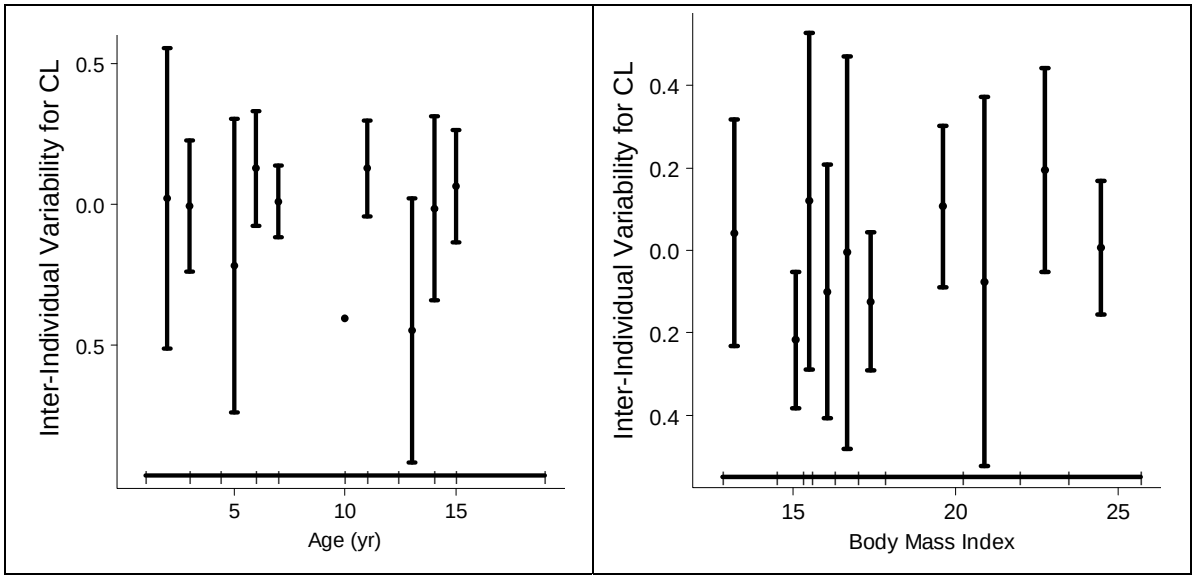


Figure 4. Plots of inter-subject variability for bendamustine CL against potential continuous covariates.



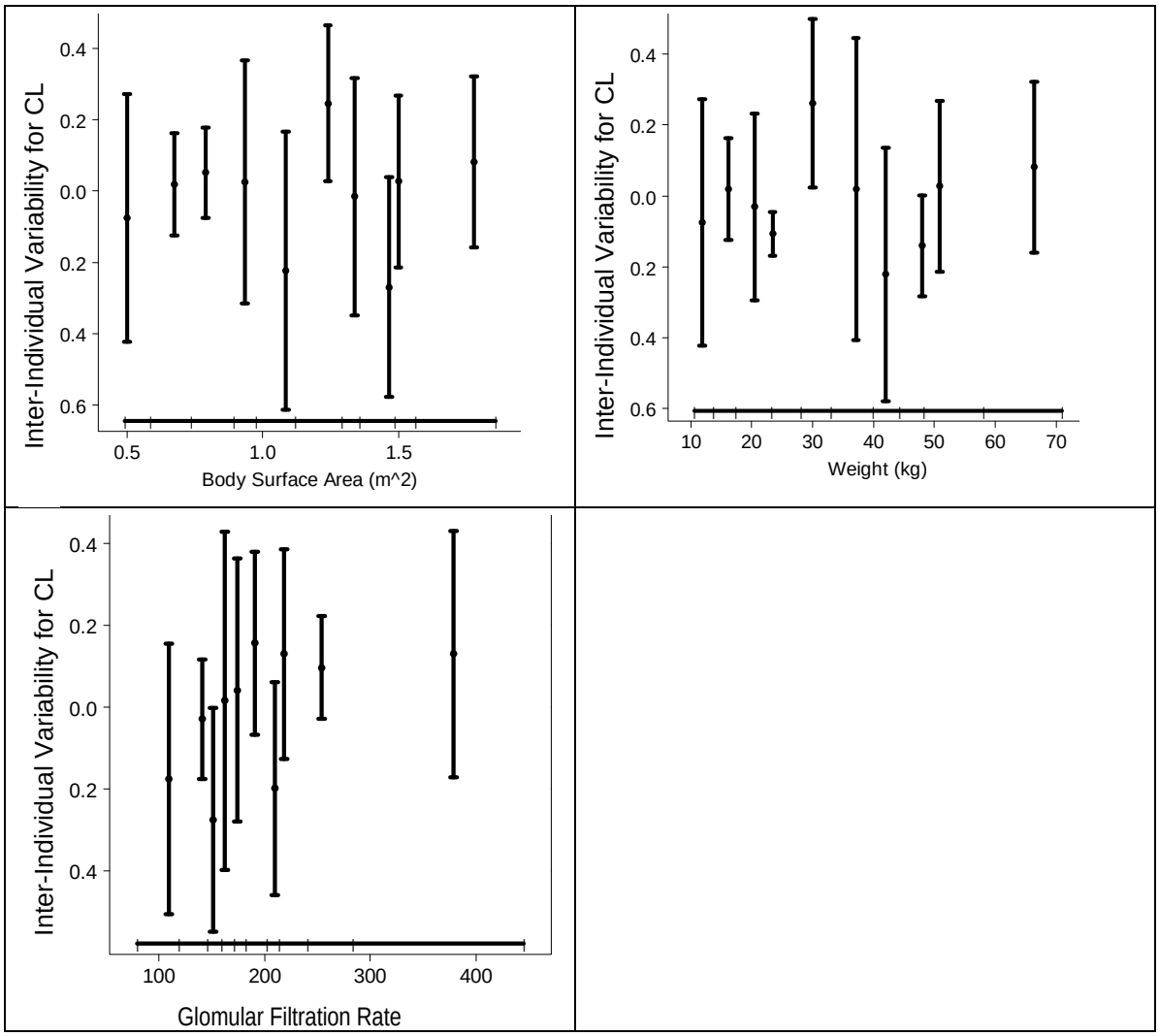
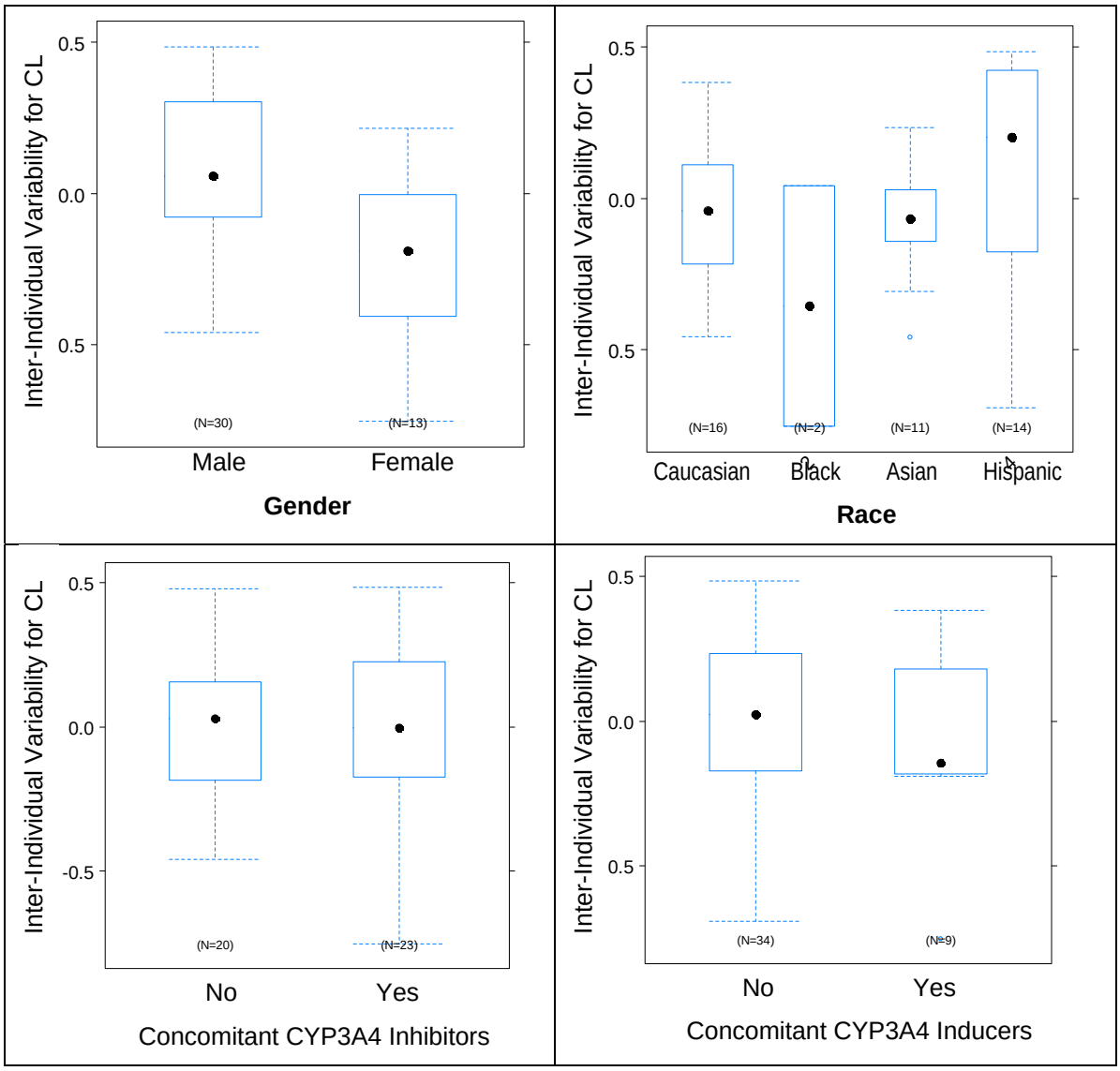

Inter-Individual Variability for CL
0.4
0.2
0.0
0.2
0.4
0.6
0.5
1.0
1.5
Body Surface Area (m^2)
Inter-Individual Variability for CL
0.4
0.2
0.0
0.2
0.4
0.6
10
20
30
40
50
60
70
Weight (kg)
Inter-Individual Variability for CL
0.4
0.2
0.0
0.2
0.4
100
200
300
400
Glomular Filtration Rate

Figure 5. Plots of inter-subject variability for bendamustine CL against potential continuous covariates.



4.4.1.2 Metabolite M3

The goodness of fit plots in Figure 6 indicate the sponsor's final PK model reasonably describes the M3 data.

BSA was also included as a covariate on all CL and V parameters in the base M3 structural model. Figure 7 showed that age, weight, BMI, or GFR did not meaningful alter the apparent clearance of M3, after accounting for the effect of BSA.

Figure 8 showed that the categorical covariates gender, race, concomitant CYP inhibitors (CINH=1), and concomitant CYP inducers (CIND=1) did not influence the PK of M3.

Figure 6. FDA-generated, goodness-of-fit plots for the sponsor's final M3 population PK model.

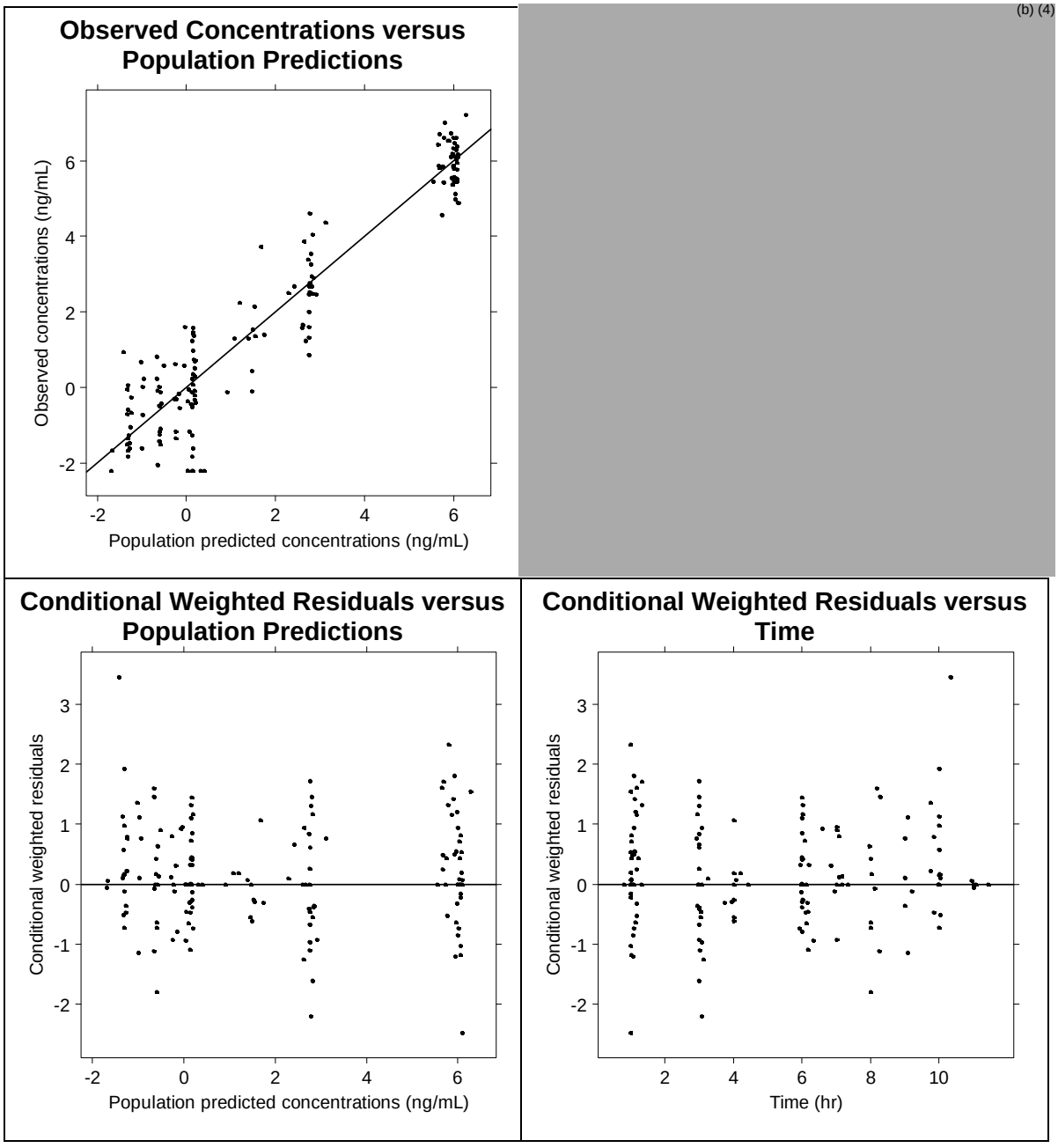
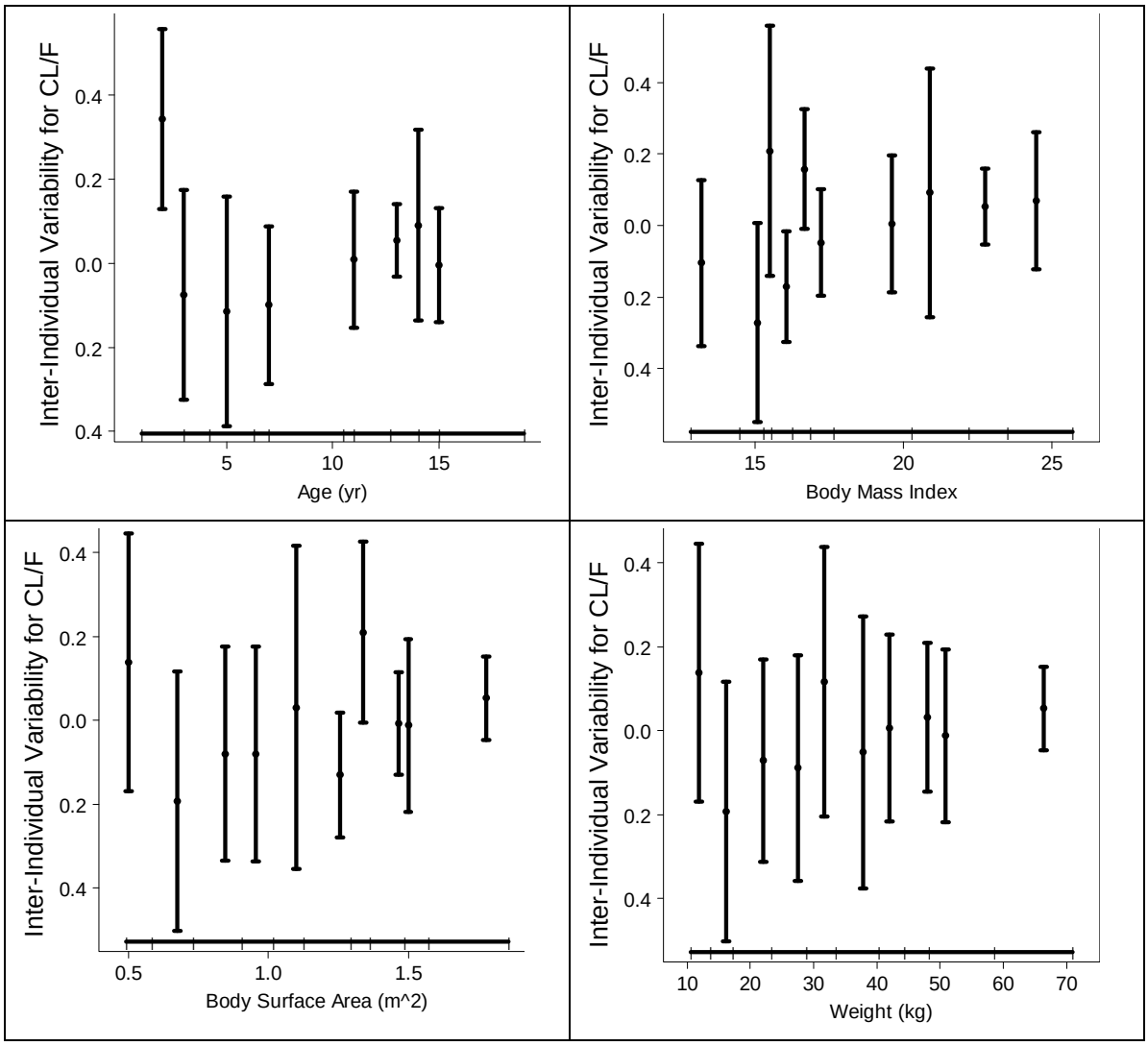


Figure 7. Plots of inter-subject variability for M3 apparent clearance (CL/F) against potential continuous covariates.


Inter-Individual Variability for CL/F
0.4
0.2
0.0
0.2
0.4
5
10
15
Age (yr)
Inter-Individual Variability for CL/F
0.4
0.2
0.0
0.2
0.4
15
20
25
Body Mass Index
Inter-Individual Variability for CL/F
0.4
0.2
0.0
0.2
0.4
0.5
1.0
1.5
Body Surface Area (m^2)
Inter-Individual Variability for CL/F
0.4
0.2
0.0
0.2
0.4
10
20
30
40
50
60
70
Weight (kg)

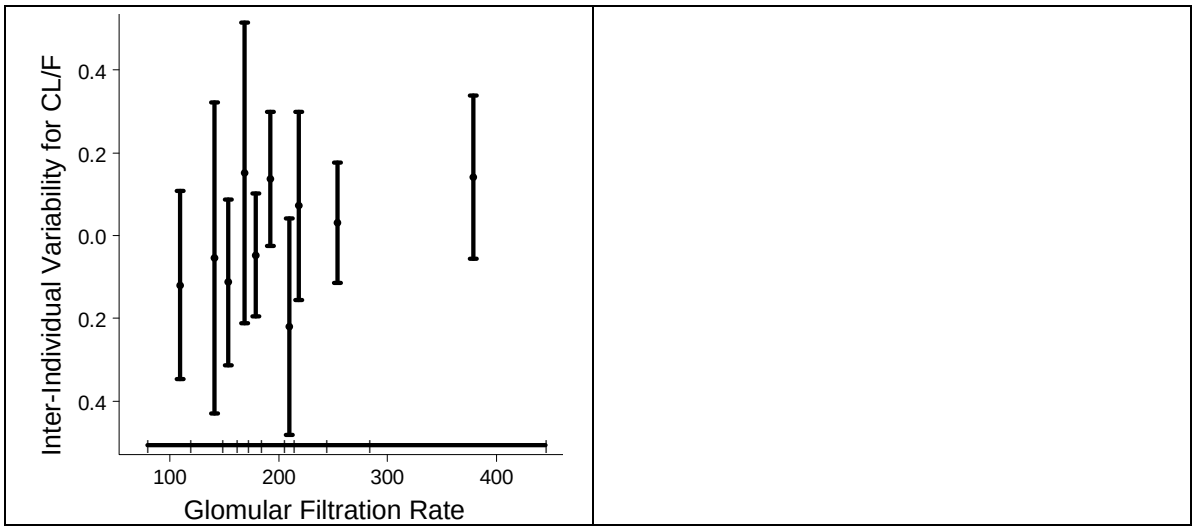
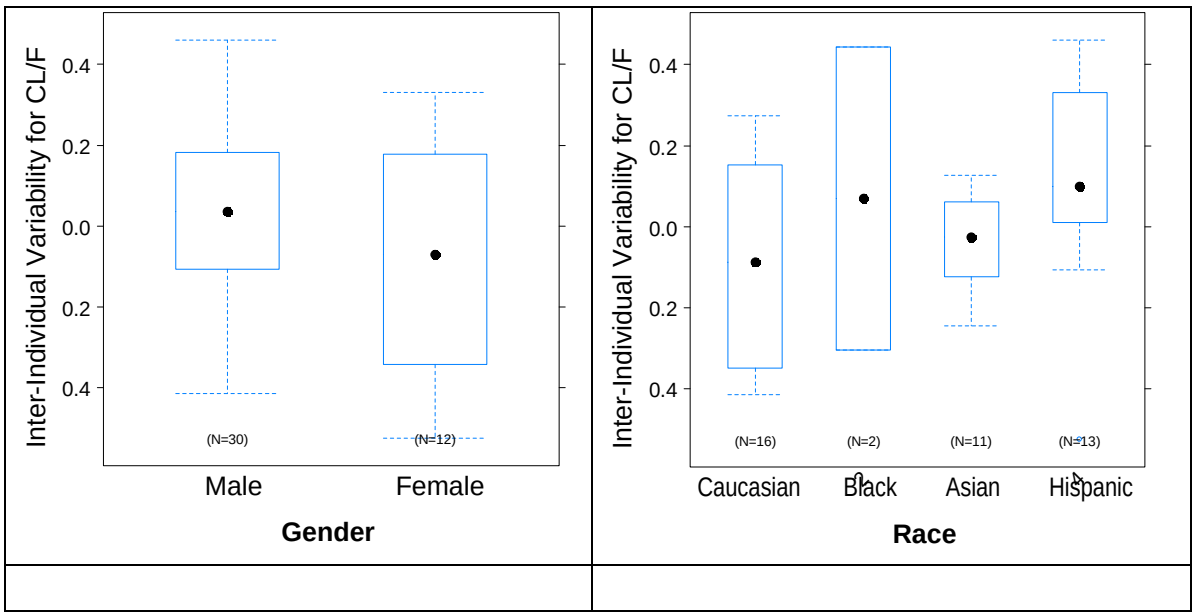
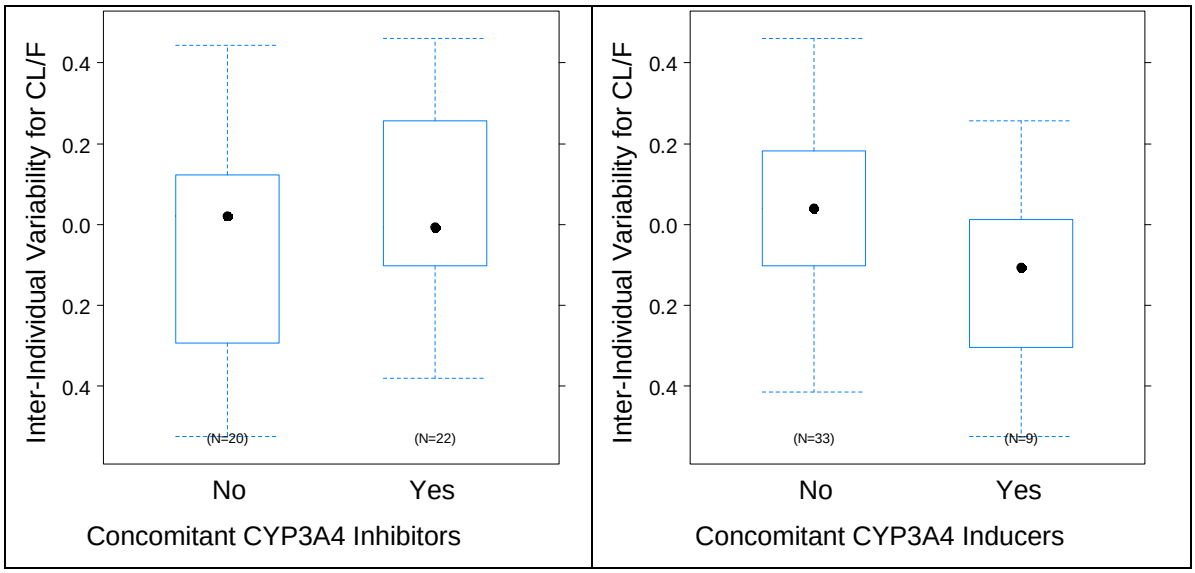


Figure 8. Plots of inter-subject variability for M3 apparent clearance (CL/F) against potential continuous covariates.





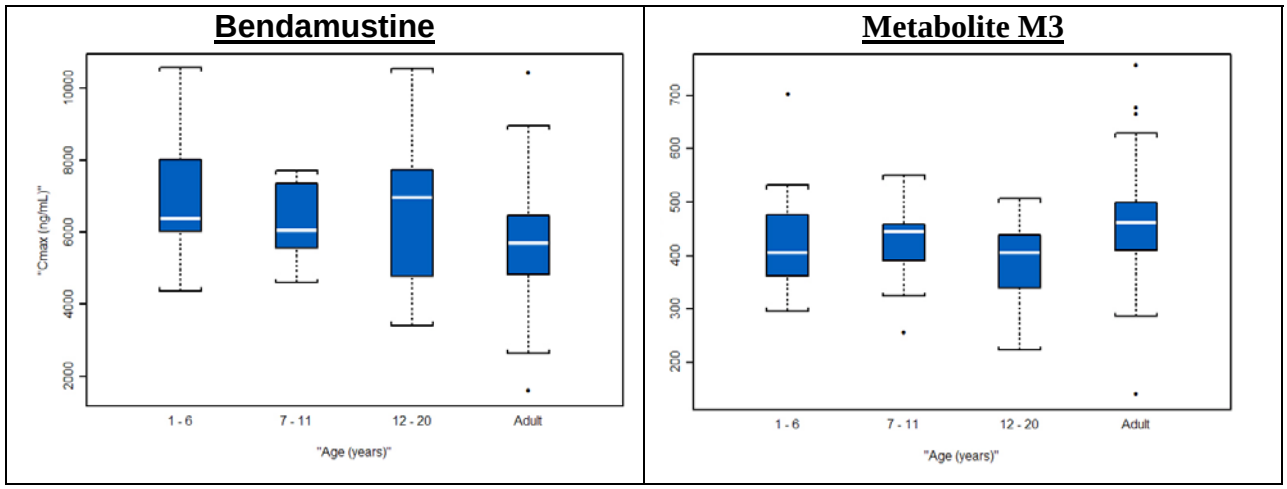
4.4.2 Additional Pharmacokinetic Exposure Comparisons

Graphical analyses using the model predicted AUC_{0-24} and C_{max} values for each individual were conducted to compare pediatric exposures with adult exposures. Bendamustine and M3 exposures by age group were examined to determine if the 120 mg/m^2 dosing in pediatrics produced comparable exposures to those in adults after the same BSA-based dose (Section 4.4.2.1). Bendamustine and M3 exposures were also plotted against BSA to determine if the BSA-based dosing regimen produced consistent exposures across the range of BSA values (Section 4.4.2.2).

4.4.2.1 Exposures by Age Group

Population PK estimates for C_{max} followed a similar pattern to the AUC_{0-24} values (Figure 1). This is due to the fact that inter-individual variability estimates were only obtained for bendamustine and M3 CL, but not volume of distribution. Thus, there was a strong correlation between AUC_{0-24} and C_{max} in the sponsor's population PK model.

Figure 9. The predicted C_{max} values for Cycle 1 are similar between pediatric and adult patients.



4.4.2.2 Exposures by Body Surface Area

Bendamustine dosing is based on BSA. Thus, the amount of bendamustine administered depended on the subjects BSA. If the dosing regimen is appropriate, then there should be consistent exposures across all body surface areas. Figure 10 and Figure 11 indicate:

- AUC_{0-24} and C_{max} values based on the population PK model are consistent across the range of BSA values studied.
- Exposures are similar between pediatrics and adults at the studied BSA-based doses.

Figure 10. AUC_{0-24} values are consistent across the range of BSA values. The mean adult exposure is plotted as the dashed black line. The blue line is a Loess fitting of the pediatric exposures across BSA values.

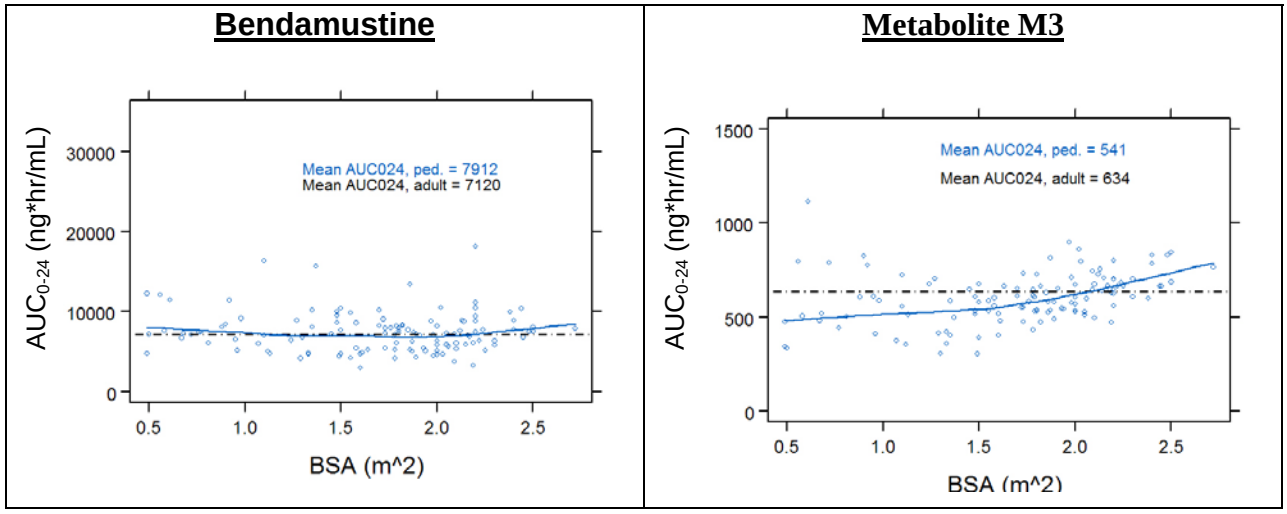
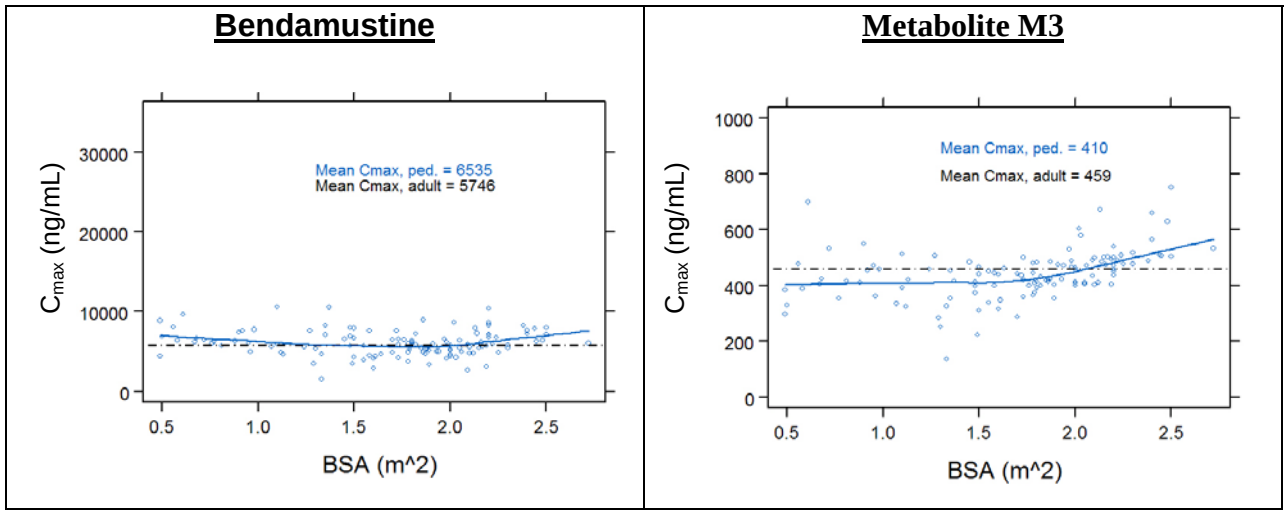


Figure 11. C_{max} values are consistent across the range of BSA values. The mean adult exposure is plotted as the dashed black line. The blue line is a Loess fitting of the pediatric exposures across BSA values.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
BendamustineRun1.R	R-code to generate diagnostic and covariate plots	\\Cdsnas\pharmacometrics\Reviews\PM Review Archive\2012\BendamustineHCL_NDA22249_JCE\PK Analyses
PKReqCheck.SSC	S-plus script for graphical analyses to compare pediatric and adult exposure parameters	\\Cdsnas\pharmacometrics\Reviews\PM Review Archive\2012\BendamustineHCL_NDA22249_JCE\PK Analyses

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