CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-954/S-004

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

sNDA 20-954

Drug:	BUSULFEX
Generic Name:	Busulfan; 1,4-butanediol dimethanesulfonate
Formulation:	60 mg (6 mg/ml) clear solution for dilution in 0.9% sodium chloride, USP or 5% dextrose, USP for intravenous injection.
Indication:	BUSULFEX is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.
Applicant:	Orphan Medical, Inc.
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	12/21/01; 01/11/02
Primary/Pharmacometric Reviewer:	Brian Booth, Ph.D.
Pharmacometric Team Leader:	Joga Gobburu, Ph.D.
Team Leader:	N.A.M. Atiqur Rahman Ph.D.
Type of Submission:	Supplemental NDA (category SE2 P)

I. Executive Summary

The applicant submitted the supplemental NDA 20-954, BUSULFEX to provide dosing instructions for pediatric patients who require BUSULFEX treatment for bone marrow ablation prior to hematopoietic progenitor cell transplantation. The applicant proposed a four-step dosing nomogram based on actual body weight of pediatric patients.

A. Overall Recommendations

The clinical pharmacology and biopharmaceutics information submitted in the sNDA for BUSULFEX is acceptable from the perspective of the Office of Clinical Pharmacology and

Biopharmaceutics. The key issue is the appropriateness of the proposed pediatric dosing regimen for BUSULFEX. Based on retrospective population pharmacokinetic modeling, the applicant proposed a

Therapeutic drug monitoring for BUSULFEX is also recommended and a dose adjustment nomogram is proposed by the FDA. The applicant should incorporate the labeling changes made by the FDA and address the comments regarding the analytical method validation if future studies of Busulfex are submitted to the NDA.

B. Comments

1. The analytical method was validated prior to the publication of the FDA Guidance for Industry entitled "Bioanalytical Method Validation". However, the analytical method for busulfan should be updated if future studies are submitted to the NDA. Specifically, the following issues should be addressed
    - Provide standard curves containing no less than six calibrators that span the dynamic range to be assayed, from the lower limit of quantification (LLOQ) to the upper limit of quantification (ULOQ). Only study samples that are bracketed by the standard curve can be reported. Samples higher than the ULOQ must be diluted with like-matrix and re-assayed. Samples below the LLOQ must be reported as "below quantification limits (BQL). Extrapolation of concentrations beyond the limits of the assay are not permissible.
    - Provide data quantifying the intra- and inter-occasion accuracy of the assay. Include the nominal amounts of drug used.
    - Provide the nominal amounts of drug used for studies of precision.
    - Provide concentration data and nominal amounts of drug used to support long-term stability studies in place of dates of use.

Briefing Date: Friday May 3, 2002.

/S/

Reviewer: Brian Booth, Ph.D.

/S/

Team Leader: NAM Atiqur Rahman, Ph.D.

CC: NDA 21-386
HFD-150/Division File
HFD-150/SpillmanD, Bradley S, DagherR, Griebel D
HFD-860/MehtaM, MarroumP, RahmanNAM, BoothB
HFD-880/ LazorJ, SelenA
CDR/Biopharm

II. Table of Contents

III. List of Abbreviations

ABW: actual body weight
Ae: Amount of drug excreted in the urine
$Ae_{0\text{-}24h}$: Amount of drug excreted in the urine up to 24 hours.
AUC: Area under the concentration vs. time curve
$AUC_{0\text{-}\tau}$: Area under the concentration vs. time curve of the dosing interval

BUS: Busulfex; busulfan
C_{end}: Peak plasma concentration of the drug at the end of the infusion
C_{max}: Peak plasma concentration of the drug
CL: Clearance
CY: cyclophosphamide
CYP450: Cytochrome P-450
HVOD: veno-occlusive disease
Hr, hrs: hours
L: Liter
LOD: lower limit of detection
LOQ: lower limit of quantification
M^2: meter, squared
Min: minutes
ml, mL: milliliter
N: Normal
NDA: New Drug Application
Ng/ml: nanograms per milliliter
Kg, kg: kilograms
PD: pharmacodynamics
PK: pharmacokinetics
PPK: population pharmacokinetics
$T_{1/2}$, $t_{1/2}$: Half-life
USP: United States Pharmacopeia
V: Volume of distribution
VOD: veno-occlusive disease
µg/L: micrograms per liter

IV. Summary of the Clinical Pharmacology Findings

BUSULFEX (BUS) is a bi-functional alkylating agent that is approved for use in combination with cyclophosphamide in adults for bone marrow ablation prior to allogeneic stem cell transplantation for chronic myelogenous leukemia. The adult dosage of BUSULFEX is 0.8 mg/kg. Hepatic veno-occlusive disease is associated with BUS AUCs of 1300 to 1500 μM•min, and failure of bone marrow ablation is associated with BUS AUC's of less than 900 μM•min. Hematopoietic progenitor cell transplantation is used to treat a variety of hematological malignancies in children, and BUSULFEX has been used off-label in this patient population for this purpose. The clearance of BUS in children 4 years or younger is reported in the scientific literature to be significantly higher than in adults. In order to provide rational pediatric dosing instructions in the BUSULFEX labeling, the applicant conducted a pediatric pharmacokinetic study in children aged 0.4 to 16.7 years who required bone marrow ablation prior to transplantation for a variety of diseases. The patients were sampled densely during two periods, and additional trough samples were also obtained. The applicant performed a retrospective population pharmacokinetic (PPK) analysis to describe the PK characteristics of BUS in children. The PPK model was then used to develop a four-step dosing regimen with different weight cut-offs fore each step. However, the proposed dosing nomogram is cumbersome and prone to error, and the PPK modeling and simulation from which it was derived contained several shortcomings that limit its reliability. FDA conducted an independent analysis and developed two simpler dosing regimens that performed equivalently from the pharmacokinetic perspective. The first dosing regimen is a two-step regimen that is based on actual body weight (1.1 mg/kg if <=12kg; 0.8 mg if > 12 kg). The second [redacted]. This latter regimen is recommended because it is the simplest and therefore the regimen that is least prone to dosing errors. The FDA modeling and simulations indicated that only 60% of patients will achieve a target AUC of 900 to 1350 μM•min with the first dose of BUS. Therefore, therapeutic drug monitoring after the first dose of BUS is recommended and FDA devised a Dose Adjustment nomogram to correct subsequent doses of BUS to achieve the target BUS exposure.

V. Question Based Review of BUSULFEX

A. Background

BUSULFEX is a an intravenous formulation of busulfan. Busulfan is a bi-functional alkylating agent. The structure of buslfan is shown in Figure 1 below.

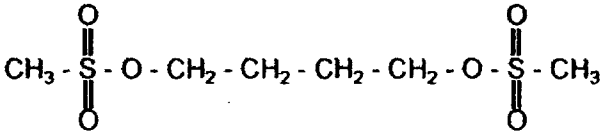

Figure 1. The structure of busulfan, M.W. 246.1

Hydrolysis leads to the release of two reactive carbonium ions that alkylate DNA. The DNA damage is believed to be the main source of cytotoxic action of busulfan.

Currently, BUSULFEX is approved for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hemaotpoietic progenitor cell transplantation for chronic myelogenous leukemia in adults. The dosing regimen in adults consists of 16 doses of BUSULFEX administered every six hours as an intravenous infusion over two hours. Dosing is based on **0.8 mg/kg** using actual or ideal body weight (kg). Cyclophosphamide (CY) is administered on two consecutive days as a 60 mg/kg infusion over one hour. Cyclophosphamide should not begin sooner than 6 hours after the last dose of BUSULFEX.

The pharmacokinetics of BUSULFEX (busulfan; BUS) are described as a one-compartment model with first order elimination. The mean clearance of BUS in adults was 2.52 ± 25% ml/min/kg (0.506 L/hr/kg) with a terminal elimination half-life of 3.17 hrs. Protein binding is between 10 and 35%, and BUS is predominantly metabolized by gluthathione-S-transferase. Thirty per cent of radiolabeled BUS was recovered in urine 48 hrs after administration to adults. The amount of intact drug excreted in the urine is unknown. For greater detail on the disposition of BUS, refer to the Clinical Pharmacology and Biopharmaceuitcs review of the original BUSULFEX application (NDA 20-954).

The toxicities associated with BUS are hepatic veno-occlusive disease (HVOD;VOD) and seizures. The latter are usually dealt prophylactically with anti-seizure medication. HVOD has been associated with BUS exposures of 1300 to 1500 μM-min. Conversely, successful bone marrow ablation and engraftment is associated with BUS exposures greater than or equal to 900 μM-min. Therefore, the target BUS exposure in adults is an AUC below 1500 μM-min and above 900 μM-min (although the latter "lower limit" is not specifically stated in the product labeling).

Several reports in the literature indicate that BUS/CY is currently used clinically in an off-label manner as a preparative regimen for stem cell transplantation for a variety of hematological malignancies. Oral busulfan (Myleran; Roche) was used prior to the availability of BUS, but the 2-mg tablets necessitated the administration of 30-40 tablets in adults (and comparable quantities

in children, scaled to weight). This therapy was marred by nausea, vomiting and inconsistent delivery of the therapeutic dose of BUS. Based on these reasons, FDA issued a Written Request to Orphan Medical in 1999 to submit pediatric pharmacokinetic studies of BUSLFEX in order to provide rational dosing instructions for pediatric patients in the product labeling. Based on reports in the scientific literature that the CL of BUS is greater in children under 4 years of age than adults, the applicant performed the pediatric pharmacokinetic study on 24 patients, in which 14 of the patients were 4 years or younger. BUS dosing targeted the mean value of the 900-1350 μM-min range (1125 μM-min).

B. Pediatric Population Pharmacokinetic (PPK) Study

1. Was a PK-PD relationship for Busulfex determined in the pediatric study?

Several reports in the scientific literature indicate that a target range of Busulfex exists for safe and effective bone marrow ablation prior to hematopoietic transplantation. Hepatic veno-occlusive disease is associated with BUS exposures greater than 1350 to 1500 μM•min. Unsuccessful ablation or engraftment has been associated with BUS exposures of less than 900 μM•min. Therefore, 900-1350 μM-min is the therapeutic window for BUS.

In the current study, the PK-PD relationship could not be determined for either safety or efficacy because there was insufficient change in the exposure of BUS; all of the pediatric patients possessed similar AUCs after BUS administration (± 25 % after the first dose; ± 16% after dose 9). Secondly, there were too few patients to address safety (n=24).

The clinical databases did reveal that in 100% of the patients, bone marrow was successfully ablated and each was successfully engrafted with new cells. The AUCs after doses 1 and 9 were 1012.3 μM•min and 1157.3 μM•min, respectively (4152 and 4747 μg•hr/L, respectively), which is well within the BUS exposure target range.

Of the 24 patients studied, four were diagnosed with VOD (a fifth patient was deemed as having HVOD by FDA). Therefore, 17 to 21% of the patients developed VOD which is apparently less than the VOD rate that is generally experienced (20-70%). Of the five patients with VOD, four had BUS exposures greater than 1350 μM•min (5537 μg•hr/L).

2. What is the best dosing regimen for pediatric patients?

Applicant Dosing Nomogram

The applicant proposed the following BUS dosing nomogram for pediatric patients

Table 1. Applicant's Proposed BUSULFEX Dosing Nomogram

[ ]

This nomogram was based on a one-compartment log-linear population PK model with zero order infusion and first order elimination. The population CL and V of BUS are described as

CL =

V=

The applicant chose this model to describe the PPK of BUS in pediatric patients based on the lowest NONMEM minimum objective function and diagnostic plots such as predicted versus observed concentrations, and CL versus log of actual body weight (ABW) (refer to Pharmacometrics review).

The applicant then conducted simulations of BUS dosing with the log-linear PPK model in comparison to fixed dosing regimens (either 0.8 or 1.0 mg/kg; and 0.8 mg/kg for children < 4 yrs, 1.0 mg/kg for children > 4 yrs) to determine the number of patients that achieved the target BUS exposure (1125 μM-min) with the first dose. Apparently using the 24 pediatric patients in the database, the applicant used the post-hoc estimates of CL in the simulations and determined that the log-linear model, and the dosing nomogram derived from the log-linear model, each achieved a greater percentage of patients within the target range (900-1350 μM•min) (79 and 67 %, respectively).

Therefore, the applicant used the log-linear model to determine the dose per each patient. The dose was then plotted against weight, and the weight ranges were visually segmented (see Figure 2 below; Pharmacometrics review).

Figure 2. Relationship between dose and weight based on Applicant's log-linear model. The segmented areas indicate dosage steps.

These dose-steps were then incorporated into the dosing nomogram presented in Table 1.

FDA Response

The review of the Applicant's PPK analysis and simulations revealed several issues that raise questions about the reliability and feasibility of the model and the dosing nomogram.

- The dosing nomogram contains four dosing steps with different weight cut-offs. In the clinical setting, this may cause confusion. Furthermore, this potential confusion may be exacerbated by the arrangement of the dosing steps (1.0 to 1.2 to 0.9 to 0.8 mg/kg) instead of incorporating a descending dosing schedule.

- The applicant's final model described the CL and V as a log-linear function. Although the data are reasonably well fit by the model, a simpler (allometric) model may be more applicable.

- The data file for the pediatric patients contained redundant NONMEM coding to indicate a steady-state measurement (SS and II and ADDL).

- The simulations performed to test the dosing regimens were not very well described. The applicant reported that "theoretical" AUC was simulated as

$$\text{Theoretical AUC} = \text{Dose}/CL_{observed}$$

for the fixed dosing regimens (e.g 0.8 mg/kg x actual body weight (kg)), and the target AUC of 1125 μM•min (4614 ug•hr/L) was used to back calculate doses for the log-linear ABW model. In each case, the dose was divided by the observed concentrations. These operations appear to have been conducted for each patient in the OMC-BUS-5 database. This approach

provides limited observations (n=24), and the applicant should have used the population CL of BUS in all cases to assess the success rate of achieving the target AUC.

- The dosing versus actual body weight curve (Figure 8 and 9) that the applicant used to develop the BUS pediatric dosing nomogram appears to be flawed. The rising portion of the curve from 6 to 9 kg is likely an artifact. The dose can be back-calculated from the log (natural log) expression for CL. The applicant then normalized dose with the linear expression of weight, which yielded the curves in Figures 8 and 9. However, it is more appropriate to normalize the dose by the natural log of the actual body weight, which generates the curve in Figure 10. Figure 10 is more consistent with the relationship for CL and weight shown in figure 3. Therefore the dosing recommendations based on the applicant's dose vs weight figure are is unreliable.

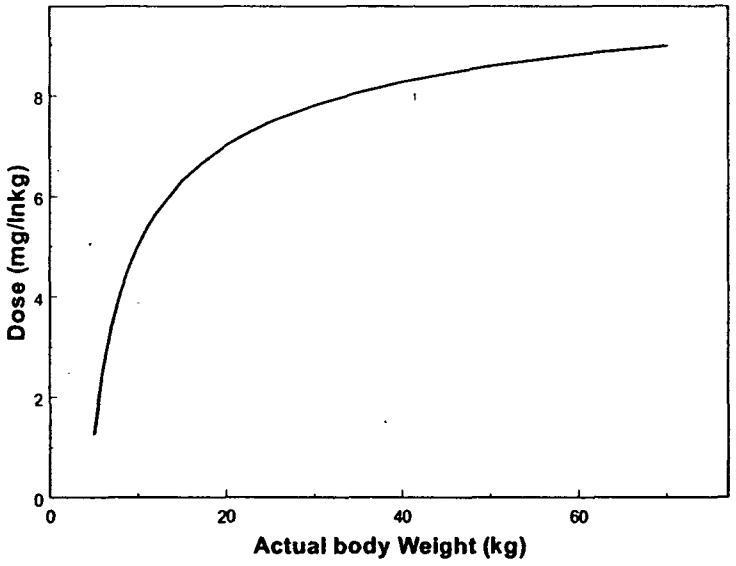

Figure 10. Relationship between Dose (mg/lnkg) and actual body weight.

FDA Analysis

FDA developed BUS PPK models based on a one-compartment open model with zero order infusion and first order elimination. Two models were chosen to develop BUS dosing regimens, based on MOF and diagnostic plots (as the applicant did). One model describes CL and V as an allometric function of ABW, and the second model

The final expressions for CL and V are

$$[CL = 4.04(ABW/20)^{0.742}];\ [V = 12.8(ABW/20)^{0.873}]$$

for the ABW PPK model.

Simulations were then conducted based on both the ABW and [redacted] PPK models to assess the percent of patients who achieved the target BUS exposure (range 900 to 1350 μM-min) using different dosing regimens, including the applicant's dosing nomogram. Simulations were conducted using 1000 datasets. The results revealed that approximately 60-65% of the patients could successfully achieve the target BUS exposure with the first dose. The most feasible ABW-based dosing regimen consists of two steps (59 % of patients achieved the target BUS AUC), and the [redacted]

The applicant's nomogram only achieved 54 % of the patients with the desired BUS exposure. This most likely resulted from the use of population PK estimates in the FDA simulations compared to the post-hoc estimates used in the applicant's simulation, which could lead to an over estimation of the dosing success.

The FDA dosing regimens are superior to that proposed by the applicant because they are less complex [redacted] and less prone to confusion. The ABW-PPK model-based regimen is described in Table 3 below.

Table 2. ABW PPK Model-Based Pediatric Dosing Nomogram for BUS

≤ 12 kgs	1.1 mg/kg
> 12 kgs	0.8 mg/kg

[redacted]

Of the two dosing regimens, the [redacted] because it is a [redacted] that is free of misunderstanding. Therefore, ***this dosing regimen is recommended.***

Therapeutic Drug Monitoring.

The simulations indicated that only 60-65% of the patients would successful achieve the target BUS exposure with the first dose. This result indicates that therapeutic drug monitoring (TDM) is necessary for BUS administration, and dose modification will be necessary to correct the BUS dose in a large proportion of the patients. To aid this modification, FDA developed a Dose Adjustment nomogram based on the relationship between BUS concentrations at 2 hr (end of infusion) and the BUS AUC. This relationship is demonstrated in Figure 4 below.

Figure 3.

The subsequent doses of BUS can be corrected to achieve the target exposure by the following adjustment below

Analytical Method

Was the assay acceptable for the determination of plasma concentrations of busulfan in pediatric patients?

Yes. The applicant used a ——— —— which is a —— method. This assay was also used in the original NDA for BUSULFEX. The assay is reportedly linear from — ng/ml to — ng/ml and selective for busulfan.

The study validation do not meet the current FDA guidance. The pediatric study and the assay validation were conducted (1997-1998) prior to the publication of the FDA Guidance for Industry entitled "Bioanalytical Method Validation", which was posted in draft form on the Agency webpage in 1999. The method is considered acceptable for the current study because of the prior determination of the Agency for the original NDA, and its use in the scientific literature. However, the validation is lacking by current standards and applicant should update the method validation if future studies are performed. The following issues should be addressed

- **Standard curves**: no standard curves were submitted in the validation. Instead, the co-efficient of variation (R^2) was reported for a number of analyses. This does not adequately describe the calibration curve. The calibration curve should be submitted in the validation package.
- **Range:** the applicant reported that the range of the standard curve was — ng/ml. However, the standard operating procedures (section 5) indicated that calibration curves were made from — ng/ml, which suggests that data from higher concentrations were extrapolated from the curve. This practice is unacceptable. Concentrations above the standard curve require adequate dilution in the same biological matrix to allow re-analysis within the range of the standard curve.
- **Accuracy**: the accuracy was of the calibrators or quality control samples were not determined. This is a requisite step that describes the limit of method reliability.
- **Precision**: Although the inter- and intra-day precision around —— ng/ml (the exact amounts used were not reported) were quite good (less than or equal to 3%), these studies were conducted at concentrations that are apparently above the upper limit of quantification on the standard curve (— ng/ml). Precision determinations should be conducted at concentrations within the range of the standard curve.
- **Lower limit of quantification (LLOQ, LOQ)**: the applicant defined the LOQ as — ng/ml, but included calibrators (— ng/ml) below this concentration on the standard curve. Concentrations below the LOQ should not be used on the standard curve.
- **Long-term stability**: The applicant reported the dates studied but not the actual concentrations determined during the study. Therefore, the stability cannot be verified.
- The applicant included a number of items that are currently not considered necessary for validation ([

VI. Detailed Labeling Recommendations

1. Applicant Labeling

CLINICAL PHARMACOLOGY section, Pharmacokinetics subsection

"....Fifty-five of fifty-nine patients (93%) administered BUSULFEX maintained AUC values below the target value «1500 μM-min) .

Table 1: Steady State Pharmacokinetic Parameters Following Busulfex® (busulfan) Infusion (0.8 mg/kg;N=59)

	Mean	CV(%)	Range
C_{max} (ng/mL)	1222	18	496-1684
AUC (μM•min)	1167	20	556-1673
CL (ml/min/kg)*	2.52	25	1.49-4.31

* Clearance normalized to actual body weight for all patients.

FDA Labeling:

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1 pages redacted from this section of the approval package consisted of draft labeling

3. Applicant Labeling
DOSAGE AND ADMINISTRATION section

[ ]

FDA Labeling:
DOSAGE AND ADMINISTRATION section

Simulations based on the pediatric population pharmacokinetic model indicate that approximately 60% of pediatric patients will achieve the target Busulfex exposure (AUC) of 900 to 1350 μM-min with the first dose of Busulfex. Therapeutic drug monitoring and dose adjustment following the first dose of Busulfex is recommended. Busulfex dose adjustment can be made using the nomogram and instructions provided below.

[

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Appendix 2

Pharmacometric report

Clinical Pharmacology and Biopharmaceutics
Pharmacometric Review

sNDA: 20-954

Compound: BUSULFEX; busulfan

Submission date: 12/21/01

Applicant: Orphan Medical Inc.

Pharmacometrics Reviewer: Brian Booth

Pharmacometrics Team Leader: Joga Gobburu

Population Pharmacokinetics Analysis of Busulfex in Pediatric Patients

Objective

1. To establish a pharmacokinetic model of busulfex in pediatric patients to assist in dose selection of Busulfex in the product labeling.

Data

The pediatric study was conducted in 24 pediatric patients who required bone marrow ablation and stem cell transplantation to treat a variety of hematological diseases. The demographic characteristics of the patients are listed in Table 1.

Table 1. Demographic Characteristics of BUSULFEX Pediatric Patients

Characteristic	Mean	Range
Gender	12 males, 12 females	
Age	6.3 ± 5.3 yrs	0.4 to 16.7 yrs; 14 patients ≤ 4yrs; 10 patients > 4 yrs, <17 yrs
BSA	0.8 ± 0.42 m^2	0.37 to 1.7 m^2
Actual Body Weight	23.8 ± 17.1 kg	7.1 to 62.6 kg

The treatment regimen consisted of four-times daily infusions of Busulfex (BUS; also busulfan) for four days, followed by one day of rest, and then by single daily 50 mg/kg doses of cyclophosphamide (Cy) for four days. An AUC between 900 and 1350 μM-min (1125 mean; 4614 μg-hr/L) was targeted in the pediatric patients based on studies in adults, in which exposures over 900 μM-min (3692 μg-hr/L) were considered necessary for successful bone

marrow ablation, and exposures greater than 1350 μM-min (5537 μg-hr/L) were associated with hepatic veno-occlusive disease. Children four years of age and under are reported to possess a greater clearance of BUS in the scientific literature. Therefore, in these studies, children under ≤ 4 yrs were treated with 1 mg/kg BUS, and children greater than > 4 years were treated with 0.8 mg/kg BUS. The pharmacokinetics (PK) of BUS were determined following the first and ninth doses of BUS with dense sampling, and trough samples were monitored after the 13th dose. The dose of BUS was modified after the first dose to achieve the target AUC based on the PK of the first dose.

APPLICANT'S ANALYSIS

Methods

Plasma concentrations of busulfan were measured with a [redacted] assay that has previously been validated.

One and two compartment structural models were used to assess the base population pharmacokinetic model. The PK parameters were assumed by log-normally distributed. Proportional, additive or combined error models were assessed. Objective function and diagnostic plots of residuals versus the posthoc Etas were used to determine the best base model. First order (FO) estimation was used in the model building. First Order Conditional Estimation (FOCE) was only used to confirm the final results.

The effect(s) of covariates were determined by progressively adding covariates to the model. The decision to test a covariate was based on a graphical examination of the relationship between PK parameters and the covariate. Then a multiple linear regression was performed to screen the covariates.

Covariates were cumulatively added to the base model. A covariate was retained in the population PK model if the minimum objective function (MOF) was decreased by 3.8. When no further improvement in the model was observed, covariate testing was terminated. The physiological "sense" of covariate inclusion was also considered.

The utility of the model to assess busulfan clearance from sparse samples was assessed by developing the model with two-thirds of the database from randomly chosen patients. Once the model was established, the remaining data was used (one or two samples vs the entire data set) to determine the bias (mean percent error) and precision (mean percent absolute error) of this approach.

Results

A one-compartment base model was chosen instead of a two-compartment base model despite the lower minimum objective function (MOF) of the latter (4840 vs 4652, respectively) because the accuracy and precision of the clearance (CL) and inter-individual variance estimates with the two-compartment model were poor and inconsistent. The final one-compartment model chosen by the applicant described CL as

$CL = 4.57 + 2.97 (Log (ABW)-3)$ (1)

And volume of distribution (V) was described as

$V= ABW^{0.85}$ (2)

where ABW is actual body weight in kilograms (kg). This model was chosen because the MOF of 4682.9 was best (see Table 2). Height and body surface area (BSA) did not improve the MOF. Inclusion of age decreased the MOF (4681.8), but it did not reach the pre-specified level of change (3.8) to be retained in the model.

Table 2. Effect of Covariate Inclusion on Population Estimate of Clearance

Model number	Covariates tested	Objective Function (With Δ from base model)	Inter-Individual Variability
1	Model without covariates (base model)	4839.8 (Δ=0)	64%
2	TVCL = 0.0362 x Height	4756.2 (Δ=-84)	33%
3	TVCL = 3.94 + 0.0684 (Height-100)	4690.6 (Δ=-149)	19%
4	TVCL = 5.32 x BSA	4701.3 (Δ=-139)	22%
5	TVCL = 5.94 x BSA-0.383	4697.6 (Δ=-142)	21%
6	**TVCL = 5.80 + 4.30 x Log[BSA])**	**4683.2 (Δ=-157)**	**18%**
7	TVCL = 0.204 x ABW	4750.3 (Δ=-90)	28%
8	TVCL = 0.152 x ABW + 0.869	4717 (Δ=-123)	25%
9	**TVCL = 4.70 + 3.15 x Log[ABW-3]**	**4682.9 (Δ=-157**	**18%**

TVCL is typical value of total clearance in L/hr. Height, BSA and ABW are expressed as cm, m^2 and kg respectively

The applicant plotted the population-predicted drug concentrations vs. the observed concentrations of BUS, as well as the weighted residuals (WRES) versus the population predicted concentrations of the final model. These data are presented in Figures 1 and 2 below.

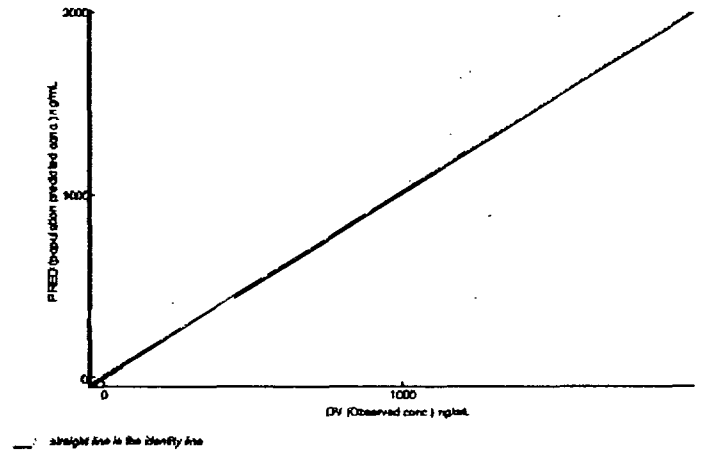

Figure 1. Predicted versus Observed concentrations of BUS from Applicant's log-linear model

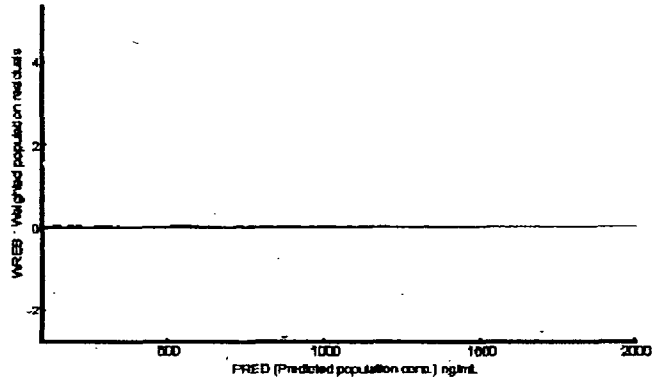

Figure 2. WRES plot versus time from the Applicant's log-linear model.

The predicted vs observed concentration plot in Figure 1 indicates that the final model under-predicts the BUS concentrations slightly. The WRES plot reveals more values above the line of identity than below, suggesting some bias in the model, which is not likely to be important. The applicant plotted the BUS clearance versus body weight for the final model. This data is presented in Figure 3 below, for the linear, directly proportional and log-linear models.

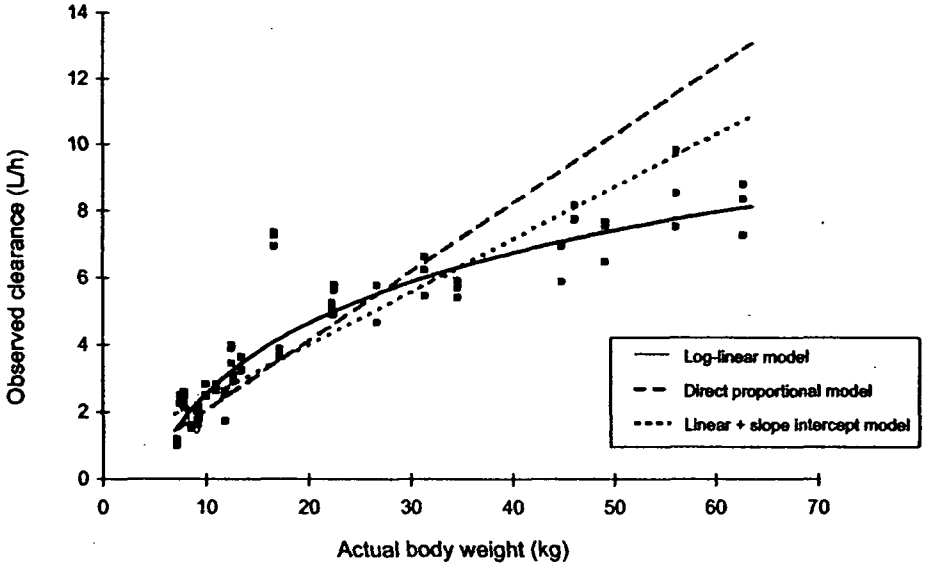

Figure 3. BUS CL versus ABW based on the Applicant's directly proportional, linear, and final log-linear models

The log-linear model revealed the best fit for BUS CL versus weight.

The applicant also reported the results of the limited sampling strategy. These data are shown for both 1 (6 hr) or 2 (2.5 hr and 6 hr) sampling schemes in the figures below.

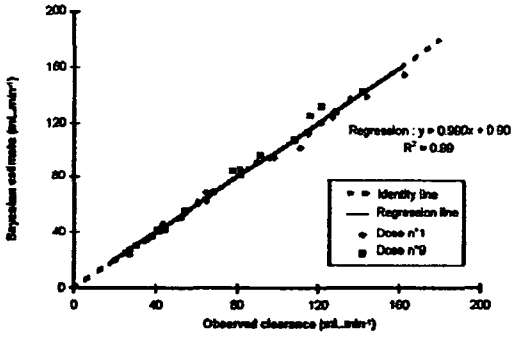

Figure 4. Estimates of CL based on Applicant's log-linear model using one sample

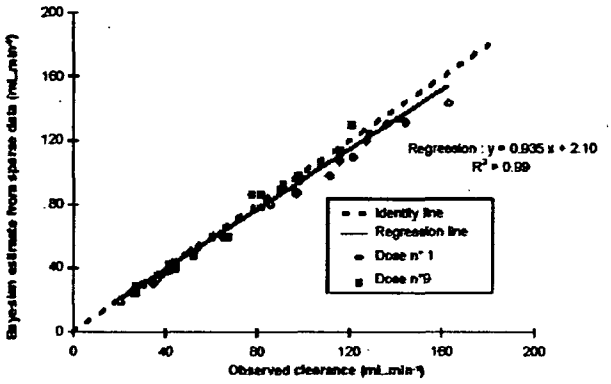

Figure 5. Estimates of CL based on Applicant's log-linear model using two samples

These data indicate that the sparse sampling appeared to be adequate in terms of estimating the clearance. The applicant then conducted simulations to assess how well the model-based dosing achieved the theoretically "safe" exposure of BUS. This result was compared to fixed dosing regimens

- Regimen 1: 0.8 mg/kg or 1 mg/kg for all patients
- Regimen 2: 0.8 mg/kg for children > 4yrs, 1.0 mg/kg for children ≤ 4yrs of age

The theoretical AUC for each regimen was calculated as

Theoretical AUC= Dose/Observed Clearance

For the model-based dosing, doses were calculated based on a target AUC of 1125 μM-min (4614 μg-hr/L).

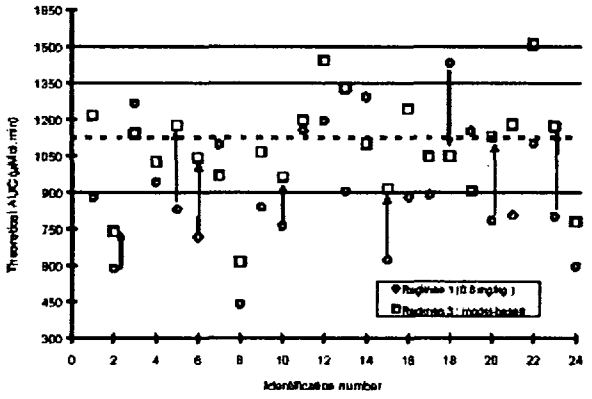

Figure 6. Applicant's simulations with fixed 0.8 mg/kg vs. log-linear model based dosing (circles-0.8 mg/kg dosing; squares model-based dosing).

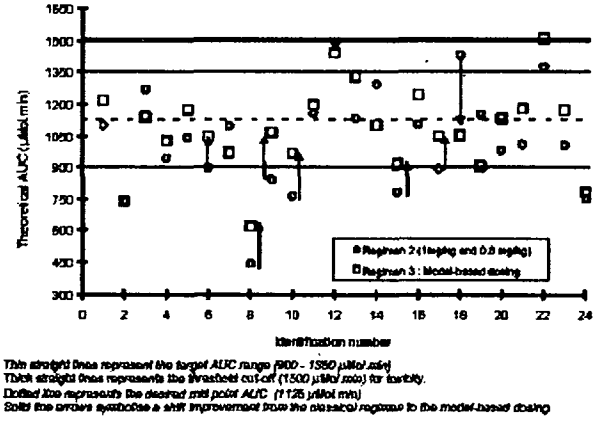

Figure 7. Applicant's simulations with fixed 0.8/1.1 mg/kg vs. log-linear model based dosing (circles-0.8/1.1 mg/kg dosing; squares model-based dosing).

The model-based dosing regimen appears to be superior to the fixed dosage regimens tested. Therefore, this model was used to plot the relationship between actual body weight and the doses that should be administered. This plot is shown in Figure 8 below.

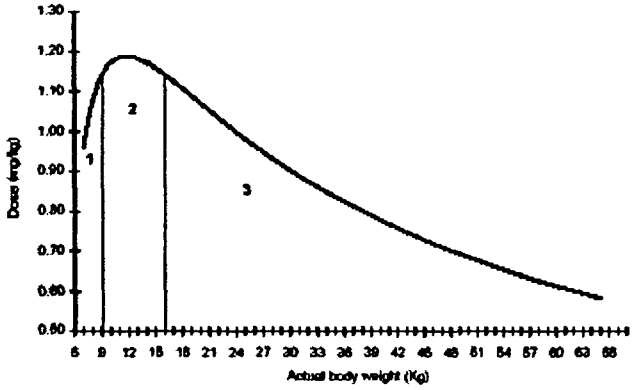

Figure 8. Relationship between dose and weight based on Applicant's log-linear model.

This relationship was segmented to provide a dosing nomogram, as shown in Figure 9 and Table 3 below.

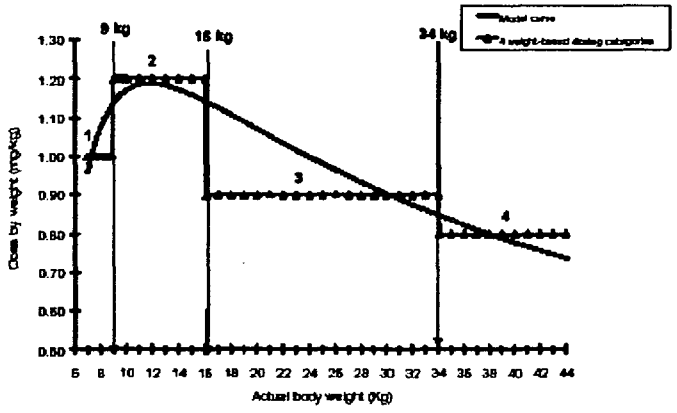

Figure 9. Relationship between dose and weight based on Applicant's log-linear model. The segmented areas indicate dosage steps.

Table 3 Applicant Proposed Dosing Regimen for BUSULFEX in Pediatric Patients

Actual body weight range	Dose

The applicant also conducted simulations using the nomogram dosing which yielded the following results.

Table 4. Simulations of BUS AUC following the First Dose

Regimen		Percentage of success to achieve AUC range (900-1350 µMol.min)	Mean AUC (CV%)
1a	all 0.8 mg/kg	38%	917 (27%)
1b	all 1 mg/kg	46%	1148 (27%)
2	0.8 or 1 mg/kg	54%	1029 (24 %)
3	model (log-linear)	79%	1082 (19%)
Nomogram	4 weight-based dosing categories*	87%	1111 (22%)

Applicant's Conclusions

- Analysis demonstrates a clear log-linear relationship between BUS and actual body weight
- Inter-individual variability of CL was 19%, and 12% for V
- Inter-occasion variability of CL was 9%
- One or two samples were sufficient to accurately and precisely estimate BUS clearance, assuming a one-compartment model.
- Simulations indicated that the log-linear model-based dosing allowed a greater percentage of patients to achieve the target exposure after the first dose of BUS
- The dosing nomogram developed from the log-linear model based dosing was also better than fixed dosing at achieving the target BUS exposure after the first dose than the fixed dosing regimens.

Reviewer's Comments on Applicant's Model

- The data file for the pediatric patients contained redundant NONMEM coding to indicate a steady-state measurement (SS and II and ADDL).

- The applicant's final model described the CL as a log-linear function and V as a power function. Although the data are reasonably well fit by the model, a simpler (allometric) model may be more applicable.

- The simulations performed to test the dosing regimens were not very well described. The applicant reported that "theoretical" AUC was simulated as

$$\text{Theoretical AUC} = \text{Dose}/CL_{observed}$$

for the fixed dosing regimens [redacted] was used to back-calculate doses for the log-linear ABW

model. In each case, the dose was divided by the observed CL. These operations appear to have been conducted for each patient in the OMC-BUS-5 database. This approach provides limited observations (n=24), and the applicant should have used the population CL of BUS in all cases to assess the success rate of achieving the target AUC in a larger population. Therefore, the ability to achieve the target AUC with the first dose of BUS is likely overestimated by the applicant's approach.

- The dosing versus actual body weight curve (Figure 8 and 9) that the applicant used to develop the BUS pediatric dosing nomogram appears to be flawed. The rising portion of the curve from 6 to 9 kg is likely an artifact. The dose can be back-calculated from the log (natural log) expression for CL. The applicant then normalized dose with the linear expression of weight, which yielded the curves in Figures 8 and 9. The figure suggests that children less than 9 kg possess a lower BUS CL than larger children, which in fact is not supported by the data. The confounding factor appears to be the choice of the denominator. It is more appropriate to normalize the dose by the natural log of the actual body weight, which generates the curve in Figure 10. Figure 10 is more consistent with the relationship for CL and weight shown in Figure 3. Therefore the dosing recommendations based on the applicant's dose vs weight figure are unreliable.

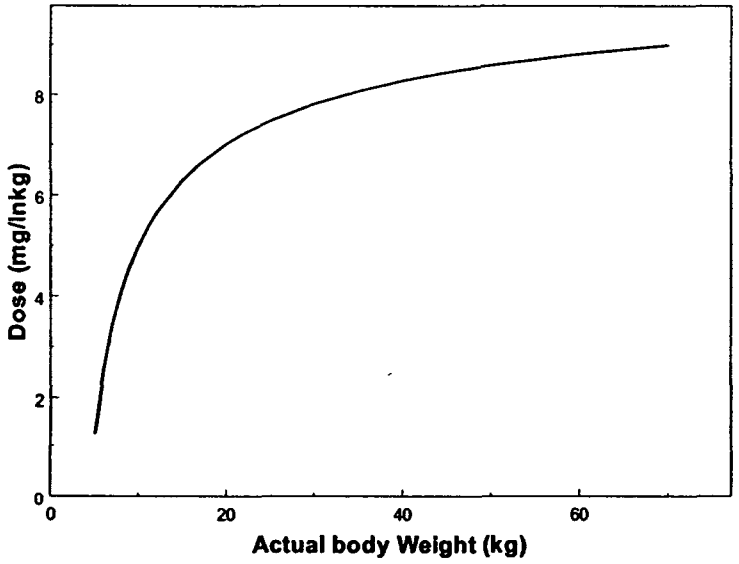

Figure 10. Relationship between Dose (mg/lnkg) and actual body weight.

REVIEWER'S ANALYSIS

The methodology employed by the FDA was essentially the same as that of the applicant. The following differences should be noted.

- Allometric scaling was used to describe the relationship between CL, V and actual body weight. The expression for CL and V are

$CL_i = TVCL*e^{\eta CL}$, where TVCL is the typical value of clearance for a 20 kg patient. TVCL is calculated as

$TVCL=\theta_{CL}*(ABW/20)^{WTCL}$.

$Vi = TVV*e^{\eta V}$, where TVV is the typical value of volume for a 20 kg patient. TVV is calculated as $TVV = \theta_v*(ABW/20)^{WTv}$.

- CL and V are also described by a PPK model based on — The expression for CL and V according to this model are

[redacted]

- Simulations of 1000 patients were conducted in NONMEM using the population PK models that described the CL and V of BUS derived by FDA and the applicant. The number of patients that achieved a BUS exposure between 900 and 1350 μM-min (3691 and 5537 μg-hr/L; mean 4614 μg-hr/L (1125 μM-min), as well as the percentage above and below these limits were determined.
- The simplest model which yielded a high success rate in BUS exposure with the first dose (based on the simulations) was used to develop a nomogram to help adjust subsequent BUS doses in order to achieve the target AUC of 4614 μg-hr/L (1125 μM-min).

Results

Two population PK (PPK) models were developed that are suitable for developing a BUS dosage regimen. One regimen is based on actual body weight (ABW) · —

— These models were chosen based on the lowest MOFs obtained, parameter estimates, diagnostic plots (e.g. predicted vs observed concentration) and physiological soundness.

Model selection began with a base model that described CL and V of a one-compartment open model with zero order input and first order elimination. Age, ABW, ABW normalized to 20 kg and —

Covariates that reduced the MOF (Δ=3.84) were retained in the model. The most successful models are listed in Table 5, which indicates the MOF observed for each model. The model based on ABW/20 (ABW PPK Model) — —

produced the largest reduction in MOF compared to the base model.

Table 5. MOFs for BUS PK Models

Model	Minimum Objective Function
Applicant	4679.2
Base (FDA)	4890
BUS_CLwt20	4767
BUS_CLVwt20	4773

BUS_CLVwt20_blk	4769
BUS_CLwt20AGE	4771
BUS_CLIOV_wt20	4702
BUS_CLVIOV_wt20 (renamed finalpk.ctl)	4697.9

Actual Body Weight PPK Model (refer to finalpk.ctl and finalpk.out in the Appendix)

The ABW PPK model provides relatively good predictions of the plasma concentrations of BUS as indicated by the diagnostic plot of predicted versus observed concentration shown in Figure 11 below.

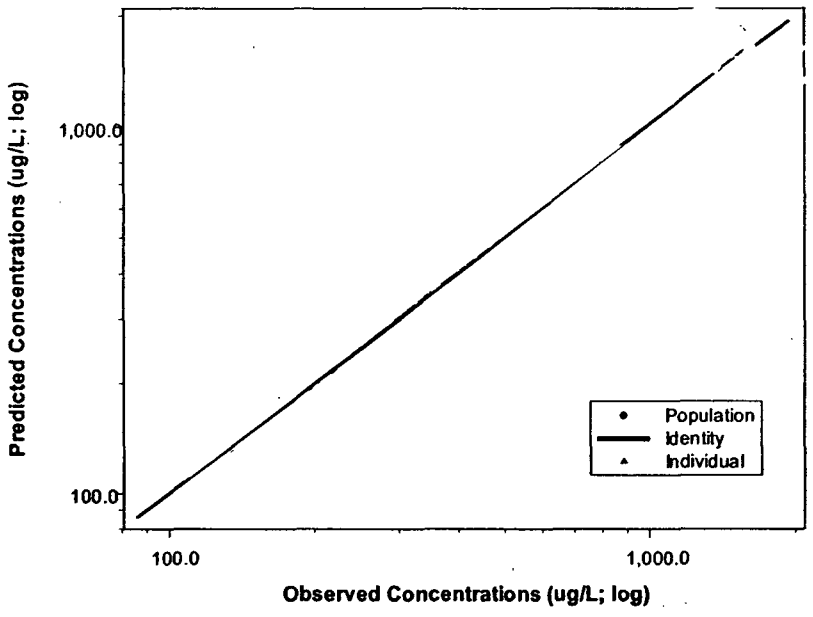

Figure 11. Predicted vs. Observed BUS concentrations based on FDA ABW PPK model.

Several examples of individual plasma concentration versus time curves based on the ABW PPK model are shown in Figure 12. These curves also indicate good performance of the model to predict BUS plasma concentrations

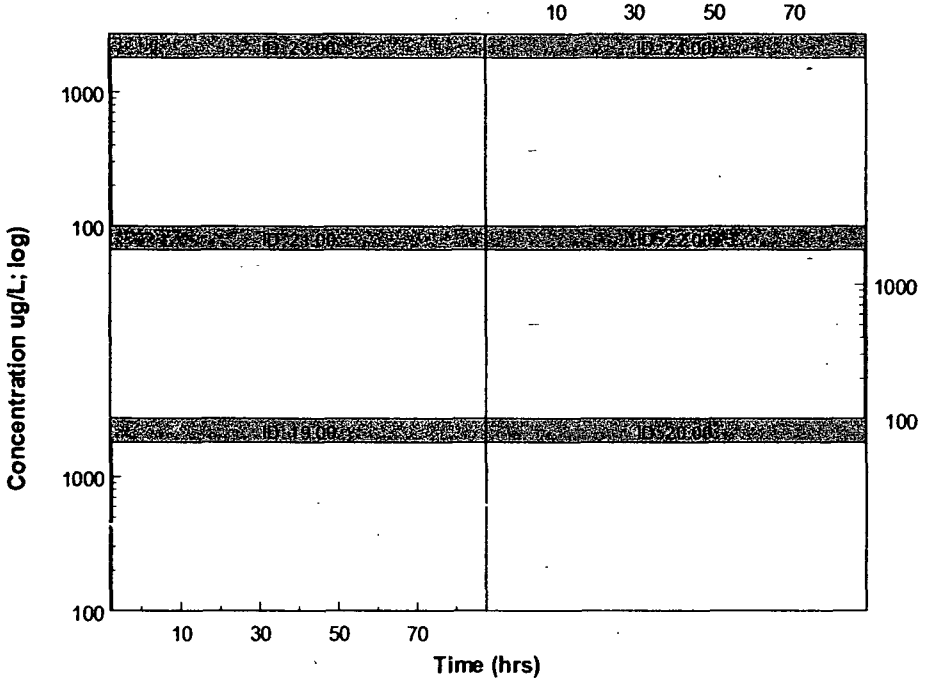

Figure 12. BUS plasma concentration vs. time curves for individuals based on the FDA ABW PPK model (circles-observed data; solid line-population fit; dotted line-individual fit)

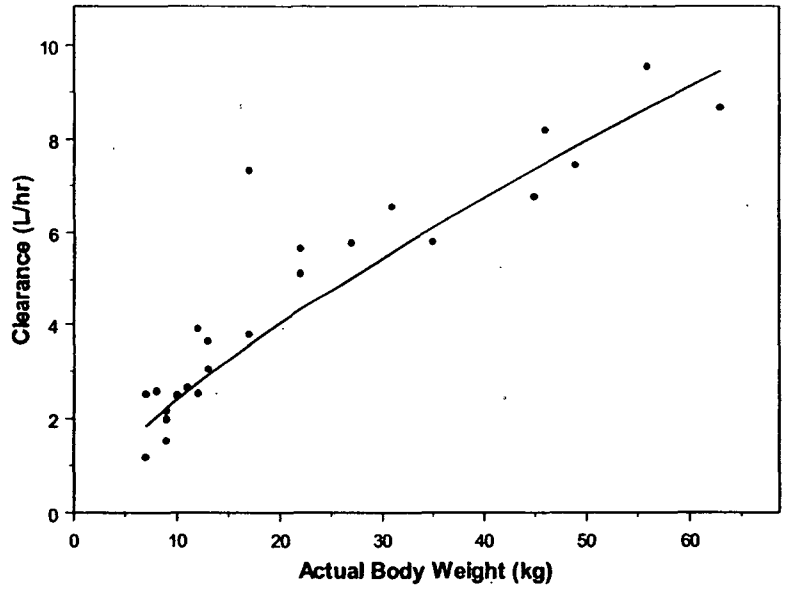

Figure 13. BUS CL vs actual body weight based on the FDA ABW PPK model

The clearance of BUS versus actual body weight based on the ABW PPK model is shown in Figure 13. The pharmacokinetic parameter estimates from the final model are shown in Table 6 below.

Table 6. BUS ABW PPK Parameter Estimates by FDA

Parameter	FDA Base Model	Units
MOF	4697.2	
θ_{CL}	4.04	(L/kg/20/hr)
WT_{CL}	0.742	-
θ_V	12.8	(L/kg/20)
Wt_V	0.843	-
Ω_{CL}	23	%
Ω_V	10.9	%
CL-Iov	9.5	%
V-iov	6.1	%
Cvcp	4.7	%
Sdcp	52.2	ug/L

-iov; inter-occasion variability

The model indicates that CL and V are dependent upon actual body weight.
The final expression for CL and V are

$$[CL= 4.04(ABW/20)^{0.742}];\ [V=12.8(ABW/20)^{0.873}]$$

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The primary objective of the analysis was to estimate PK parameters in the pediatric population. Therefore, confidence limits on these estimates were derived using bootstrap re-analysis with NONMEM. The purpose of bootstrapping is to learn about the statistical parameters of a distribution e.g. mean, standard error when the true distribution is unknown and one just has a set of observations. The key idea is to use the set of observations as an empirical representation of the true distribution. If we sample many times from the study observations, the distribution of the population and its properties (e.g. its standard error or its 95% confidence interval) can be described. This kind of sampling is "sampling with replacement" i.e. it is possible to get one of the original observations more than once in the bootstrap sample.

In the current procedure, one thousand data-sets were sampled from the BUS database. Each subject was replaced once sampled. The results are shown in Table XX below. For the ABW PPK model, the following results were obtained

Table 8. Mean ± 90% Confidence Intervals for BUS CL and V

Parameter	Mean	Lower 90% C.I.	Upper 90% C.I.
CL	4.05	3.71	4.43
CLWT	0.741	0.612	0.889
Ω_{CL}	0.22	0.13	0.31
IOV_{CL}	0.093	0.066	0.12
V	12.8	12.0	13.4
VWT	0.874	0.807	0.933
Ω_V	0.10	0.053	0.15
IOV_V	0.059	0.0003	0.091
cvcp	0.046	0.00001	0.076
sdcp	51.7	27.4	69.7

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Dosing Simulations

To determine how many patients achieved the target exposure of BUS (mean 4614 μg-min/L or 1125 μM-min) with the first dose of BUS, simulations were conducted using NONMEM. One thousand replications were done in each simulation using the ABW PPK model. In each

simulation, and the percentage of patients that were above below or within the BUS $AUC_{0-\tau}$ of 3692 to 5537 μg-min/L (900-1350 μM-min) were determined. Dosing regimens that contained between one to seven steps were tested. In addition, different weight cut-offs for each dosing step were also tested. Fifty dosing scenarios were tested. The best results for each multiple-step dosing regimen are shown below.

Table 10. Simulation: Percentage of Patients Achieving Target BUS Exposure with Different Dosing Regimens

Dose Levels	Dosage Regimens (mg/kg)	Subjects with 900 to 1350 μM-min		
		Average-%	Missed LL-%	Missed UL-%
One 1doselv1c.ctl	0.8	44.1	45.5	10.4
	1.0	39.8	5.7	54.5
	1.2	49.6	19.2	31.2
Two 2doselv1H.ctl	0.8, 1.2	**56.1**	**27.3**	**16.3**
Three Dose_Sim12.ctl	0.7, 0.9,1.0;wts 18, 47, 80	56.9	25.8	17.3
Four Dose_Sim5C.ctl	0.8, 0.9, 1.0, 1.2 wtmax:47	59.6	18.3	21.3
Five Dose_Sim10.ctl	0.7, 0.8, 0.9, 1.0, 1.1	59.0	19.0	22.0
Six Dose_Sim5A.ctl	0.7, 0.8, 0.9, 1.0, 1.1, 1.2	59.4	17.0	22.9
Seven Dose_Sim5.ctl	0.6 0.7, 0.8, 0.9, 1.0, 1.1, 1.2	58.9	18.7	22.4
Applicant's regimen Dose_SimOM.ctl	0.8, 0.9, 1.0, 1.2	**52.4**	**16.8**	**30.8**

% LL indicates percentage of subjects below the lower limit of BUS exposure (900 μM-min; 3692 μg-hr/L); % UL indicates the percentage of subjects above the upper limit of BUS exposure (1350 μM-min; 5537 μg-hr/L)

The simulations indicated that no more than 60% of the patients could successfully achieve the target BUS exposure with the first dose based on actual body weight.

The nomogram proposed by the applicant was the least successful (excluding the single ABW-based dosing regimens). This result contrasts with that reported by the applicant (67%). This difference is probably the result of using the FDA ABW *population* PK model in these simulations, as opposed to individual estimates.

These analyses have provided two possible dosing regimens. Based on the ABW PPK model, the two to seven step regimens are relatively equivalent. Therefore, the two-step regimen was chosen for simplicity and ease of use. The dosing regimen proposed by FDA is listed in Table 9 below.

Table 11. ABW PPK Model-Based Pediatric Dosing Nomogram for BUS

≤ 12 kgs	1.1 mg/kg
> 12 kgs	0.8 mg/kg

[ ]

THERAPEUTIC DRUG MONITORING

The dosing simulations indicate that approximately 40% of pediatric patients will not achieve the target BUS exposure, regardless of the dosing regimen that is employed. Therefore, further adjustment of BUS is warranted to prevent either a failure of bone marrow ablation or hepatic veno-occlusive disease. To address this, a nomogram was designed that relates the concentration of BUS at two hours into the infusion (end of infusion; C2hr) to the amount of change necessary to correct BUS dosing to achieve the target exposure (4614 µg-min/L; 1125 µM-min). This nomogram is based on the linear relationship between C2hr and AUC. The target C2hr was then calculated, and the dose adjustment factor is determined by the ratio the target C2hr to the observed C2hr. This relationship was derived for both dosing steps (0.8 and 1.1 mg/kg) in the ABW PPK model,

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ABW PPK Model

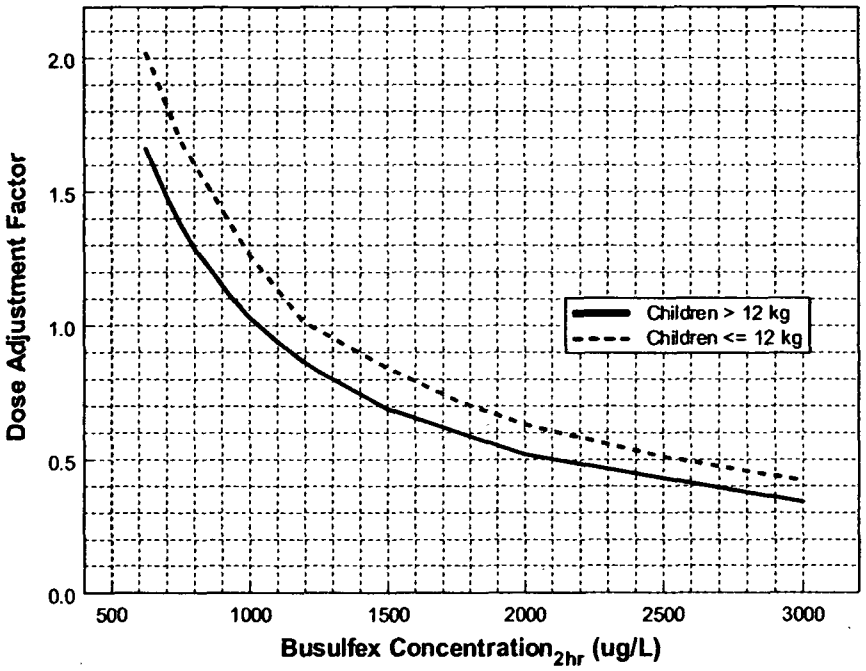

Figure 17. FDA Dose Adjustment Nomogram for ABW-Based BUS Dosing.
After visually determining the dose adjustment factor based on the patient's observed C2hr, the dose can be corrected as follows

- For pediatric patients ≤ 12kgs, 1.1 mg/kg x actual body weight (kg) x dose adjustment factor
- For pediatric patients >12kgs, 0.8 mg/kg x actual body weight (kg) x dose adjustment factor

PPK Model

Figure 18. FDA Dose Adjustment Nomogram for BUS Dosing.

In a fashion similar to the ABW PPK model, the subsequent doses of BUS can be corrected to achieve the target exposure by the following adjustment

Both the ABW based dosing regimens produce relatively similar BUS doses. A comparison of the two dosing regimens is shown in Table 10 below.

Table 12. Comparison of BUS Doses Derived from the ABW PPK Models

ABW (kg)	ABW-Dose (mg)	% difference
7	7.7	13
12	13.2	3.8
27	21.6	11
49	39.2	-12

PK-PD Relationship

Several reports in the scientific literature indicate that a target range of Busulfex exists for safe and effective bone marrow ablation prior to hematopoietic transplantation. Hepatic veno-occlusive disease is associated with BUS exposures greater than 1350 to 1500 μM-min.

Unsuccessful ablation or engraftment has been associated with BUS exposures of less than 900 μM-min. Therefore, 900-1350 μM-min is the therapeutic window for BUS.

In the current study, the PK-PD relationship could not be determined for either safety or efficacy because there was insufficient change in the exposure of BUS; all of the pediatric patients possessed similar AUCs after BUS administration (± 25 % after the first dose; ± 16% after dose 9). Secondly, there were too few patients to address safety (n=24).

The clinical databases did reveal that in 100% of the patients, bone marrow was successfully ablated and each was successfully engrafted with new cells. The AUCs after doses 1 and 9 were 1012.3 μM-min and 1157.3 μM-min, respectively (4152 and 4747 μg-hr/L, respectively), which is well within the BUS exposure target range.

Of the 24 patients studied, four were diagnosed with VOD (a fifth patient was deemed as having HVOD by FDA). Therefore, 17 to 21% of the patients developed VOD which is apparently less than the VOD rate that is generally experienced (20-70%). Of the five patients with VOD, four had BUS exposures greater than 1350 μM-min (5537 μg-hr/L).

CONCLUSIONS

- The ABW PPK model describes CL and V of BUS allometrically as a function of actual body weight. These estimate are described as

  $[CL = 4.04(ABW/20)^{0.742}]$

  $[V = 12.8(ABW/20)^{0.873}]$

-

- Simulations using both the ABW — PPK models indicated that approximately sixty per cent of the patients will achieve the target BUS exposure with the first dose of BUS.

- A two-step dosing regimen is the simplest dosing regimen that can achieve the target AUC using the ABW PPK model.

≤ 12 kgs	1.1 mg/kg
> 12 kgs	0.8 mg/kg

-

- BUS dosing should incorporate therapeutic drug monitoring to correct subsequent doses of BUS in order to achieve the target exposure range for BUS.

LABELING RECOMMENDATIONS

The — PPK model provided the best PK performance and the simplest dosing scheme. Although the current BUSULFEX label indicates adult dosage based on actual body weight,

. Therefore, the Office of Clinical Pharmacology and Biopharmaceutics Pharmacometric recommendations are

1.

2. Change the dosing — DOSAGE AND ADMINISTRATION section of the BUSULFEX LABELING.

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