Population Pharmacokinetic Modeling & Simulation-Derived Dosing of Intravenous Busulfan in Pediatric Patients

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Background

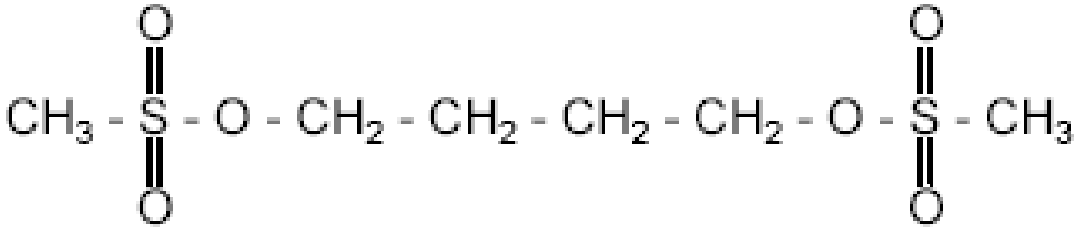


Figure 1. Busulfan; MW 246.1

Busulfan:
Myleran (Roche) 2 mg tablets;
up to 8 mg daily for palliation of CML

current application: bone marrow ablation
at 1 mg/kg-- 35-40 tablets 4x daily!

Background

Busulfex (Orphan Medical)-1999:

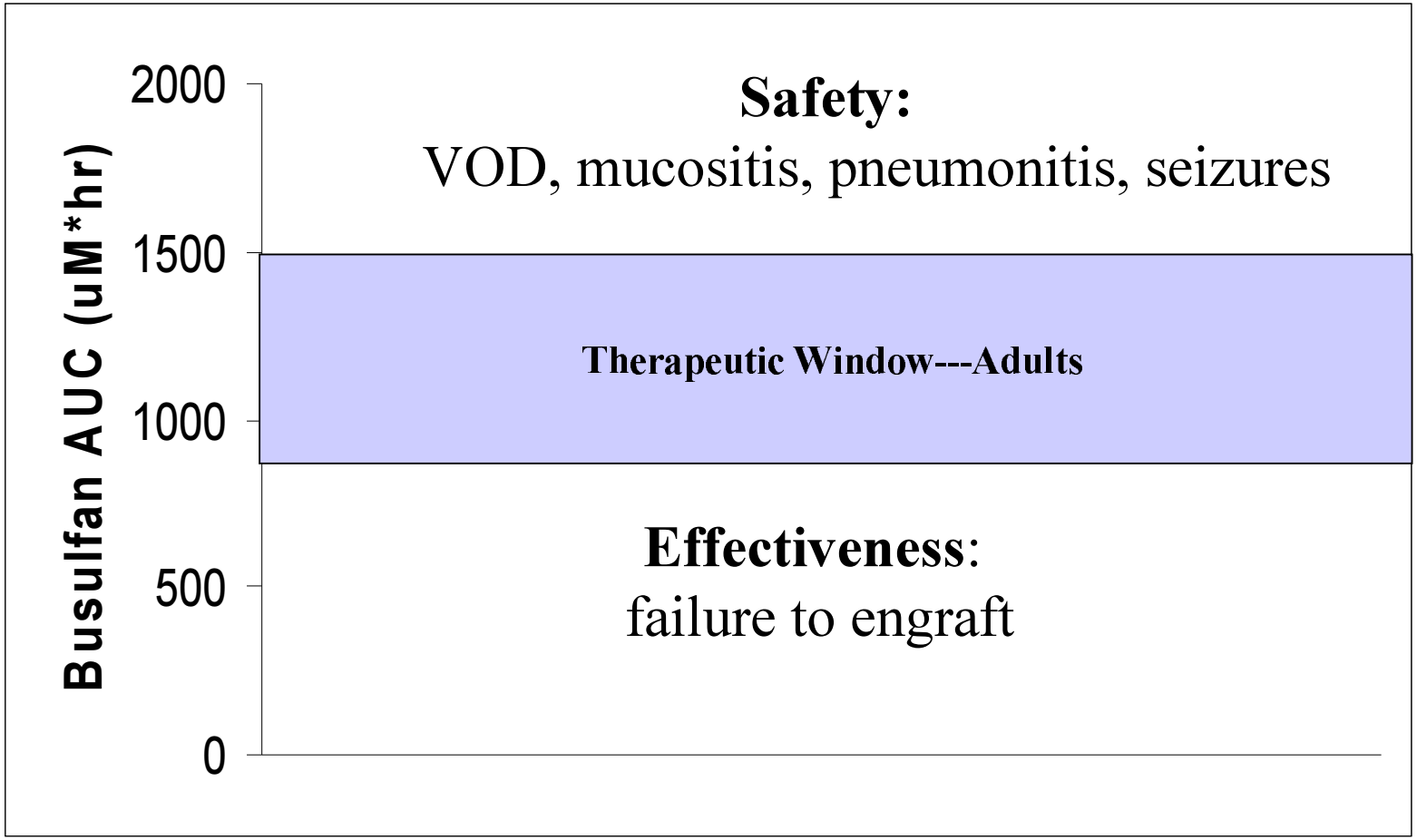
Formulation: 6 mg/ml for I.V. infusion

Indication:

In combination with cyclophosphamide, as a conditioning regimen prior to allogeneic hematopoietic stem cell transplantation (HSCT) for CML in adults.

Adult Dosage: 0.8 mg/kg

Busulfan Therapeutic Window



HSCT: Pediatric Disease Settings

- Malignant :
  - Leukemias (ALL, AML)
  - Solid Tumors (Neuroblastoma, Wilms Tumor)
- Non-Malignant
  - Hematologic (thalassemia, sickle cell)
  - Immune deficiency
  - Storage disorders

HSCT for Pediatric Disease

What is the appropriate dosage/regimen for pediatric use?

Study Design

FDA Written Request for Pediatric Dosing Instructions

1 Pharmacokinetic Study (OMC-BUS-5)

- 24 pediatric patients (variety of diseases)

Table 1. Demographic Characteristics of Pediatric Patients

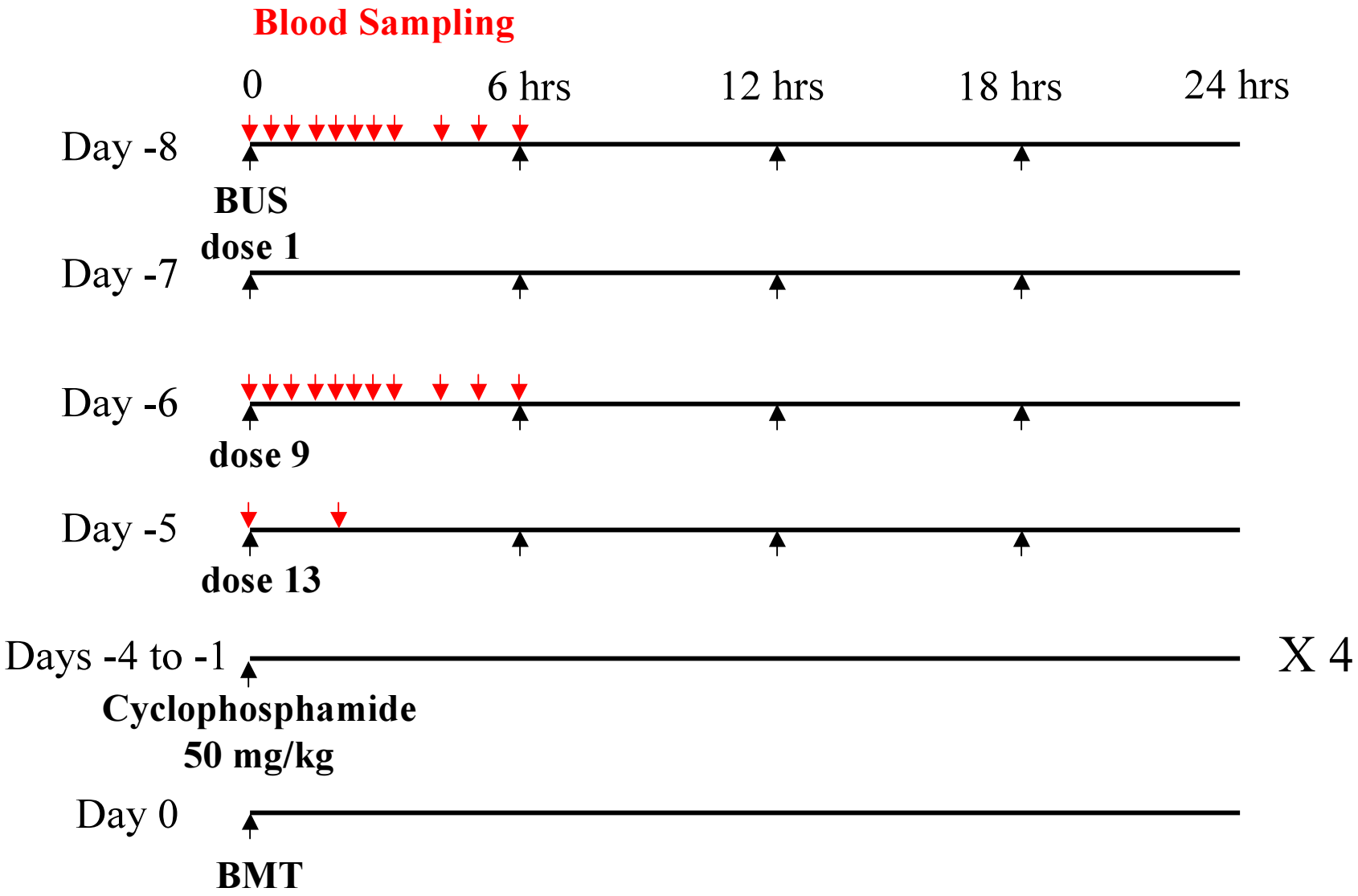
Characteristic	Mean	Range
Gender	12 males, 12 females	
Age	6.3 ± 5.3 yrs	0.4 to 16.7 yrs; 14 patients ≤ 4yrs; 10 patients > 4 yrs, <17 yrs
BSA	0.8 ± 0.42 m^2	0.37 to 1.7 m^2
Actual Body Weight (ABW)	23.8 ± 17.1 kg	7.1 to 62.6 kg

Study Design

- BUS Target AUC: 1125 uM-min (range 900-1350)

- BUS Dosage
  - 1 mg/kg BUS i.v. if ≤ 4 yrs
  - 0.8 mg/kg BUS i.v if > 4yrs
  - dose adjustment based on dose 1 PK
  - 4 days of cyclophosphamide (CY)

Study Design



PPK Modeling

- One-compartment open model
  - zero-order input
  - first-order elimination

- Allometric scaling of CL, V employed.

- Choice based on lowest MOF, diagnostic plots and "physiological sense"

PPK Modeling

Base Model:

$$C(t) = (Dose/Vd)\cdot(e^{-CL/Vd\cdot t})$$

Random Effects:

$$CL_i = \Theta_{CL}\cdot e^{(\eta CLbsv + \eta CLbov)}$$
$$Vd_i = \Theta_{Vd}\cdot e^{(\eta Vdbsv + \eta Vdbov)}$$

Residual Error:

$$C_i = F\bullet e^{cvcp} + sdcp$$

Covariates: age, gender, weight, BSA

PPK Modeling

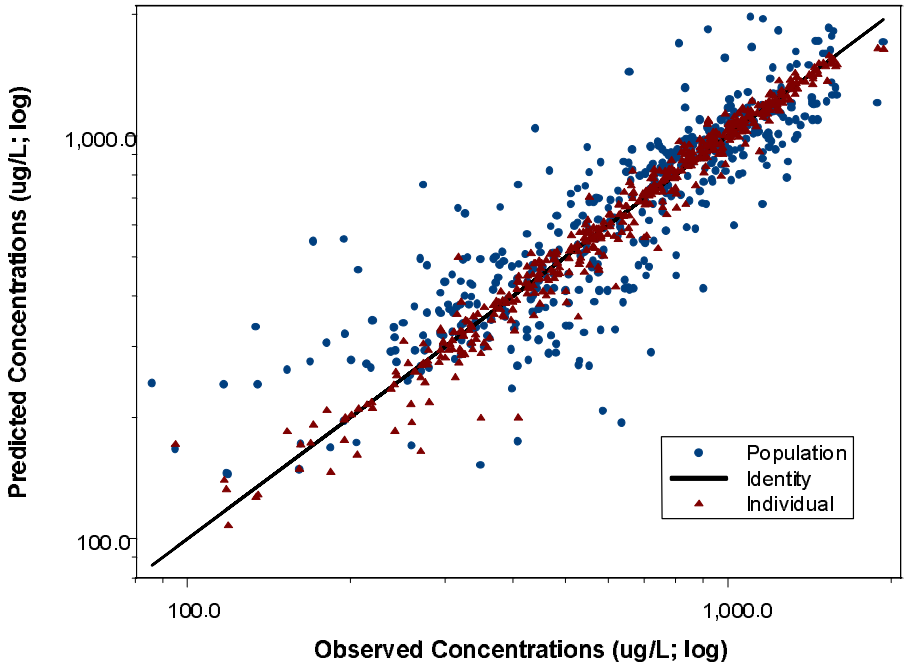
Table 2. Effect of Covariates on the Busulfan PPK Model

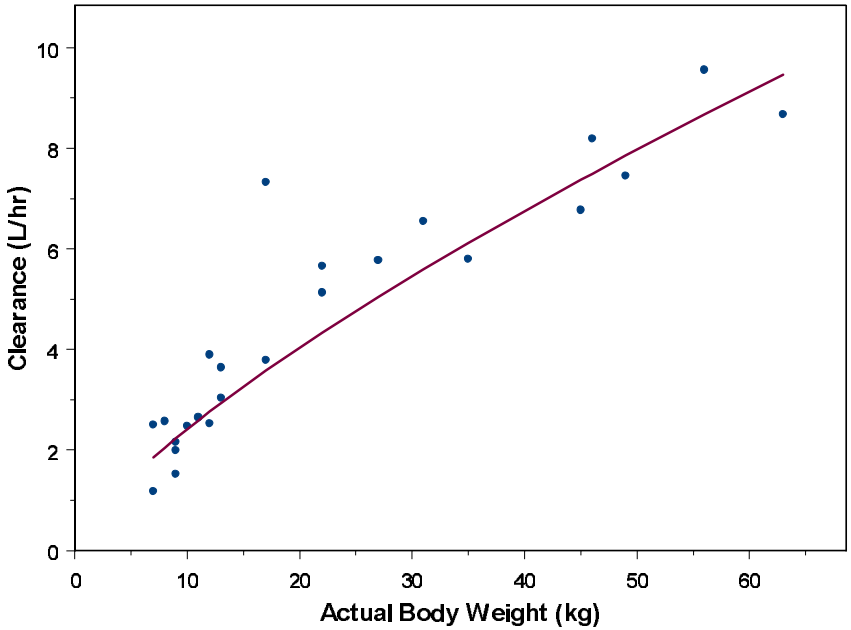
Model	**Minimum Objective Function (MOF)**
Base	4890
Base + weight* on CL	4767
Base + weight* on CL and Vd	4773
Base + weight* on CL and Vd + r (CL,Vd)!	4769
Base + weight* and Age on CL	4771
Base + weight* and inter-occasion variability on CL	4702
Base + weight* and inter-occasion variability on CL and Vd	**4697.9**
Base + BSA on CL and V	**4696.8**

*weight (ABW;kg) normalized to the population mean, 20 kg. ! a random correlation of individual CL and V BSA: body surface area.

PPK Modeling

ABW PPK Model: Predicted vs. Observed BUS concentrations (left) and BUS CL vs. ABW (right)





Final PPK Model

$$CL = 4.04 \bullet (ABW/20)^{0.742}$$

$$V = 12.8 \bullet (ABW/20)^{0.873}$$

PPK Modeling

Table 3. Busulfan Parameter Estimates and 90 % Confidence Intervals (Bootstrap) for the Final Pharmacokinetic Parameter Estimates

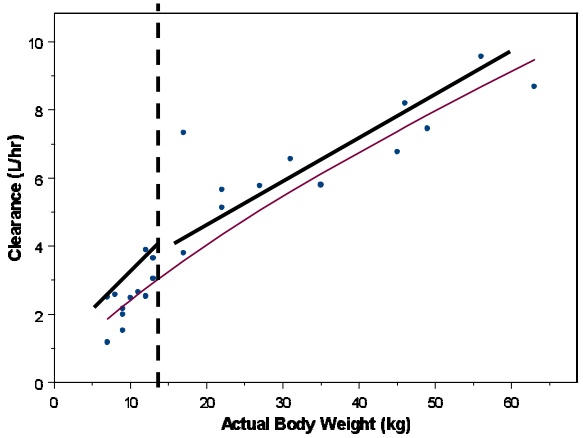
Parameter	FDA Base Model	Lower 90% C.I.	Upper 90% C.I.
CL (L/hr/20kg)	4.04	3.71	4.43
WT_{CL}	0.742	0.612	0.889
V (L/20kg)	12.8	12.0	13.4
Wt_V	0.843	0.807	0.933
CL-bsv %	23	13	31
V-bsv %	10.9	5.3	15.0
CL-bov %	9.5	6.6	12.0
V-bov %	6.1	0.03	9.1
Cvcp %	4.7	0.001	7.6
Sdcp (ug/L)	52.2	27.4	69.7

-bsv: between subject variability; bov; between-occasion variability

Simulations

•**Simulations**:

% patients with target AUC after BUS dose$_1$



•**Regimens**:

ABW PPK Model

- •1 to 7 steps
- •different weight cut-offs, different dosing steps

e.g. 2 step regimen

0.8 mg/kg for patients < 10 kgs,

0.9 mg/kg for patients ≥ 10 kgs

•**Conditions**

simulated 1000 patients

determined % patients above, below and within 900 to 1350 uM-min

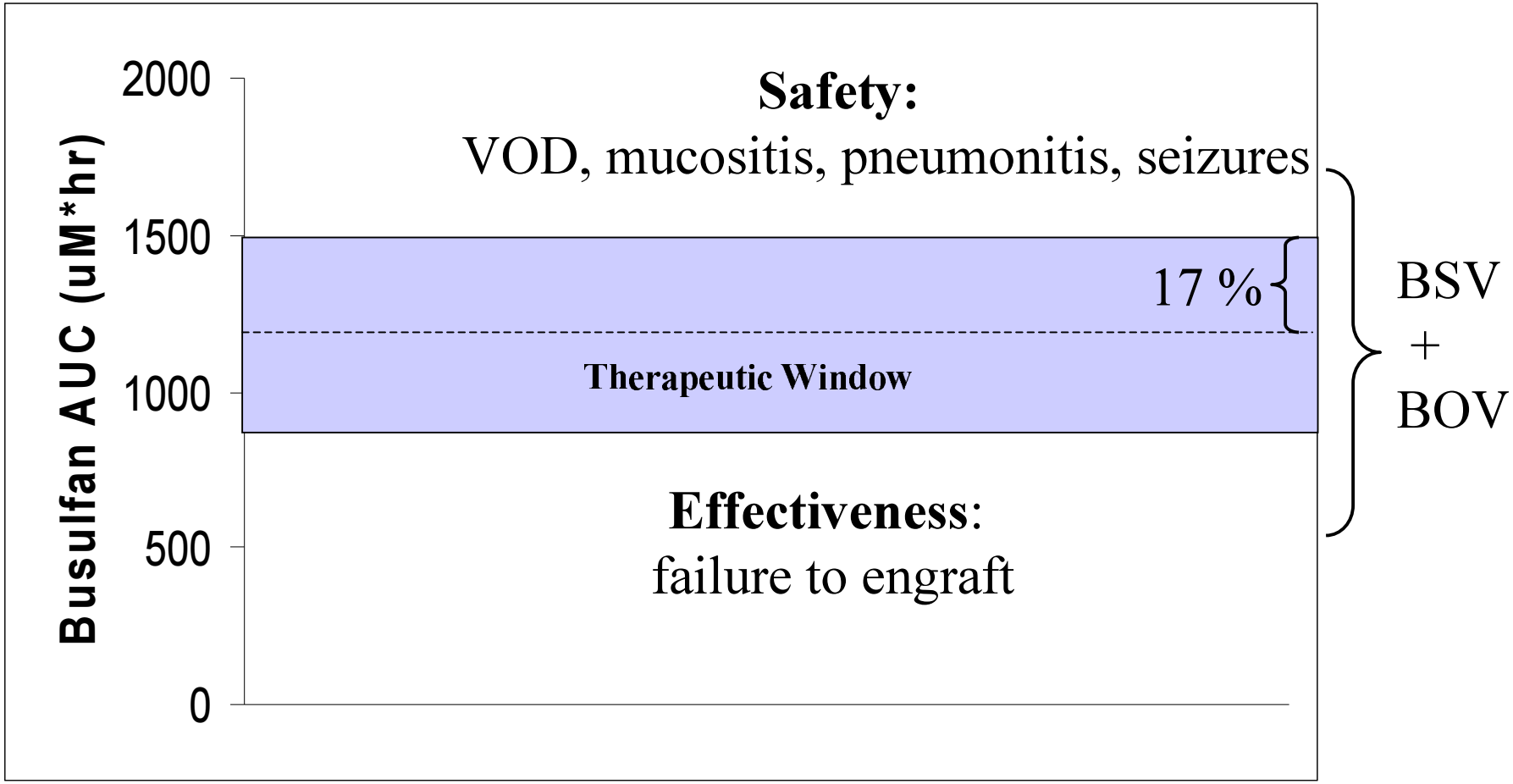
Simulations

Table 4. Simulation: Percentage of Patients Achieving Target BUS Exposure with Different Dosing Regimens

Dose Levels	Dosage Regimen (mg/kg)	% Subjects with Target AUC (900 to 1350 μM-min)		
		Average-%	Missed LL-%	Missed UL-%
One	1.2	49.6	19.2	31.2
Two	0.8, 1.1	**56.1**	**27.3**	**16.3**
Three	0.7, 0.9,1.0;wts 18, 47, 80	56.9	25.8	17.3
Four	0.8, 0.9, 1.0, 1.2 wtmax:47	59.6	18.3	21.3
Five	0.7, 0.8, 0.9, 1.0, 1.1	59.0	19.0	22.0
Six	0.7, 0.8, 0.9, 1.0, 1.1, 1.2	59.4	17.0	22.9
Seven	0.6 0.7, 0.8, 0.9, 1.0, 1.1, 1.2	58.9	18.7	22.4

% 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). Note: for each dose-level, multiple dosing scenarios were tested. The highest average % of each scenario is listed.

Busulfan Therapeutic Window



Dosing Recommendation

1.1 mg/kg if $\leq$ 12 kgs

0.8 mg/kg if $>$ 12 kgs

Therapeutic Drug Monitoring

Simulations indicate only 60% of patients will achieve target AUC (bov was low).

Therefore, dose adjustment necessary

Therapeutic Drug Monitoring (TDM)

Recommendation: Use TDM of dose 1 busulfan AUC to adjust subsequent doses to maintain target AUC.

-Tested this approach: Used commercial software to determine AUC of dose 1 busulfan using 2, 4 and 6 hr samples, and compared AUC from full profiles.

Results: mean (± s.d.) difference between full profile and TDM: 0.2 ± 5.3%

Current Busulfex Labeling

Pediatric section of label:

1.1 mg/kg if ≤ 12kgs
0.8 mg/kg if > 12 kgs

and

Therapeutic Drug Monitoring with 3 samples.

FDA/Sponsor Interaction: Busulfex

1. Good Study Design.

2. Diligent sample collection/analysis

3. Excellent Scientific Discourse

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