

A Semi-Mechanistic Model with Glutathione S-transferase Activity to Optimize Busulfan Dosing in Pediatric Hematopoietic Stem Cell Transplantation

Junjun Mao¹, Di Cao², Xiaowen Qian², Ping Wang², Xinyi Zheng¹, Shan Huang³, Zhonglin Wei⁴, Wenjin Jiang², Ling Yu², Xin Jiang², Ying Yu², Xiaowen Zhai^{2,*}

1 Department of Pharmacy, Huashan Hospital of Fudan University, China 2 Department of Hematology, National Children's Medical Center, Children's Hospital of Fudan University, China 3 Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China 4 Department of Hematology and Oncology, Children's Hospital of Soochow University, China

Background

- Busulfan is known for its **high inter- and intra-individual** pharmacokinetics/pharmacodynamics (PK/PD) **variability**, particularly in children.
- It is distributed rapidly after IV administration and binds extensively to erythrocytes (approximately 47%) and plasma proteins (approximately 32%), then predominantly **metabolized** by conjugation with glutathione (**GSH**) mainly **through** glutathione S-transferases (**GSTs**) in the liver.
- Time-varying clearance** was observed over a 4-day treatment with an every-6-h dosing regimen of busulfan, **busulfan-mediated GSH depletion may cause nonlinear elimination**.
- GST activity** decreases from infancy to early adolescence, and developmental differences in activity **can markedly alter drug disposition**.
- Strong knowledge of PK characteristics is necessary to **achieve busulfan target exposure**.

Objective

- Employing semi-mechanistic population PK model to:
 - (1) quantify sources of PK variability in IV busulfan exposure among pediatric HSCT recipients;
 - (2) mechanistically characterize GST-mediated metabolic pathways influencing drug disposition;
 - (3) virtual clinical trials were conducted to compare different dosing strategies, and a model-based optimal dosing regimen was recommended.

Method

- 636 busulfan whole-blood samples were prospectively obtained from 65 HSCT recipients (Figure 1).
- A semi-mechanistic population PK model was developed to describe busulfan metabolism in response to GSH depletion (Figure 2).
- Four body size metrics [WT, BSA, FFM, and NFM] were used to determine the most suitable body size descriptor, GST enzyme activity was tested as a continuous covariate on S_{GSH} (Equation 1).
- Virtual clinical trials were conducted to compare WT-based dosing strategy and AGE-base dosing strategy, and model-based optimal dosing regimen was recommended.

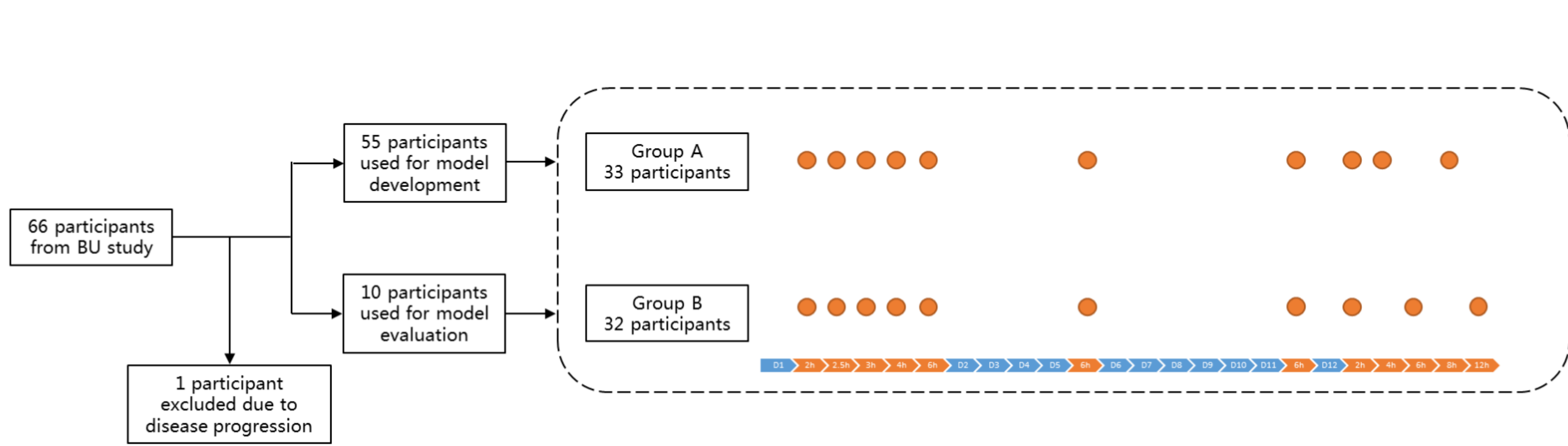
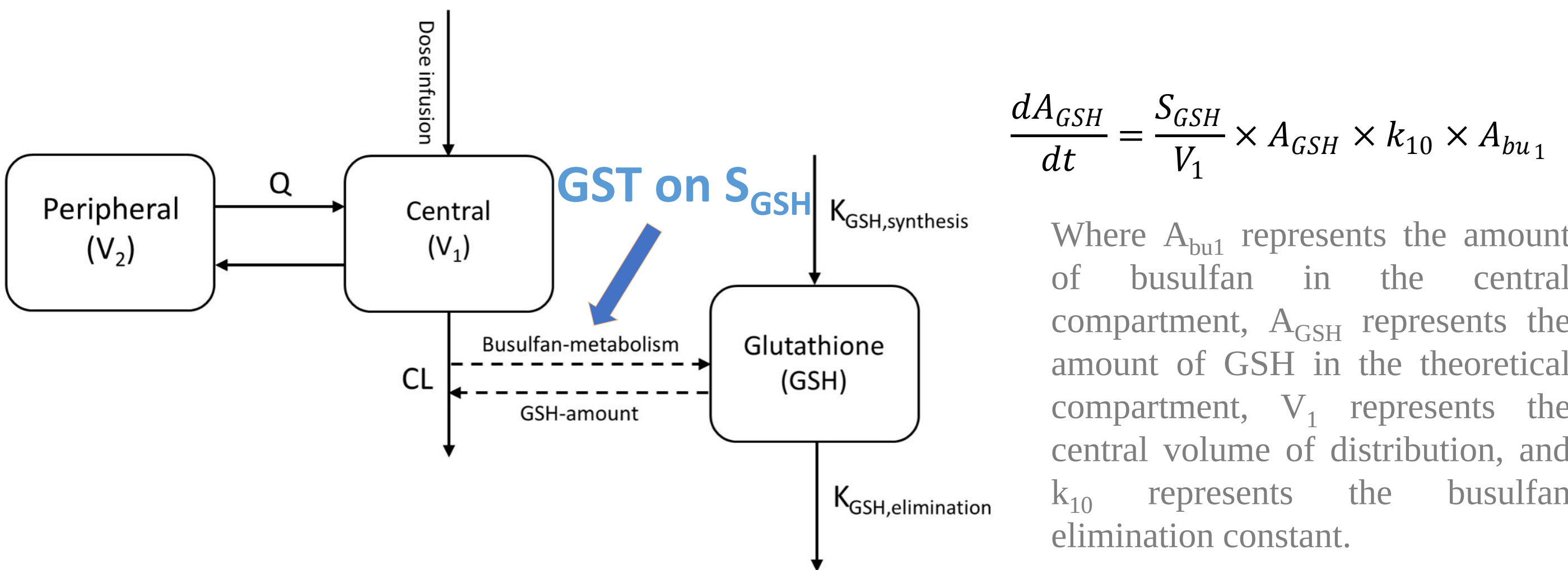


Figure 1. Diagram showing the prospective study dataset and trial design.



$$\frac{dA_{GSH}}{dt} = \frac{S_{GSH}}{V_1} \times A_{GSH} \times k_{10} \times A_{bu1}$$

Where A_{bu1} represents the amount of busulfan in the central compartment, A_{GSH} represents the amount of GSH in the theoretical compartment, V_1 represents the central volume of distribution, and k_{10} represents the busulfan elimination constant.

Figure 2. Busulfan semi-mechanistic population pharmacokinetic model structure.

Results

- The estimated mean clearance of busulfan was 9.57 L h^{-1} (RSE: 10.8%).
- Busulfan disposition was best described by including NFM allometrically and GST enzyme activity on S_{GSH} exponentially.
- GST significantly increased S_{GSH} by 40.6% across the observed activity range (Figure 3).
- Patients weighing 9-16 kg receiving WT-based regimens had increased risks of sinusoidal obstructive syndrome.
- Age-based dosing reduced toxicity, but required Bayesian adaptive dosing to ensure therapeutic exposure.

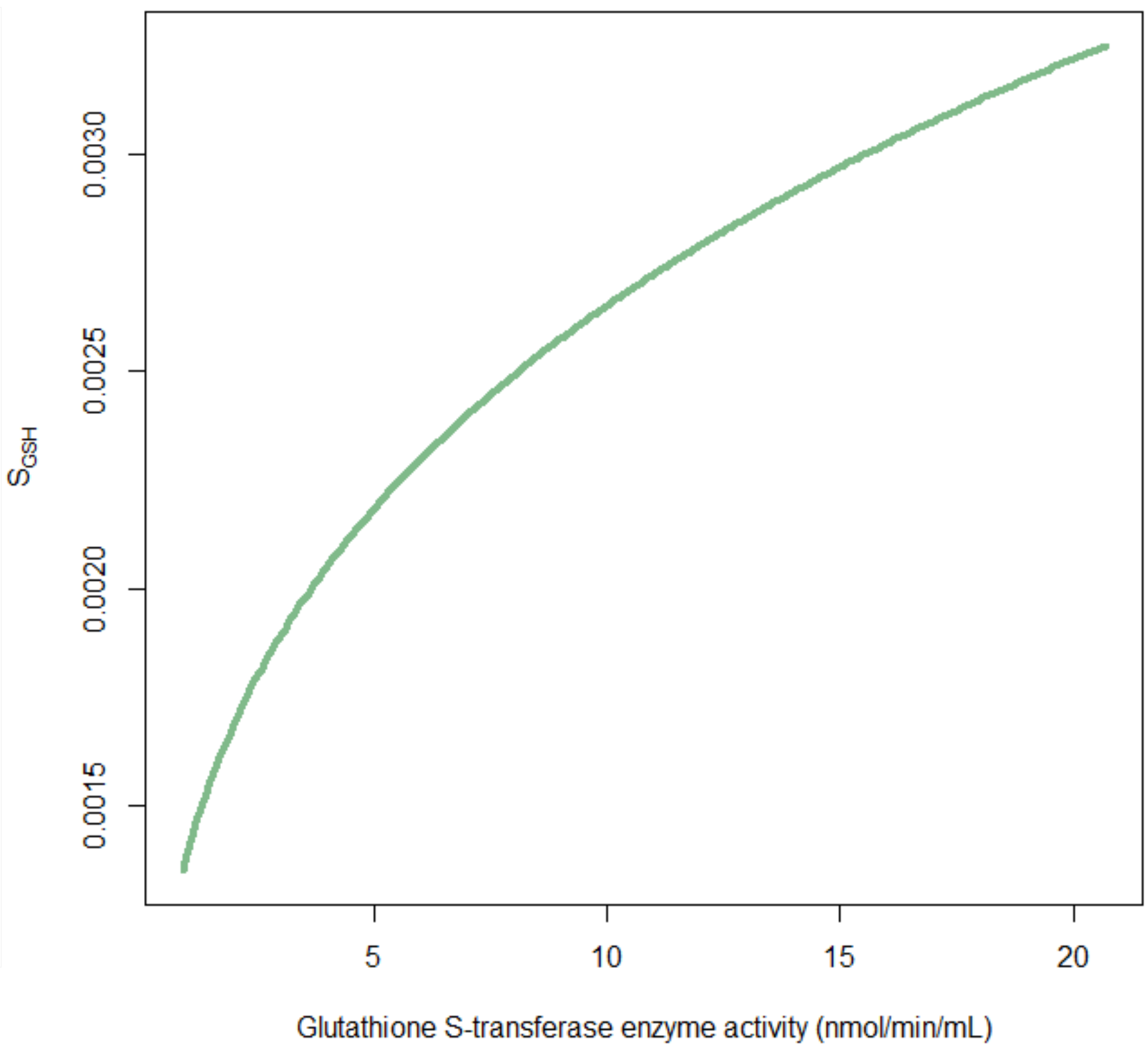


Figure 3. Fraction of the factor S_{GSH} versus GST enzyme activity.

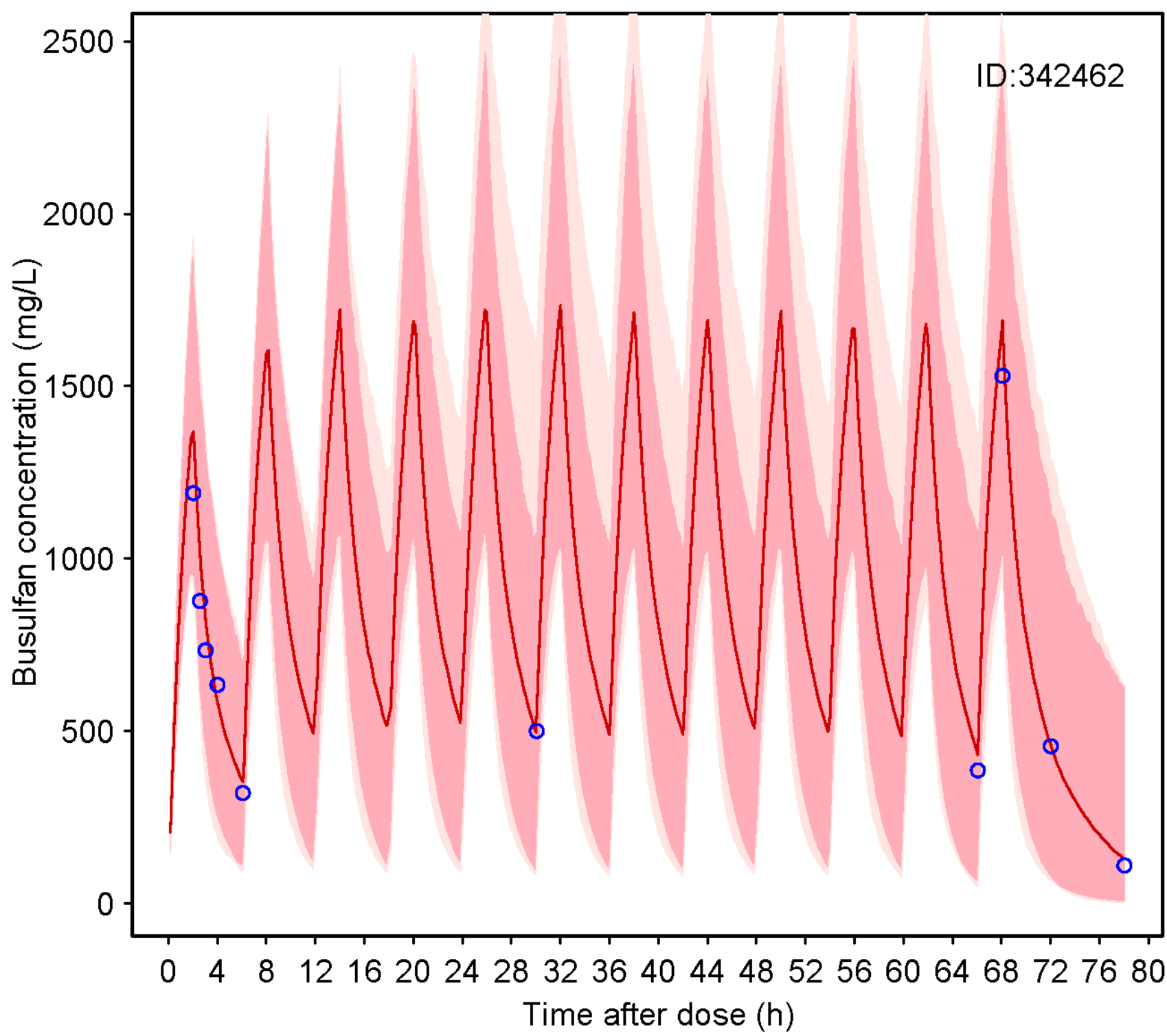


Figure 4. The predicted time course of busulfan concentrations in the individual involved in the evaluation dataset.