



# MECHANISTIC MODEL OF THE MYELOABLATIVE EFFECTS OF TREOSULFAN AND BUSULFAN IN PEDIATRIC PATIENTS UNDERGOING BONE MARROW TRANSPLANT

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## BACKGROUND

Haematopoietic Stem Cell Transplantation (**HSCT**) is a procedure where healthy donor cells are infused to a recipient with the intention of replacing the haematopoietic system in total or in part [1], being one of the most common treatments of a wide range of malignant and non-malignant disorders in children [2]. Prior to HSCT, the ablation of the host immune system is achieved by administering conditioning drugs and/or total body irradiation. There is currently a debate surrounding the relative merits of busulfan (Bu) and treosulfan (Treo), which are used to deplete myeloid cells prior to transplantation.

The **objectives** of the study where: (i) to build a **joint mechanistic PKPD model** of neutrophil count over time and establish a relationship with Bu and Treo plasma concentrations, (ii) **compare the myeloablative effects** of Bu and Treo in the shape of the PD effect curve and (iii) **identify patient characteristics** associated with inter-individual variability in myeloid cell dynamics

## METHODS

In this retrospective single-center study, blood concentrations of Bu were quantified in samples acquired from a routine drug therapeutic monitoring (TDM) program. The PK characteristics of Treo were obtained from a model developed as part of a previous study [manuscript under preparation]. **Daily neutrophil count data from the start of drug administration until 3 months post-transplant** are available from electronic health records. In total, **11,555 observations from 152 paediatric patients, 85 receiving Bu, and 67 receiving Treo** were included. Integrating all available data, a PK/PD model was built in NONMEM 7.3. The analysis was performed **simultaneously** for both drugs.

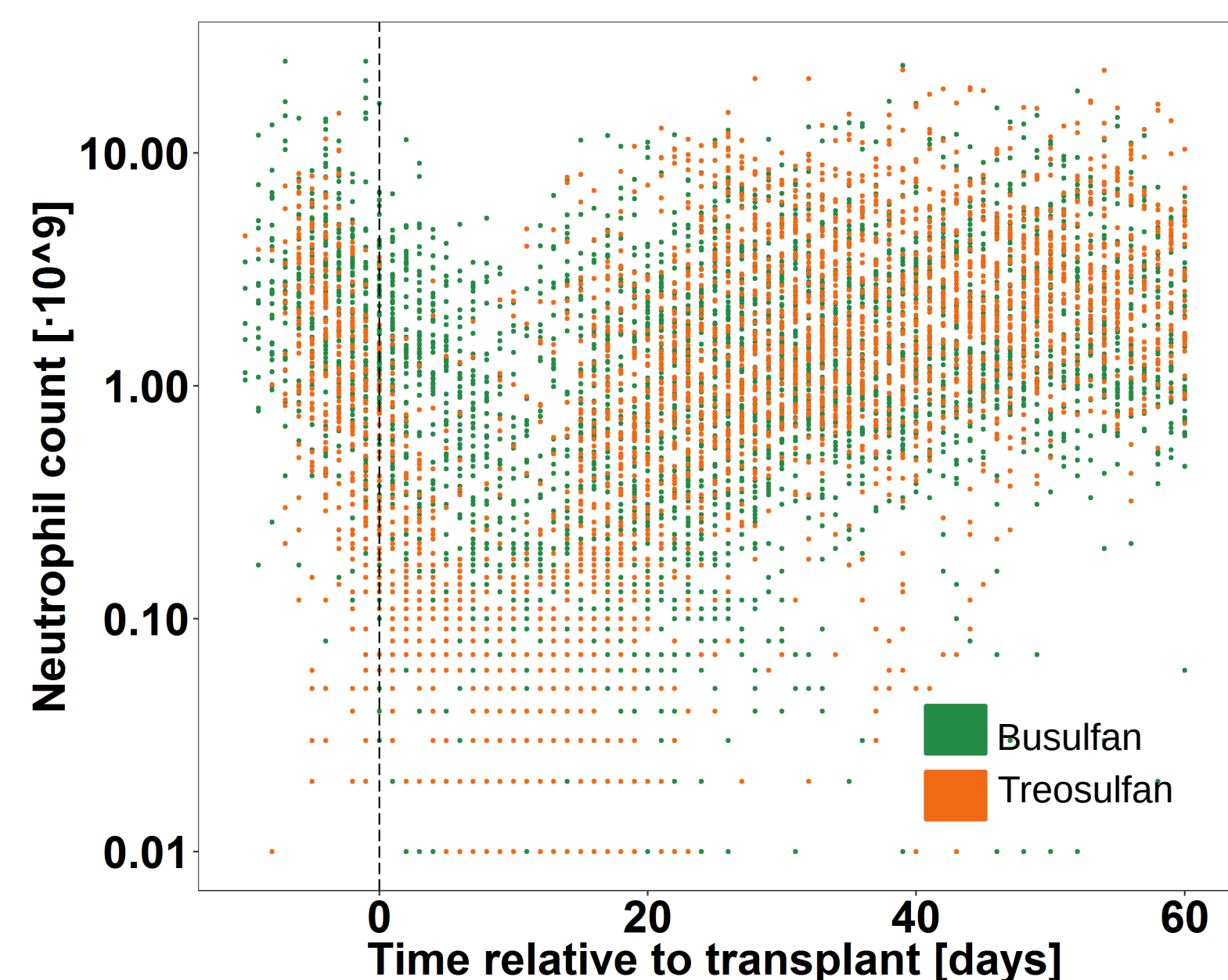


Figure I. Raw data of neutrophil count over time

Neutrophil count over time stratified on principal conditioning drug

Table I. Drug administration summary

|                          | Bu                              | Treo                                                                                     |
|--------------------------|---------------------------------|------------------------------------------------------------------------------------------|
| Typical dose             | 1 – 2 mg/kg                     | 10 g/m <sup>2</sup> (<3m)<br>12 g/m <sup>2</sup> (3 – 12m)<br>14 g/m <sup>2</sup> (>12m) |
| Route                    | IV                              | IV                                                                                       |
| Duration of the infusion | 2-3 h                           | 2-3 h                                                                                    |
| Frequency                | Twice daily or four times a day | Once daily                                                                               |
| Days given               | Over 4 days<br>(-7,-6,-5,-4)    | Over 3 days<br>(-7,-6,-5)                                                                |

Table II. Data summary

N=152. Paediatric patients treated either with Busulfan or Treosulfan and undergoing HSCT

|                                          | Busulfan (85)         | Treosulfan (67)       |
|------------------------------------------|-----------------------|-----------------------|
| Age (months) <sup>a</sup>                | 44.07 (7.93 – 227.14) | 20.54 (1.93 – 209.97) |
| Diagnosis <sup>b</sup>                   | Immunodeficiency      | 38 (44.70)            |
|                                          | Cancer                | 32 (37.65)            |
|                                          | Others                | 15 (17.65)            |
| Type of cells in transplant <sup>b</sup> | Bone marrow           | 46 (54.12)            |
|                                          | Peripheral blood      | 14 (16.47)            |
|                                          | Umbilical cord        | 12 (14.11)            |
|                                          | Unknown               | 13 (15.29)            |
| G-CSF <sup>b</sup>                       | No                    | 28 (32.94)            |
|                                          | Yes                   | 55 (64.71)            |
|                                          | Unknown               | 2 (2.35)              |

<sup>a</sup>Showing median (range); <sup>b</sup>Showing count (%)

## RESULTS

A joint mechanistic PKPD model of neutrophil count over time for Bu and Treo was successfully developed. The blood concentration vs time profile of Bu and Treo were described by a **two-compartment model** for both drugs. The drug effects were modelled using **EMAX model** for both of the drugs, which resulted significantly better ( $p < 0.001$ ) than a linear model. System parameters (steady-state neutrophil count after transplant (**CIRCO**), mean transit time (**MTT**), and feedback parameter (**GAMMA**)) were **consistent across drugs**. Inter-Individual variability (IIV) could be estimated for all of the parameters. Since patients may not enter the study at steady state and/or post-transplant steady-state a different homeostatic set point than baseline, a **different steady state for neutrophils was estimated after transplant and at baseline**. The main **differences** of patients receiving both drugs was the **baseline neutrophil value (3.87 for Bu patients vs 1.02 for Treo patients)**. The **myeloablative effects of Treo were steeper and produced earlier in time** than those of Bu. A covariate analysis showed that **type of cells in transplant** was a significant covariate associated to CIRCO, and the administration of **G-CSF on MTT**.

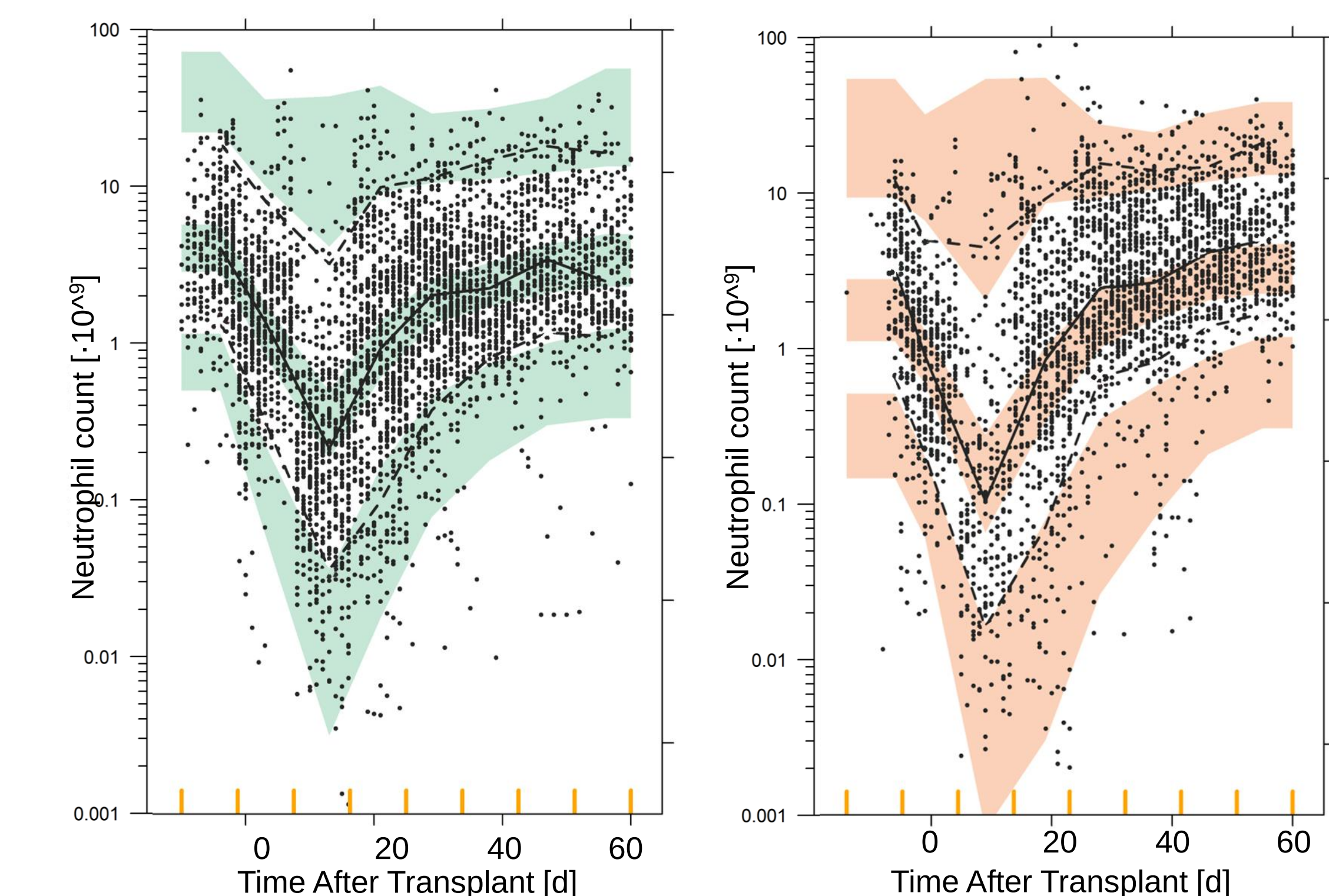


Figure III. Visual Predictive Checks

Stratified on drug: Busulfan (left), treosulfan (right)

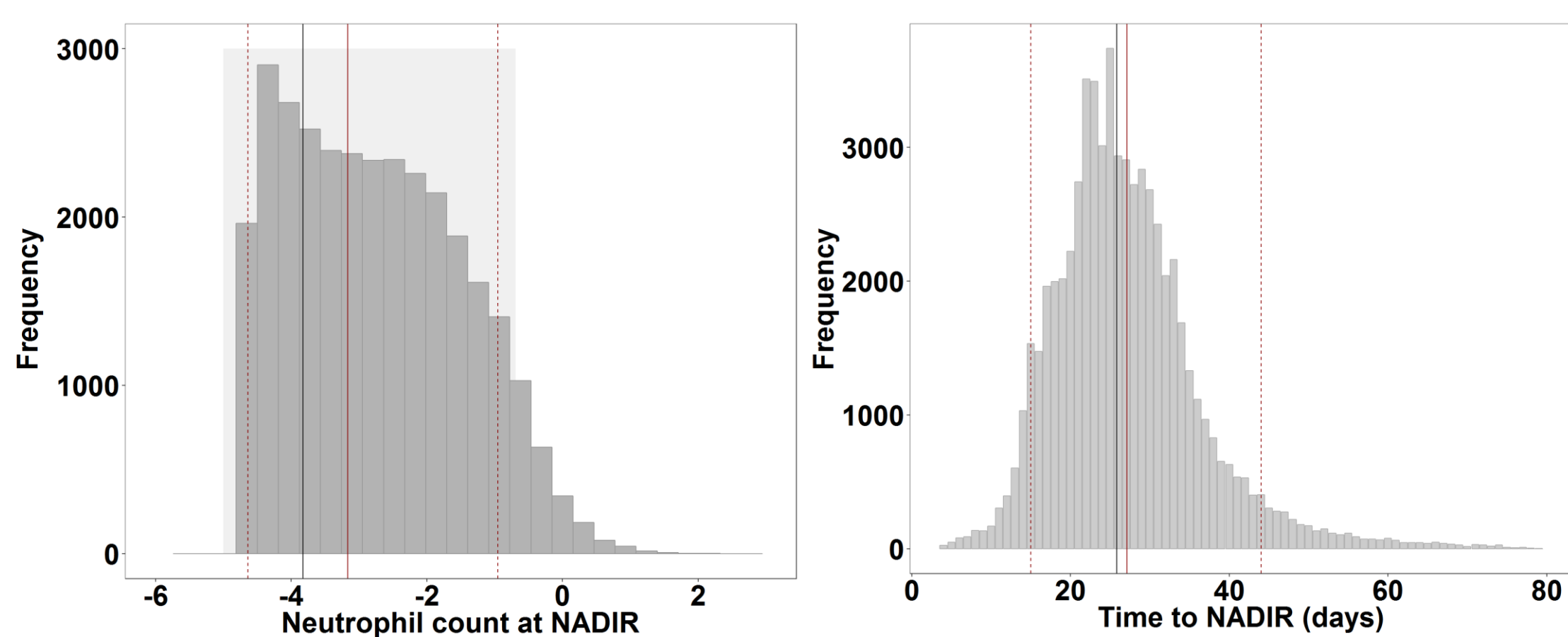


Figure V. Numerical Predictive Checks

Left: Neutrophil count at nadir, median observed (black solid line) vs predicted (red solid line) and the 95% confidence intervals of the predicted neutrophil count at nadir (dashed lines) all within the grade-4 neutropenia (shaded area); Right: time to nadir, median observed (black solid line) vs predicted (red solid line) and the 95% confidence intervals of the predicted neutrophil count at nadir (dashed lines)

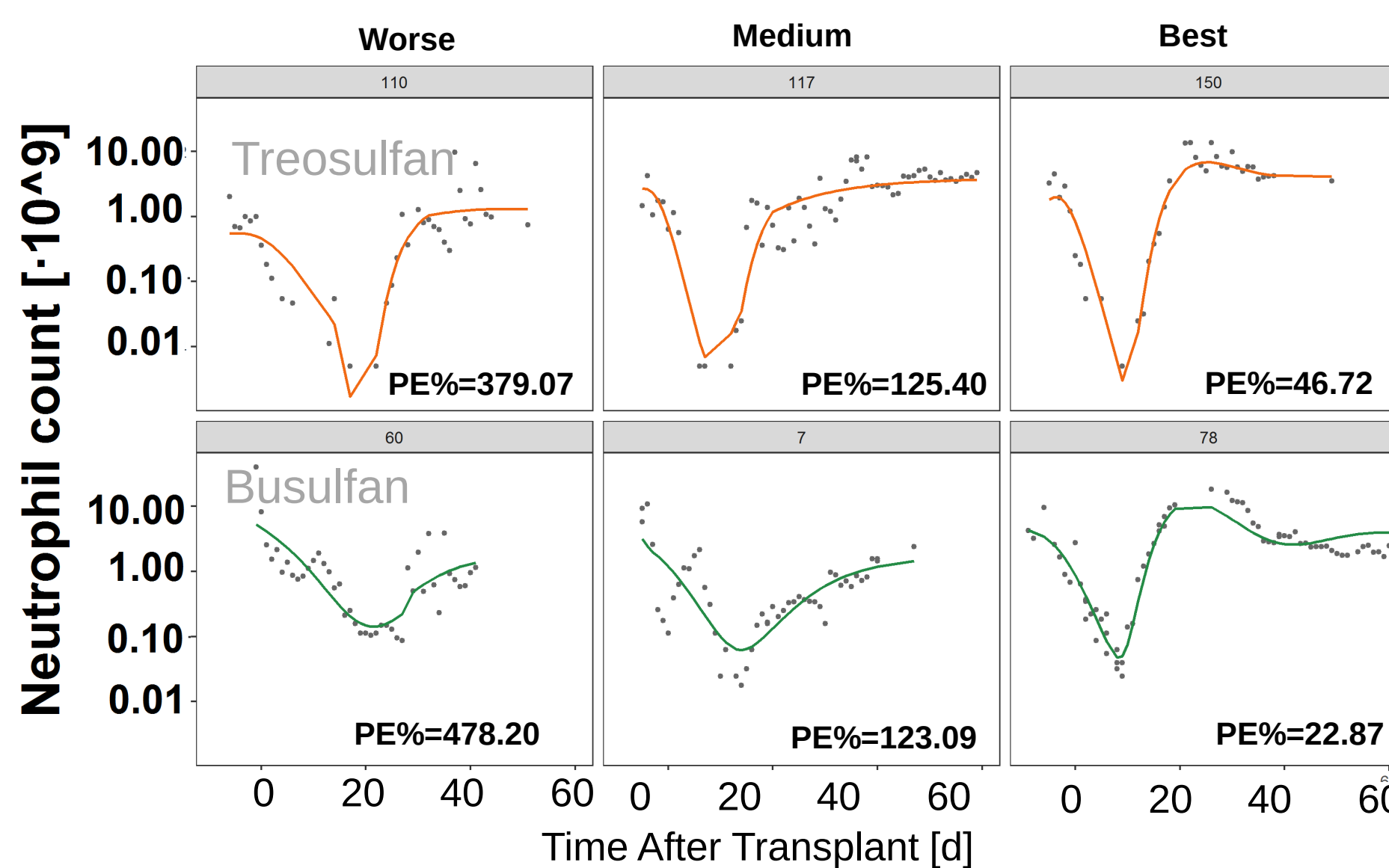


Figure IV. Individual Predictions

Selected individuals for both drugs with worse, medium and best fit based on prediction error

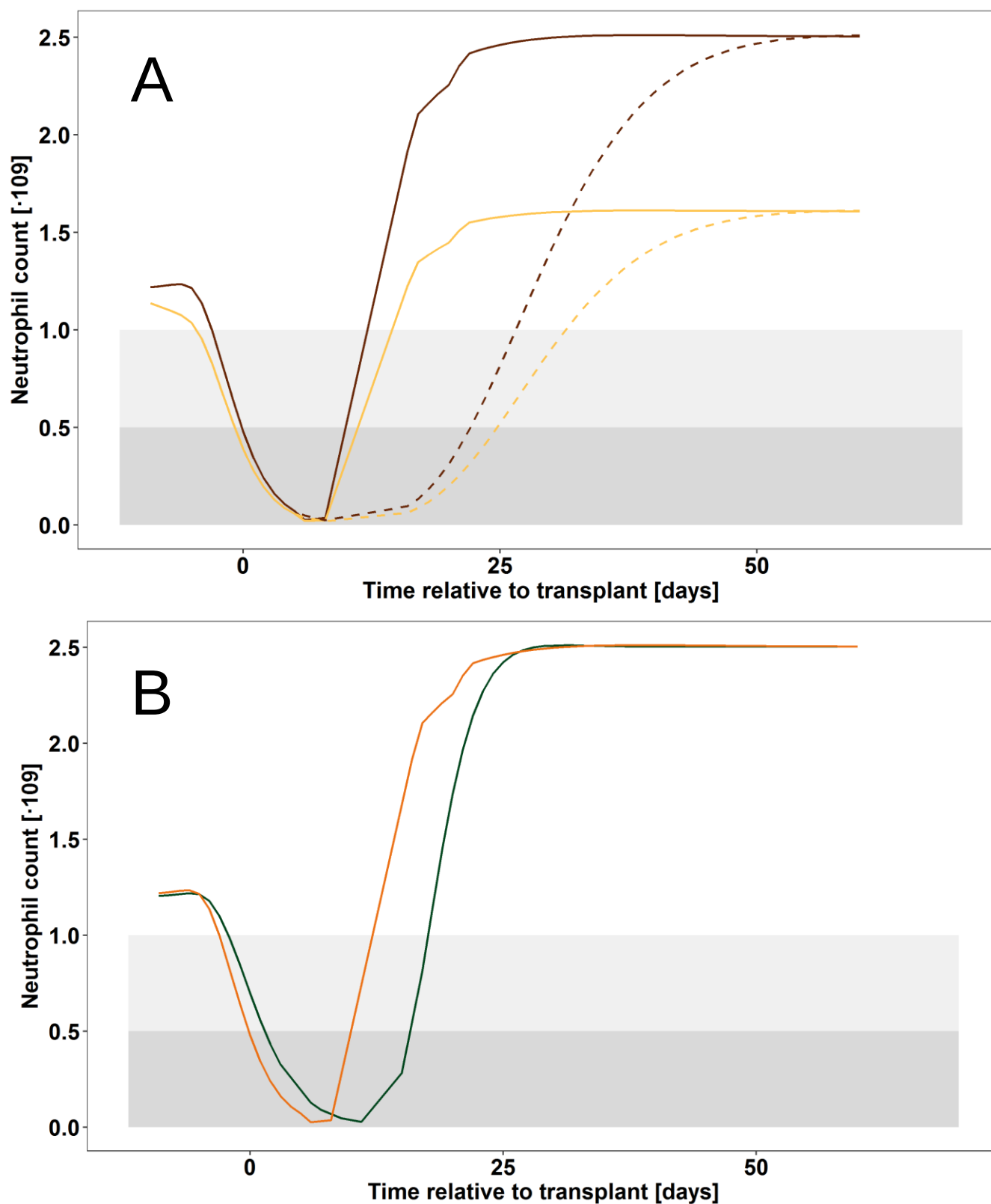


Figure VI.

### Model exploration

**A. Covariate exploration:** The effect of G-CSF (solid lines) shortening the recovery time can be seen. The darker vs the lighter lines highlight the differences observed between transplant with umbilical cord cells (light) recovering slower.

**B. Bu vs Treo:** In this simulation it can be seen how Treo effect (orange line) is steeper than Bu effect (green).

**Grey shaded areas correspond to neutropenia G3 and G4**

Blood concentration vs time profile of Bu and Treo were described by a two compartmental model for each of the drugs. Between-Occasion variability could be estimated in both cases. For Bu and Treo, Body weight was included as a covariate on CL and V and an age function was included on the CL.

Table III. Estimated pharmacokinetic model parameters

|                       | Bu          | Treo        |
|-----------------------|-------------|-------------|
| CL (L/h)              | 11.9 (15.7) | 17.3 (30.2) |
| Q <sub>12</sub> (L/h) | 0.634 (-)   | 7.29 (-)    |
| Total volume (L)      | 71.7 (4.2)  | 45.7 (39.4) |

Table IV. Estimated pharmacodynamic model parameters

| Parameters                               | Typical estimate (RSE%) |
|------------------------------------------|-------------------------|
| CIRCO (10 <sup>9</sup> /L)               | 1.29 (11.38)            |
| IIV CIRCO (CV%)                          | 73.70 (23.53)           |
| MTT (days)                               | 5.76 (4.69)             |
| IIV MTT (CV%)                            | 34.40 (23.14)           |
| GAMMA                                    | 0.089 (8.53)            |
| IIV GAMMA (CV%)                          | 81 (28.43)              |
| EMAX BU                                  | 0.67 (9.52)             |
| EMAX TREO                                | 2.25 (8.94)             |
| IIV EMAX (CV%)                           | 24.50 (22.45)           |
| C50 BU (nmol/L)                          | 0.5 (19.16)             |
| C50 TREO (nmol/L)                        | 0.04 (9.78)             |
| BASELINE BU (10 <sup>9</sup> /L)         | 4.09 (13.26)            |
| IIV BASELINE BU (CV%)                    | 124.10 (32.44)          |
| BASELINE TREO (10 <sup>9</sup> /L)       | 0.94 (19.10)            |
| IIV BASELINE TREO (CV%)                  | 164.60 (40.73)          |
| STEROID EFFECT                           | 1.03 (0.65)             |
| G-CSF EFFECT ON MTT (days)               | 2.15 (17.47)            |
| Transplant type: umbilical Cord on CIRCO | -0.32 (38.66)           |
| Residual error (10 <sup>9</sup> /L) add  | 0.67 (3.42)             |

## CONCLUSIONS & FUTURE PERSPECTIVES

Drug exposure to the main conditioning drugs given to paediatric patients receiving HSCT was successfully described by a two compartment model for each of the drugs, and was linked to neutrophil count dynamics over time through mixed-effects modelling, and thus, a joint mechanistic PKPD model was built. Further work will seek to link early neutrophil dynamics to long-term myeloid recovery measured through chimerism and survival analysis.

## References

- [1] Sureda A *et al.* Bone Marrow Transplant. 2015;50(8):1037-56
- [2] Bartelink IH *et al.* Biol. Blood Marrow Transplant. 2013;19(2):305 – 13
- [3] McCunne *et al.* Clin Cancer Res. 2014;20(3):754-63

