

# Population PK/PD modelling to evaluate the effect of siremadlin and disease features on platelet dynamics in haematological malignancies

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## Introduction

### Siremadlin: a MDM2 inhibitor

- Overexpression of murine double minute 2 (MDM2), a key negative regulator of the tumour suppressor protein p53, has been reported in a variety of cancers [1].
- Siremadlin, a MDM2 inhibitor, is being investigated as a new treatment for acute myeloid leukaemia (AML). Its effect on delayed thrombocytopenia in patients with solid tumours (SOL) and haematological malignancies (HEM) have been previously reported [2,3,4].

### Platelet dynamics in haematological malignancies

- In haematological malignancies, the underlying disease may impact the clinical manifestation of thrombocytopenia. The intertwining effects of drug and disease on platelet dynamics have not been fully evaluated.
- A population PK/PD model characterising the effect of siremadlin on platelets considering disease features in haematological malignancies can therefore be invaluable to support dosing decision.

## Objective

### Model-informed dose optimisation

- This work aims to develop a population PK/PD model characterising the effect of siremadlin on platelet dynamics in patients with haematological malignancies to support dose selection.

## Methods

### Model development

- Plasma drug concentrations and platelet data were obtained from a phase I study on patients (n=153) with p53 wild-type solid tumours and haematological malignancies following different dosing regimens [2]. The data were analysed using a population approach.
- Initially, a population PK (PopPK) model was developed using the PK data [1]. Individual PK predictions from the PopPK model were then used to drive drug effect in the platelet model. The model was adapted from Friberg et al (2002) [5] and different drug effect functions and disease features were evaluated.

### Simulation

- The selected model was built into a Shiny application [6,7] to allow interactive exploration of model properties. In the population simulation, platelet profiles from 1000 virtual subjects with SOL and HEM were generated to assess the risk of thrombocytopenia in these patients following siremadlin treatment from 5 to 40 mg QD for 5 days every 28 days for 6 cycles.

## Results

### The selected model describes the data

- The latest model incorporated two subpopulations (S and R) to represent myeloid cells in the bone marrow with different susceptibility to the drug (Figure 1, Table 1). Drug effect, driven by drug concentration in the central compartment, was described by potentiating apoptosis of the sensitive cells (S). Notably, the model was able to capture the observed change in drug effect over time (Figure 2).

Figure 1. A schematic illustration of the PK/PD model

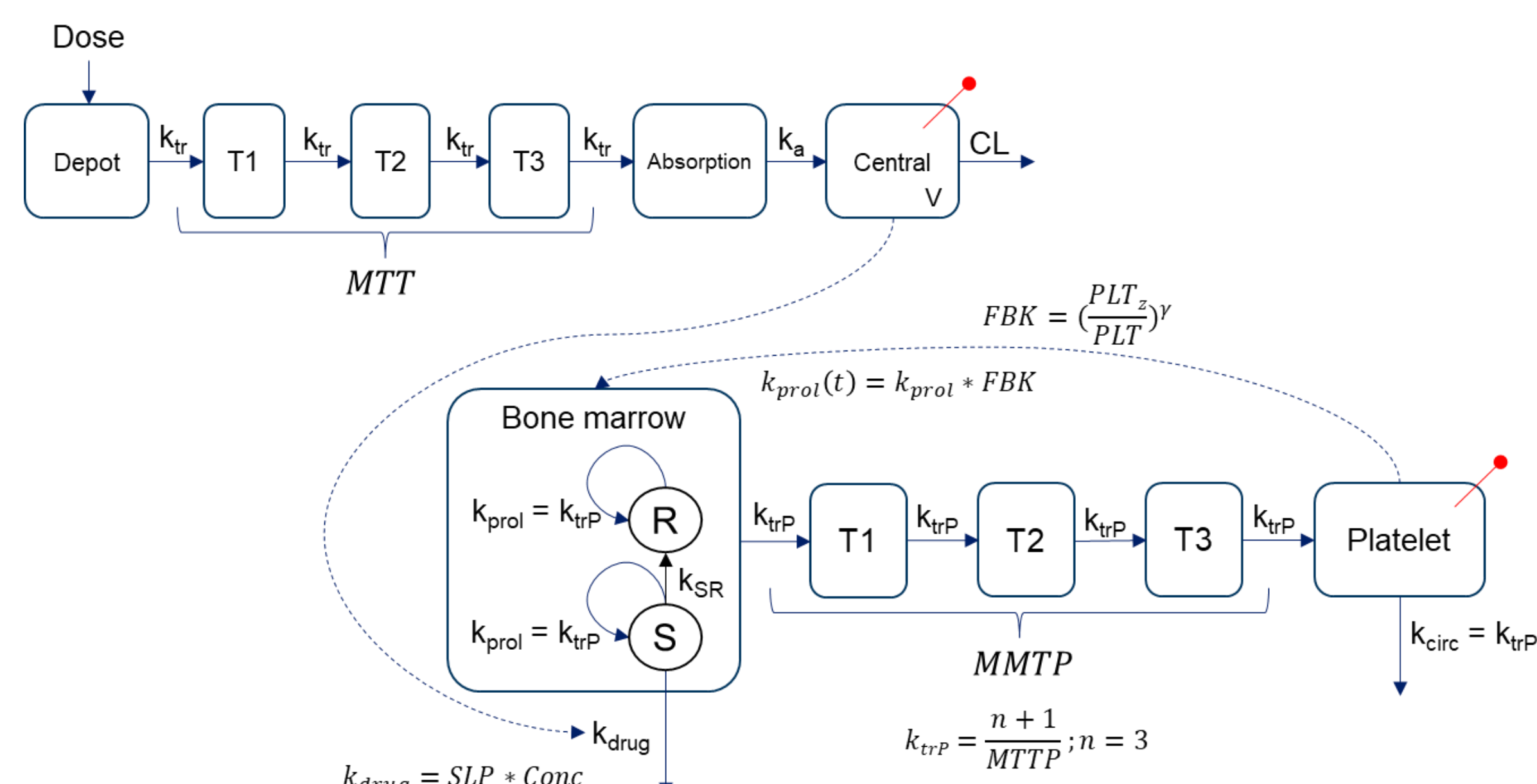
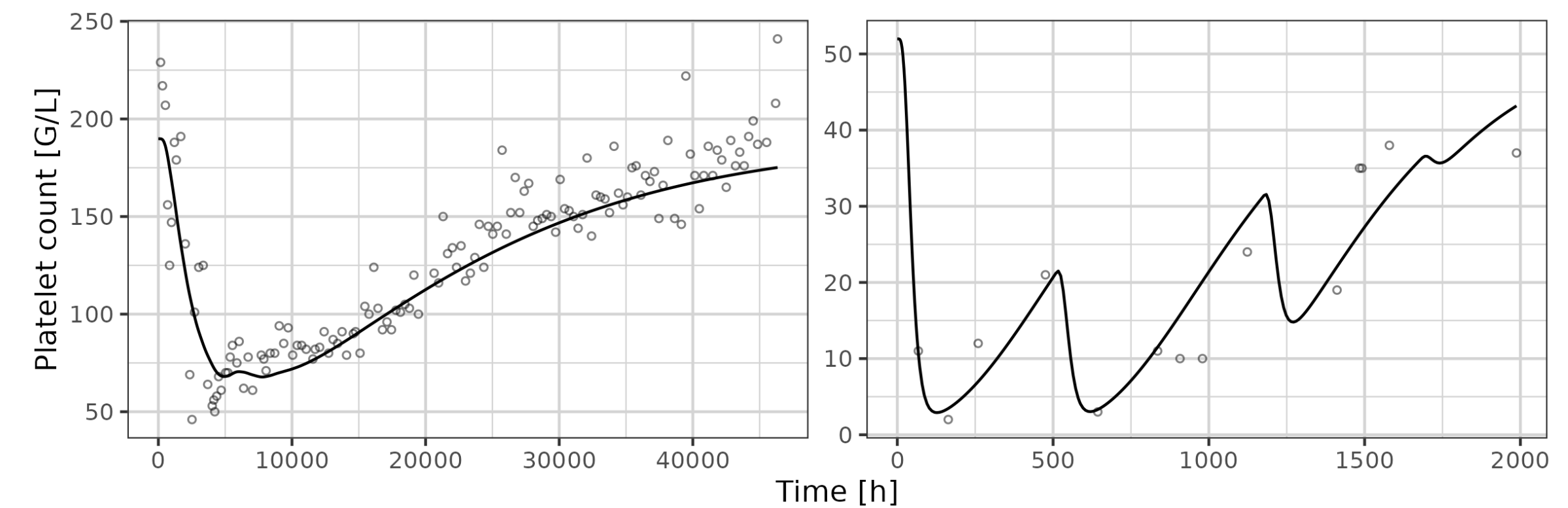


Table 1. Parameter estimates of the PK/PD model

Parameter	Unit	Description	Value (RSE%)	IIV (RSE%)
<b>PK</b>				
K <sub>tr</sub>	h <sup>-1</sup>	Transit rate constant	6.69 (8.31)	0.619 (9.82)
MTT	h	Mean transit time	0.793 (4.27)	0.322 (8.54)
k <sub>a</sub>	h <sup>-1</sup>	First order absorption rate constant	3.69 (19.5)	1.44 (10.1)
Cl/F	L/h	Apparent clearance	115 (2.58)	0.315 (6.45)
V/F	L	Apparent volume of distribution	5.9 (4.22)	0.558 (5.74)
beta_V_tBWKG	-	Body weight effect on V	0.883 (9.36)	--
corr_V_Cl	-	Correlation: V and CL	0.631 (9.0.9)	--
a1	ng/mL	Additive error	0.559 (13.7)	--
b1	-	Proportional error	0.337 (1.80)	--
<b>PD</b>				
PLTZ_HEM	G/L	Baseline platelet count in HEM	30.8 (10.5)	0.779 (9.11)
PLTZ_SOL	G/L	Baseline platelet count in SOL	229 (3.81)	0.348 (8.29)
MMT_HEM	h	Mean maturation time in HEM	142 (14.8)	1.00 (12.0)
MMT_SOL	h	Mean maturation time in SOL	844 (13.3)	0.66 (16.0)
gam	-	Sigmoidicity factor	0.113 (13.8)	1.07 (9.09)
SLP	-	Drug effect	0.00184 (11.2)	0.914 (9.56)
k <sub>SR</sub>	-	Transition rate constant from S to R	1.31E-05 (74.8)	4.8 (13.1)
b2	-	Proportional error	0.275 (1.73)	--

IIV: Interindividual variability (in SD scale); RSE: Relative standard error; HEM: Haematological malignancies; SOL: Solid tumours.

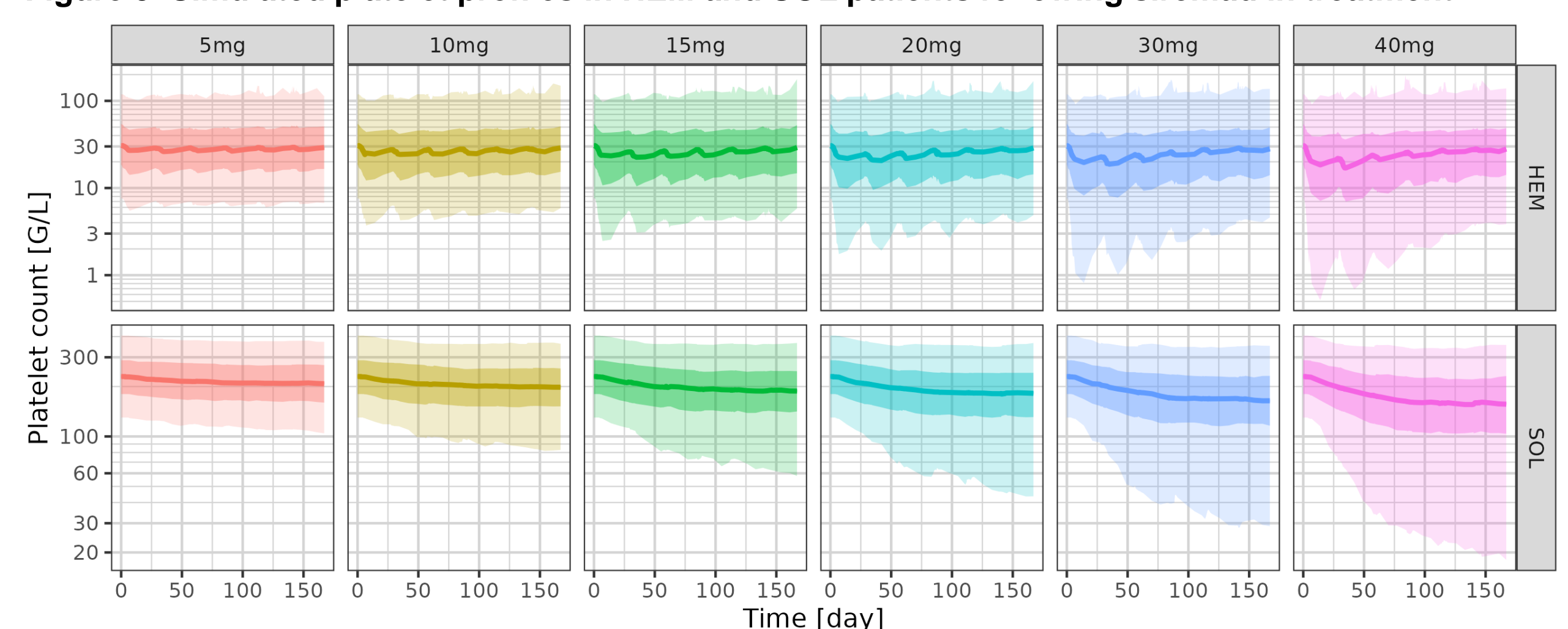
Figure 2. Examples of individual plots showing the observed (circles) and predicted (solid line) time-course of platelet levels in patients with solid tumour (left) and haematological malignancy (right)



### Simulation

- Based on the simulations, platelet dynamics in HEM patients is expected to be more responsive to drug treatment compared to SOL patients, showing more pronounced decline and recovery in response to the treatment cycles (Figure 3).
- The result is consistent with the pathophysiology of HEM, characterised by over-proliferation of myeloid cells in the bone marrow, leading to more rapid propagation of drug effect from the bone marrow to the observed platelets in the circulation.

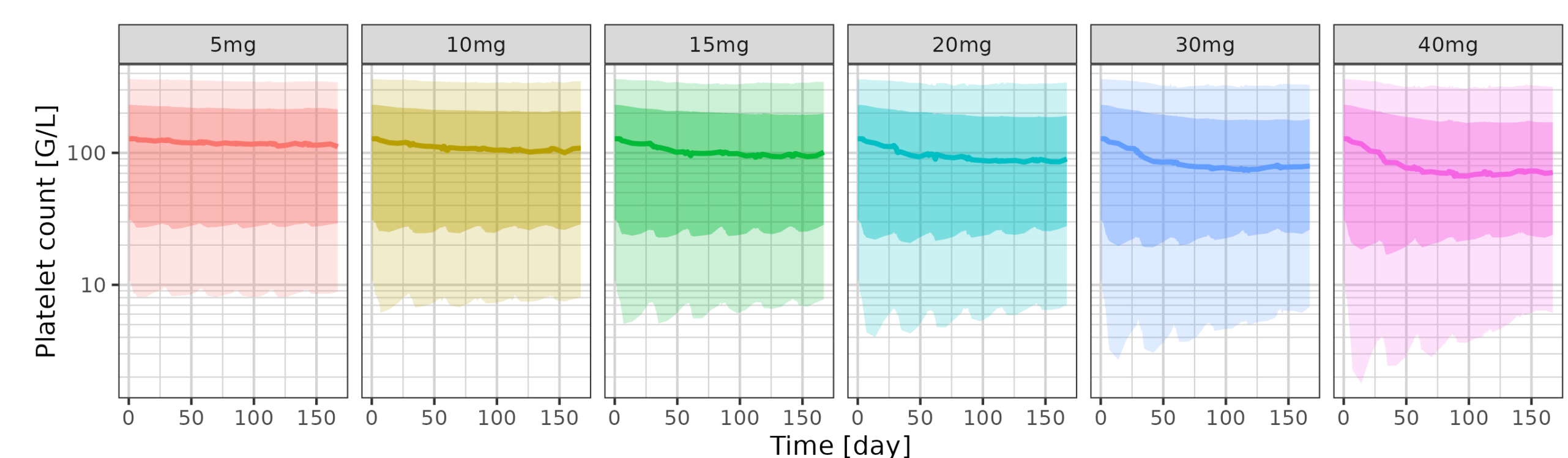
Figure 3. Simulated platelet profiles in HEM and SOL patients following siremadlin treatment



The results are summarised as the median (line) and the 50% and 90% prediction intervals (shaded).

- To evaluate the utility of the models in predicting platelet profiles in patients with disease characteristics potentially between HEM and SOL, such as patients following haematopoietic stem cell transplantation (post-HSCT) in complete remission without clinical thrombocytopenia, the averaged prediction of the HEM and SOL models was examined (Figure 4). The predicted probabilities of thrombocytopenia coincided with the observed values in our study (Table 2).

Figure 4. Simulated platelet profiles in post-HSCT patients following siremadlin treatment



The results are summarised as the median (line) and the 50% and 90% prediction intervals (shaded).

Table 2. Predicted probabilities of thrombocytopenia in post-HSCT patients

Dose [mg]	Gr ≥ 1 (<100 G/L)	Gr ≥ 2 (<75 G/L)	Gr ≥ 3 (<50 G/L)	Gr 4 (<25 G/L)
5	0.503	0.467	0.412	0.278
10	0.537	0.499	0.441	0.317
15	0.558	0.524	0.464	0.349
20	0.589	0.543	0.492	0.370
30	0.626	0.581	0.526	0.413
40	0.665	0.610	0.553	0.459

Gr: Grade.

## Conclusions

### Population PK/PD modelling for dose optimisation

- This work shows the invaluable role population PK/PD modelling can play in dose selection. In particular, the semi-mechanistic model helped investigate the intertwining effects of drug and disease on platelet dynamics in haematological malignancies to support dosing decision.
- The modelling approach is particularly relevant when drug and disease have concurrent effects, as it provides a means to evaluate their respective contributions, by incorporating prior knowledge of scientific relevance, to allow prediction of the observed outcome.

## References

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