

# Population PK Modelling of Treosulfan in Paediatric Allogeneic Transplant Patients



Venn Life Sciences

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medac

## Introduction

Treosulfan, a bifunctional alkylating prodrug, is currently being developed by medac GmbH as a component of conditioning treatment prior to haematopoietic stem cell transplantation (HSCT) in adults and children. An initial population PK model was developed to provide dose recommendations for the new medac-sponsored trials MC-FludT.16/NM (EudraCT-Number: 2013-005508-33) and MC-FludT.17/M (EudraCT-Number: 2013-003604-39) in paediatric patients from 1 month to 18 years of age. During interim analyses, this model was updated with new paediatric PK-data from trials MC-FludT.16/NM and MC-FludT.17/M to verify (in addition to clinical safety and efficacy data) the current dose recommendations or support a potential dose modification. In addition to the data covering different age groups, the model also needed to handle data that was measured with different bioanalytical methods.

## Objectives

- Build a population PK model that adequately characterizes Treosulfan pharmacokinetics in the paediatric target population
- Investigate which covariates influence Treosulfan exposure
- Draft model-based dose recommendations for paediatric patients
- Update the population PK model after new paediatric patients data becomes available

## Data

- Historical PK data: 7 previously conducted clinical trials: 93 PK profiles from adults & 23 children
- New PK data: 2 paediatric clinical trials: 17 & 59 children
- PK samples from new paediatric trials are measured with a new validated bioanalytical method

BSA Group	Hist1	Hist2	Hist3	Hist4	Hist5	Hist6	Hist7
≤ 0.5 m <sup>2</sup>	0	1	0	0	7	0	0
> 0.5 – 1.0 m <sup>2</sup>	2	0	0	0	6	0	0
> 1.0 m <sup>2</sup>	18	4	20	18	1	24	15
Total	20	5	20	18	14	24	15

BSA Group	MC-FludT.16/NM	MC-FludT.17/M
≤ 0.5 m <sup>2</sup>	4	7
> 0.5 – 1.0 m <sup>2</sup>	11	25
> 1.0 m <sup>2</sup>	2	27
Total	17	59

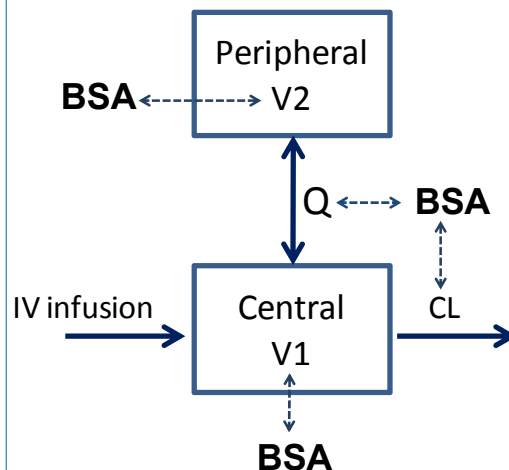
## Approach

- Identify covariate-PK model parameter relations that explain differences between adult and paediatric subpopulations
- Introduce additional SHIFT parameter in population PK model to explain differences between historical and new datasets caused by usage of different bioanalytical methods
- For modelling different subpopulations (adult vs. children) both a dichotomization approach and use of a Bayesian prior were evaluated

Both approaches gave similar results, ultimately the approach closest to the initial population PK model, the dichotomization approach, was chosen.

## PK model Treosulfan in Paediatric Patients

- The population PK model for Treosulfan consisted of two compartments with first-order distribution and elimination processes
- Covariate analysis revealed that body surface area (BSA) was the only relevant covariate for clearances and volumes of distribution (other covariates tested: age, weight, sex, creatinine clearance and use of diuretics)
- New paediatric patients data resulted in inclusion of a shift parameter (on model prediction parameter F in \$ERROR) allowing modelling of data from the new paediatric trials measured with a different validated bioanalytical method



### Implementation in NONMEM

- V1: Volume of distribution of central compartment [L]
- CL: Clearance [L/h]
- V2: Volume of distribution of peripheral compartment [L]
- Q: Inter-compartmental clearance [L/h]
- BSA: Body Surface Area [m<sup>2</sup>]
- SHIFT: Compensation for different bioanalytical methods

### Software

Non-linear mixed effects modelling was performed using NONMEM (v7.1.0, Method FOCE INTER) with gfortran (v4.5.0) together with PsN (v3.4.2) and R (v3.2.2).

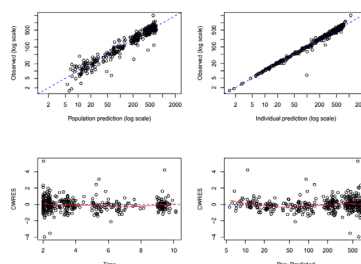
## Results Population PK Modelling of Treosulfan

Parameter Table

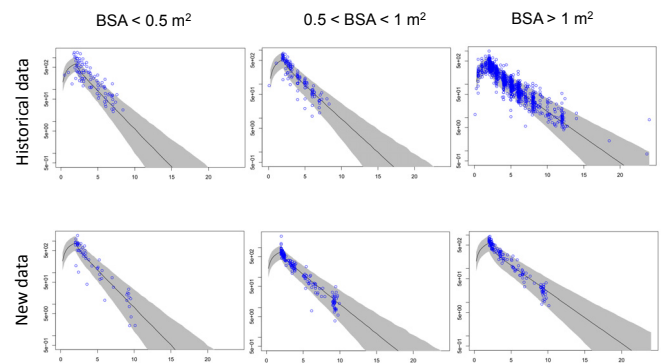
Parameter	Estimate	% SE
V1	19.0	11.6
CL	17.7	2.41
V2	20.3	7.24
Q	26.1	14.3
β(BSA,V1)	1.22	9.87
β(BSA,CL)	1.18	4.57
β(BSA,V2)	1.74	11.3
β(BSA,Q)	1.45	22.6
SHIFT	1.36	4.83
Ω(V1)	0.149	21.0
Ω(CL)	0.0616	16.2
Ω(V2)	0.0668	33.7
Ω(Q)	0.203	33.7
σ	0.0482	9.91

Final estimates of the fixed and random parameters: β denotes the allometric coefficient of the covariate for the model parameter, Ω denotes the variance of the inter-individual variability on the model parameter and σ denotes the variance of the residual error.

### Goodness-of-Fit Plots



### Visual Predictive Checks



Shaded areas indicate concentration regions in which 95% of the simulated concentration values are contained and circles display measured concentration values [ug/mL] over time [hr].

### Dose Recommendations

$$DOSE_{model}(g) = \frac{AUC_{target}(ug \cdot h/mL)}{1000} * CL * \frac{BSA^{BSA on CL}}{1.75}$$

BSA	Daily Treosulfan Dose
≤ 0.4 m <sup>2</sup>	10 g/m <sup>2</sup>
> 0.4 – 0.8 m <sup>2</sup>	12 g/m <sup>2</sup>
> 0.8 m <sup>2</sup>	14 g/m <sup>2</sup>

Based on the estimated population PK model, the functional relationship between clearance and BSA was derived. The dose resulting in a similar exposure as the effective exposure in adults was calculated for paediatric patients and translated into the simplified scheme above.

## Conclusion

The population PK model for Treosulfan is robust and does accurately predict exposure in adults and children. Inclusion of interim PK-data from newly included paediatric patients resulted in a significant update of the model. From a population PK modelling perspective, a slight refined dosing for some patients was recommended. Final dose recommendation will be provided after end of paediatric trials and final population PK modelling.