Population PK Modelling of Treosulfan in Paediatric Allogeneic Transplant Patients

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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 m²	0	1	0	0	7	0	0
> 0.5 – 1.0 m²	2	0	0	0	6	0	0
> 1.0 m²	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 m²	4	7
> 0.5 – 1.0 m²	11	25
> 1.0 m²	2	27
Total	17	59

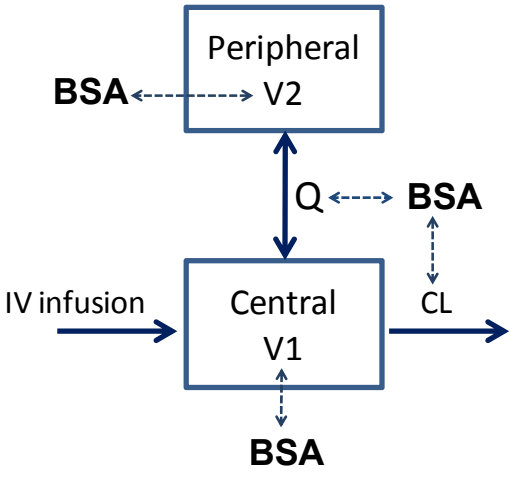
Approach

- 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 [m²]
- 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).

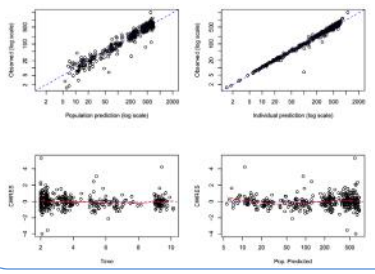
Results Population PK Modelling of Treosulfan

Parameter Table

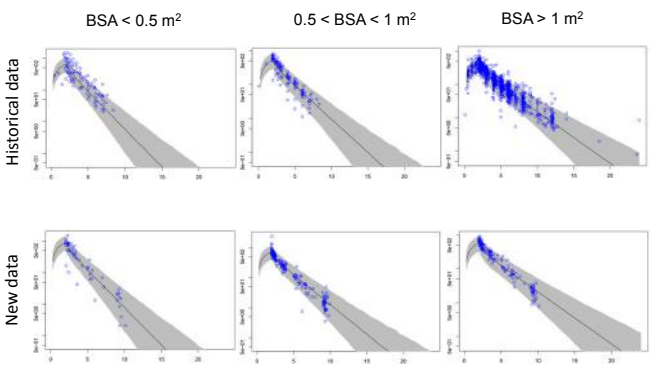
Parameter	Estimate	% SE
V1	19.0	11.6
CL	17.7	2.41
V2	20.3	7.24
Q	26.1	14.3
β(BSA,V1)	1.22	9.87
β(BSA,CL)	1.18	4.57
β(BSA,V2)	1.74	11.3
β(BSA,Q)	1.45	22.6
SHIFT	1.36	4.83
Ω(V1)	0.149	21.0
Ω(CL)	0.0616	16.2
Ω(V2)	0.0668	33.7
Ω(Q)	0.203	33.7
σ	0.0482	9.91

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

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

BSA	Daily Treosulfan Dose
≤ 0.4 m²	10 g/m²
> 0.4 – 0.8 m²	12 g/m²
> 0.8 m²	14 g/m²

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.

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