heparan sulfate (HS) in MPS type I, II and III. This and other relevant mech-anisms indicate TNF-alpha and IL-1 as most promising targets. Systematic analysis of the clinical pharmacology of all relevant candidates and several expert focus group meetings identified Anakinra, Adalimumab, Cladribine and Abatacept as top candidate's dependent on the individual clinical situation.

Conclusions These results provide the rational for individual treatment trials (ITTs) with the aim to evaluate immunomodulatory molecules, repurposed in MPS. Furthermore, they will – together with the results of the ITTs – be utilized for the development of a decision tool for the personalized treatment of unmet clinical needs in these patients.

20 PREDICTING TREATMENT RESPONSE TO VANCOMYCIN USING BACTERIAL DNA LOAD AS A PHARMACODYNAMIC MARKER IN PREMATURE AND VERY LOW BIRTH WEIGHT NEONATES: A POPULATION PKPD STUDY

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Introduction LOS has a high risk of morbidity and mortality among premature and VLBW newborns. Whilst positive blood cultures are the gold standard for the diagnosis and subsequent treatment of sepsis, this is time-consuming and results in suboptimal antibiotic treatment regimens. The objective of the present study was to investigate whether treatment response to vancomycin could be quantified using BDL based on RT-qPCR.

Methods VLWB and premature neonates with suspected late-onset sepsis were included in a single-centre, observational study. Serial blood samples were collected for measurement of BDL and vancomycin concentration (t=0, 1, 2, 4, 8, 12, 24 and 48h). BDL were measured with RT-qPCR, whereas vancomycin concentrations were measured using LC-MS. A population PKPD model was developed with NONMEM software.

Results 28 patients with LOS that were treated with vancomycin were included. A total of 94 vancomycin concentrations and 103 BDLs levels were available. A one- compartment model with PMA and serum creatinine was used to describe vancomycin PK. In 12 patients there was no decrease in BDL over time. Close inspection of the clinical records explained the underlying mechanism of the lack of effect. In 16 patients time profiles of BDL were described with a PD turnover model. The relationship between vancomycin concentration and the increase in first-order BDL elimination was described with a linear effect model. The slope of this model increased with rising PMA.

Conclusions BDLs determined through RT-qPCR could be predicted with the population PKPD model. Our findings demonstrate that using RT-qPCR, treatment response to vancomycin may be evaluated as early as 4 hours after treatment initiation, allowing early assessment of efficacy of vancomycin in LOS.

21 PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL TO SIMULATE MIDAZOLAM PHARMACOKINETICS IN A PAEDIATRIC US POPULATION

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There has been a lot of academic and regulatory interest regarding bridging clinical trials between different populations. The aims of this study were to:

1. Develop a PBPK model for the US paediatric population (USPP) incorporating demographic and CYP3A5 phenotype frequency of different ethnic groups (White, Hispanic, Black and Asian).
2. Apply the USPP to predict midazolam pharmacokinetics (PK) of a clinical study performed in the US.

Demographic information, height for age and weight for height relationships, and CYP3A5 phenotype frequencies were established for each US ethnic group using NHANES and literature data. Four separate US paediatric PBPK populations were defined within the Simcyp Simulator (v21).

Simulations of IV and oral midazolam PK were made in the USPP and a North European paediatric population (NECP) and compared with the clinical study. The reported trial design was matched as closely as possible and 400 subjects, 0.5 female, age 0.5 to 16y were run for each population.

For a 0.25mg/kg oral dose, the predicted AUC0-inf was 143±109 and 225±136 ng/ml.h and Cmax was 57.4 and 79.4ng/ml for the USPP and NECP, respectively. The observed AUC0-inf and Cmax was 137±86 ng/ml.h and 55.6ng/ml, respectively. The predicted AUC was 195, 115, 150 and 135 ng/ml.h for the White, Black, Hispanic and Asian USPP and Cmax was 72, 48, 58 and 54ng/ml, respectively.

Prediction of midazolam PK was improved by including the different ethnic groups for the USPP. However, significant differences can be observed between these groups for drugs where elimination changes due to phenotypic enzyme expression (e.g. CYP3A5) and it is important that clinical studies present this information.

22 FAVIPIRAVIR PHARMACOKINETICS IN IMMUNOCOMPROMISED INFANTS AND CHILDREN WITH CHRONIC RNA VIRAL INFECTIONS

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Introduction Favipiravir selectively inhibits RNA polymerase responsible for single-stranded viral replication. It is licensed for treating influenza and repurposed to treat other diseases such as Ebola and COVID-19. It is metabolised by hepatic