Population Pharmacokinetics, Enterohepatic Recirculation and Gender Differences of Roxithromycin in Humans
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Purpose
Macrolide antibiotics undergo extensive enterohepatic recirculation (EHC) which affects their pharmacokinetics (PK). However, we are not aware of PK models to describe EHC for macrolides or for any other antibiotic. The aim of this study was to characterize the population PK and EHC of roxithromycin, a macrolide antibiotic, in humans over a range of doses and to assess potential gender differences.

Methods
We characterized the plasma concentration time profiles for roxithromycin given as a single oral dose of 50 mg (oral suspension), 150 or 300 mg (film-coated tablets) in healthy volunteers (in total: n=112; 55 females and 57 males). Roxithromycin plasma concentrations (n=2312 in total) were determined via a validated LC-MS/MS assay and simultaneously modeled using a population approach in the S-ADAPT software via an importance sampling algorithm.

Results
Compared to the 50 mg oral suspension, the relative bioavailability was 85% for the 150 mg tablet and 65% for the 300 mg tablet. After a short lag-time, the absorption kinetics was described by a Michaelis-Menten dissolution followed by a first-order absorption process. The final model contained compartments for undissolved drug, gut, liver, hepatocytes, and bile, as well as the central and peripheral compartment. We implemented a bile-flow turnover model which described a pulsatile release of drug from the bile into the gut compartment. The model provided reasonably precise and unbiased curve fits (correlation coefficient: 0.997 for observed vs. individual fitted concentrations and 0.78 for observed vs. population fitted concentrations). Transfer of drug from the hepatocyte into the bile compartment was described by Michaelis-Menten kinetics. Females had a 17% smaller maximum transfer rate compared to males (p<0.05) leading to more extensive metabolism in females. This explained why females had a higher apparent total clearance compared to males (i.e. 27% higher when clearance was expressed as L/h and 49% higher when it was expressed as L/h/kg) based on non-compartmental methods.

Conclusion
The developed model for EHC excellently described the time-course of roxithromycin plasma concentrations. Bioavailability was smaller for the higher dose film-coated tablets compared to the low-dose suspension. The significantly higher clearances in females compared to males were well explained by a slower transfer of drug from hepatocytes into bile in agreement with previous literature reports on gender difference in P-glycoprotein.