Non-linear mixed effects modelling of limited data on a candidate drug based on prior knowledge of a frontrunner

C. Ahlström*[,1], LO. Larsson[1], B. Rosengren[2] and E. Lundborg[1]

[1] CVGI iMed DMPK, AstraZeneca R&D Mölndal, Pepparedsleden 1, SE-431 83 Mölndal, Sweden
[2] CVGI iMed Bioscience, AstraZeneca R&D Mölndal

Aim: The primary aim of this work was to explore if pharmacodynamic parameters for a candidate drug could be estimated using very limited *in vivo* data, based on information about baseline and system parameters previously generated in a more extensive *in vivo* study with a frontrunner and a reference compound.

Methods: The candidate drug, an enzyme inhibitor, was administered orally (n=3) and iv (n=3) to cynomolgus monkey. In a previous, more extensive study the frontrunner and the reference compound were orally administered to cynomolgus monkeys in three dose groups per compound (n=6) with a vehicle group (n=12) included. In both studies, the drug concentration and the response, *ex vivo* enzyme inhibition, were measured in plasma. A non-linear mixed effects model describing the baseline behaviour as observed in the vehicle group, and the drug-induced reduction of the response, were simultaneously fitted to all data for the three compounds. The varying baseline was modelled as a "stress" function describing a transient increase in the response above the predose value which then returns towards the predose value as the "stress" declines. The onset of the drug effect was rapid and the inhibitory drug function therefore acts directly on the formation of response whereas the stress affects the response with a delay that was captured by two transit compartments. The baseline behaviour observed in the vehicle treated animals in the extended frontrunner study was assumed to be similar for the candidate drug.

Results: The model-predicted and experimental data were consistent for all three compounds and vehicle and no trends in goodness of fit analysis could be observed. The drug-specific parameters (IC_{50}, I_{max} and γ) of the candidate drug could be estimated with high precision, based on the assumption of similar baseline behaviour in the candidate study as in the frontrunner study.

Discussion: The simultaneous analysis of all available data facilitated the estimation of the drug-specific parameters (IC_{50}, I_{max} and γ) for the candidate drug, despite the limited number of animals and doses. Using this approach, and assuming that the system parameters (k_{in} and k_{out}) and "stress" related parameters were similar to that described in the frontrunner study (including interindividual variability) a more extensive study with the candidate drug was not performed. This resulted in significant cost avoidance and reduced animal use.