Background and Objectives

- A previously developed inhalation pharmacokinetic (PK) model described the PK of an inhaled olodaterol solution, administered utilizing a Respimat®, with three parallel absorption processes, s. Tab. 1 [1].
- A computational fluid dynamics (CFD) model (Fig. 1) predicted a pronounced peripheral deposition of another drug (tiotropium) inhalating a Respimat®.
- The inhalation PK model (Tab. 1) indicated a more central deposition of the drug when associating the slow absorption process to the central airways and the fast absorption process to the alveoli.

Deposition and Conclusions

- The terminal half-life was 82.4 h compared to 14.0 h of the previously developed three CMT disposition model (no urine data).

Results

1) Final IV model:
- Four compartment (CMT) systemic disposition model with simultaneous clearance processes from the central CMT (renal) and non-renal (CL_NR) (Tab. 3, Fig. 2-3).

Methods

Data
- Three trials in healthy volunteers (HV): IV (urine, plasma data), inhalation (plasma data) (Tab. 2).

Model Development

1) Compared to the previous approach [1], additional urine data was used for IV PK model development to more accurate characterisation of the terminal phase of the plasma concentration-time profile.
- Inhalation: Structural parameter estimates and interindividual (IIIV) parameter estimates of the IV model were fixed and different absorption models were investigated: i) single absorption process; ii) two to four parallel absorption processes iii) transit absorption model.
- Model selection was based on several criteria, such as goodness-of-fit (GOF) plots, precision of parameter estimates, and the changes in OFV.

Discussion and Conclusions

The modelling results demonstrated that three parallel pulmonary absorption processes are necessary to accurately describe the PK of inhaled olodaterol. Furthermore, the benefit of including urine data after IV dosing to better characterise the terminal half-life was demonstrated.

The results obtained support the hypothesis of a slow systemic distribution process that is relevant after IV dosing of olodaterol and not specific for olodaterol inhalation. A likely process due to drug characteristics (basic character of olodaterol [3]) and lung characteristics (high amount of lysosomes [4]) is lysosomal trapping. This aspect may also explain that a high fraction is slowly absorbed if the drug is directly administered to the lysosome rich lung, compared to the low relevance of the slow distribution process after IV dosing.

Assuming lysosomal trapping, the three different fractions absorbed might be interpreted as absorption to the plasma from only two areas of the lung. Slow absorption (after lysosomal trapping) in the conducting airways, intermediate absorption might represent indirect (after lysosomal trapping) absorption to the alveolar space, and fast absorption might represent direct absorption in the alveolar space (Fig. 7).

Associating two absorption processes instead of only the fast process to the alveolar space might also explain most of the discrepancy between predicted deposition patterns (CFD) and the estimated absorbed fractions (PK model).

Additional in vitro / ex vivo assays should be performed to evaluate this hypothesis and to further increase the understanding about possible PK characteristics after drug inhalation.

References