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Paper Poster Session
New treatment options for mycobacterial infections

Predicting the human dose for a novel LeuRS inhibitor, GSK070, for the treatment of tuberculosis

Sabrinia Crouch*[1], Fatima Ortega[1], Ruben Gomez[2], Laura Alameda[1], Santiago Ferrer[1], David Barros[1], M. R. K. Alley[3], Xianfeng LI[3]

[1]*Glaxosmithkline, Tres Cantos, Spain*

[2]*Glaxosmithkline, Stevenage, United Kingdom*

[3]*Anacor Pharmaceuticals, Palo Alto, United States*

Background: GSK070 is a selective inhibitor of mycobacterial leucyl t-RNA synthetase (LeuRS) with a novel MoA for the treatment of tuberculosis (TB). After achieving positive results in the murine chronic assay for TB, preliminary human dose projections were performed to aid in clinical progression.

Material/methods: Following in-vivo intravenous dosing in the preclincal species (mouse, rat and dog), the human pharmacokientic parameters of clearance and volume of distribution were derived using in-vitro/in-vivo extrapolation (IVIVE), allometry and simple PBPK modeling (CloePK Software, Cyprotex). A target efficacious exposure in human was determined using the dose (1.3mg/kg) at the maximum effect (EDmax) level observed in the therapeutic efficacy murine chronic assay. Human dose estimations were calculated using a target efficacious exposure of 3481ng*hr/ml which corresponds to the efficacious $AUC_{0\text{-}24h}$ at steady state measured in whole blood.

Results: With the PK parameters from allometry and PBPK multiple scenarios were designed for the human dose projection in order to achieve the efficacious target exposure (whole blood and unbound). Predicted Vdss was moderate in all cases, while clearance was variable (low to moderate) depending on the modelling strategy used. All methodologies projected a low human dose (<200mg) to achieve the therapeutic target in whole blood (3481ng*h/mL).

Conclusions: GSK070, a novel clinical candidate for the treatment of tuberculosis, provides favorable predicted human pharmacokinetic parameters with a low projected human dose.

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals.