P0142
Paper Poster Session
New treatment options for mycobacterial infections

Early safety of GSK070 - a new antitubercular agent

Elena Jimenez*[1], Stephanie Gresham[2], Sharon Robinson[2], Rachael Lincoln[2], Samantha Turner[2], Paul Bushdid[3], Xianfeng LI[4], M. R. K. Alley[4], David Barros[5]

[1]*Gsk, I+d, Sl, Ddw, Tres Cantos, Spain*

[2]*Gsk, Ware, United Kingdom*

[3]*Gsk, Philadelphia, United States*

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

[5]*Glaxosmithkline (Gsk), Tres Cantos Medicines Development Campus, Tres Cantos, Madrid, Spain*

Background: Oxaborols series are inhibitors of Leucyl t-RNA synthetase and selective anti-tubercular agents with a remarkable activity against a selection of DS-TB, MDR-TB and XDR-TB clinical isolates. This series exhibits excellent physicochemical properties and has demonstrated *in vivo* antitubercuular activity.

Material/methods: GSK070 has been evaluated to discharge the following toxicology risks: general, genetic, reproductive, cardiovascular, and safety pharmacology. It has been tested through eXP cross functional panel of human receptors, enzymes and transporters. Ames test and MLA was performed to evaluate genetic toxicology. Inhibition of cardiac ion channels, hERG, Cav1.2 and Nav1.2 were tested by Patch clamp platforms and ex vivo rabbit ventricular wedge was assessed to evaluate cardiovascular liability and a 7 day repeat dose toxicity study in male rats.

Results: GSK070 inhibited hERG and CaV1.2 receptors with IC_{50} of 10uM for both channels. In a subsequent rabbit ventricular wedge study there were no changes in any of the parameters measured, and from the cardiovascular rat study there is a >60-fold cover to the estimated free C_{max} at a clinical dose of 33mg/day from the 10mg/kg/day dose at which no effects were observed. GSK070 was tested in a bacterial mutation screening assay (Ames test) +/- S9 fraction and was not mutagenic in any of the strains investigated and it was also negative in the MLA in the presence and absence of S9. GSK070 was tested in the rat whole embryo culture (WEC) in vitro test system and there is a minimum of an 18-fold margin from the NOEL at 10uM in the WEC and a 151-fold margin at 100mg/kg/day in a rat 7 day study.

Conclusions: based on an integrated assessment of all the safety findings (general tox, safety pharmacology, genotoxicity, reproductive toxicity) and taking into consideration that there are biomarkers and/or monitoring available for the toxicities observed *in vivo*. The preliminary toxicological profile (*in vitro* and *in vivo*) indicates an acceptable therapeutic window and the risk-benefit profile is such that there is no data that would preclude the progresion of this molecule.

All animal studies were ethically reviewed and carried out in accordance with European Directive 86/609/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals