Predicting the human dose for a novel leucyl-tRNA synthetase inhibitor, GSK070, for the treatment of tuberculosis

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Creation Date: 03/03/2016

Introduction

GSK070 is an 3-aminomethylbenzoxaborole that is a selective inhibitor of mycobacterial leucyl tRNA synthetase (LeuRS) with a novel MoA for the treatment of tuberculosis (TB). Leucyl-tRNA synthetase plays an essential role in cellular translation and is an attractive drug target for antimicrobial development. GSK070 was designed to utilize the OBORT mechanism, which inhibits LeuRS by trapping the 3´-end of $tRNA^{Leu}$ in the editing site[1].

Once positive results in the murine chronic assay for TB were achieved, preliminary human dose projections were performed to aid in clinical progression of the asset. In order to estimate the efficacious dose in humans, we assumed that systemic exposure (measured as Area Under the Curve, AUC) in blood that induces the maximum bacterial killing (ED_{max}) is a reasonable estimate of the PK driver for efficacy in mouse models. This assumption is supported by the fact that the efficacy of most antituberculars in mice is driven by AUC.[2-4]

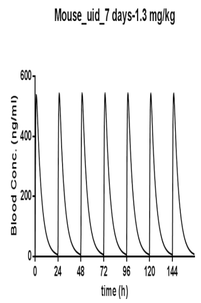
For the human dose projection, the corresponding human pharmacokinetic parameters were calculated based on *in vitro* and *in vivo* data from preclinical species using different approaches (allometry, PBPK models).

Pharmacodynamic estimates of exposure

- In order to obtain the PK parameter estimates for the multi-day dosing, the PK parameters from the mono-compartmental modelling were derived following a single oral dose administration of 1 mg/kg to C57BLJ6 mice.

- The target exposure to be achieved in human was calculated based on the dose at the maximum effect (ED_{max}) in mouse observed from the therapeutic efficacy murine chronic assay: 1.3 mg/kg (IC_{95} 0.7-3.4mg/kg).

- With the corresponding PK parameters, a simulation was performed for administration of 1.3 mg/kg to C57BLJ6 mice following single daily dosing for 7 days.



- Although modelling was simulated for 7 days, it was observed that the steady state (SS) was achieved on day 4 and corresponds to the whole blood total daily exposure (AUC_{0-24h}) of **3481 ng*h/mL.** This value was considered as the whole blood daily target exposure needed to achieve efficacy in humans.

Summary of Approaches

- The *in vivo* PK parameters obtained in preclinical species (CD1 mouse, SD rat and Beagle dog) after 1 mg/kg intravenous administration and the *in vitro* parameters (Cl from microsomes and hepatocytes, plasma protein binding, and blood to plasma) were used for the calculations.
- The GlaxoSmithKline software package PK Predictor Pro (GUI v1.1.45 Calculation Engine v1.4.4) was used for IVIVE, Liver Blood Flow (LBF) and allometric scaling. CloePK software (Cyprotex) was utilized for the Physiology-based PK (PBPK) modeling.

IVIVE approach. This approach used the *in vitro* intrinsic clearance from microsomes and hepatocytes to generate a prediction of hepatic clearance taking into account that the metabolic clearance was the major mechanism of clearance (other routes such as renal elimination were considered not significant).

-LBF (Liver Blood Flow). This approach assumed that the compound was hepatically cleared and used the principle that the systemic clearance of compounds in pre-clinical species can be scaled to humans using the ratio of blood flows to the extracting organ e.g. the liver.

The LBF approach presumed that hepatic extraction, volume of distribution and absorption in human were the same as in the animal species.

PBPK approach.

- The PBPK model implemented in CloePK (Cyprotex) allowed the integration of *in vitro* ADME and physicochemical data (pKa, logP, molecular weight, solubility and permeability in Caco-2 cells) for PK parameters calculation.

- The PBPK modeling was performed for mouse, rat and human at 1 mg/kg intravenous dose and 10 mg/kg oral dose.

- The fold error between experimental and predicted parameters by PBPK was lower than 2 for mouse. The experimental oral bioavailability values obtained in preclinical species were very high (>100%), so the fold error was close to 2 for mouse and rat. For rat, Vss and t1/2 were under predicted by PBPK (fold error higher than 2).

- Additional PBPK modelling performed with GastroPlus® software provide human dose projections in the same range (not shown).

Summary of human PK parameters obtained with different approaches

Prediction Approach		Species /method	Cl (mL/min/kg)	Vss (L/kg)	t1/2 (h)	%F
IVIVE	Microsomes	Human	<8	(-)	(-)	(-)
IVIVE	Hepatocytes	Human	<6	(-)	(-)	(-)
LBF	Non-restricted	Human (from mouse)	1.9	(-)	16.0	91
		Human (from rat)	1.9	(-)	23.9	91
		Human (from dog)	1.7	(-)	17.8	92
Allometric scaling	Non-restricted	Simple	1.9	3.0	18.1	91
		MLP	0.7	(-)	49.1	97
		BrW	0.5	(-)	72.0	98
PBPK		Human	4.8	2.3	12.0	78

Assumptions For Performing the Human Dose Predictions

- An absorption rate (ka) of 3.5 (1/h) was used for human dose prediction (mean of the ka in preclinical species).

- A monocompartmental model with first order absorption rate constant was used to predict human oral profiles.

- Linear PK behaviour was assumed across human dose range with a bioavailability of 100%

- A single volume of distribution of 3.0 L/kg was derived using simple allometry.

- For the human dose projection, two approaches were selected to design different scenarios to cover the clearance range to represent the best case **(allometric MLP : 0.7 mL/min/kg)** and worst case **(PBPK : 4.8 mL/min/kg)** predictions.

Conclusions

- For the human dose projection, the corresponding human pharmacokinetic parameters were calculated based on *in vitro* and *in vivo* data from preclinical species using different approaches.

- Applying these different scenarios, the estimated human efficacious dose for GSK070A ranges from **0.5mg/kg/day (best case) to 2.7mg/kg/mg/day (worst case).**

- Regardless of the methodology chosen for the prediction, the predicted clinical dose for GSK070 is <3mg/kg/day. This low predicted efficacious dose, compared with other antituberculars, makes GSK070 a potential partner of choice for fixed-dose combination treatments.

Comparison of predicted human efficacious doses for GSK070 with therapeutic doses of standard antituberculars.[5]

Compound	Human dose (mg/kg)
Isoniazid	6.2
Rifampicin	10 to 15
Pyrazinamide	27
Ethambutol	24.5
Linezolid	8.6
GSK070	<2.7

Acknowledgements

The authors would like to thank the team members and scientists at GlaxoSmithKline and Anacor Pharmaceutical Inc. with a special thanks to the DMPK groups at GSK (Tres Cantos and UK) for their support and guidance.

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.

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