EARLY SAFETY OF GSK070 – A NEW ANTITUBERCULAR AGENT

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ECCMID 2016, 9-12 April, Amsterdam, NETHERLANDS

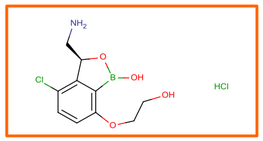
Introduction

GSK070 is an inhibitor of Leucyl t-RNA synthetase and a selective anti-tubercular agent (inactive against a panel of bacterial pathogens and towards a panel of mammalian cell lines) with a remarkable activity against a selection of DS-TB, MDR-TB and XDR-TB clinical isolates. GSK070 exhibits excellent physicochemical properties. It is a potent compound *in vivo* (ED_{max}~1mg/kg in acute and chronic murine models) with scalable pharmacokinetics to higher species.

Objectives

Integrated risk assessment of all safety findings: genetic toxicology, cardiovastuclar toxicology, reproducitve toxicology, safety pharmacology and general toxicology to define toxiological profile of GSK070 to allow its progression to preclinical development.

Methods



Enhanced Cross Screen Panel

- *In vitro* assays in protein free media
- **Parameteres**: Human Receptors, Ion channels, Transporters, Enzymes and Phenotypic assays

Ames test

- *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and *Escherichia coli* WP2uvrA (pKM101)
- Presence and absence S9-mix
- Maximal concentration 5000 µg/plate
- **Parameters**: Revertants per plate. Ratio treated / Solvent

Mouse Lymphoma Assay

- L5178Y TK+/-
- 240 µg/mL for 3h +S9-mix (1mM)
- 80 µg/mL for 24h –S9-mix (0.33mM)
- **Parameters**: Mutation Frequency @ RTG < 20%

Rabbit Ventricular Wedge (RVW)

- Pacing 1 and 0.5 Hz
- Perfusion time: approx. 35 min for each concentration.
- Concentrations: 0, 1, 10, 30, 100 µM
- **Parameters:** QRS interval (cardiac conduction).QT interval, Tp-e, Tp-e/QT ratio (cardiac repolarisation and repolarisation dispersion). TdP score (pro-TdP potential).

7 days rat toxicity study

- Male Wistar Han rat.
- Doses: 0, 31.95, 106.5 and 319.5 mg/kg (n=4) P.O., o.d. X7d. 10mL/Kg
- 1% (w/v) methylcellulose
- **Parameters:** Clinical observations, body weights, food consumption, macroscopic and microscopic observations. On day 8: clinical chemistry and haematology, brain, heart, liver and spleen weights

Rat Cardiovascular study

- Male Wistar Han rat. Conscious unrestrained telemetered
- Doses: 10.65, 31.95 and 106.5 mg/kg (n=6) x1day
- 1% (w/v) methylcellulose
- **Parameters:** Arterial pressures, heart rate, body temperature, QRS complex duration, PR and QA (cardiac contractility) intervals. At 2h prior and 24h after dose

Whole Embryo Culture (WEC)

- Rat embryos at day 9 postcoitum
- 41h incubation period
- Concentrations: 0, 0.01, 0.1, 1 10, 25, 50 and 100 µM
- **Parameters:** Embryos: morphology, size (crown-rump lenght) and somites number. Visceral Yolk: morphology and size (diameter)

Results

	eXP Data Profile
Other CV targets	Green
Drug abuse liability	Green
Pro-convulsant liability	Green
Emetic liability	Green
Kinases	Green
Phospholipidosis	Green
Cell Health	Green

Fig. 1 Safety Pharmacology results

	Ames		MLA	
	-S9 mix	+S9 mix	3h +S9	24h-S9
Max Conc.	5000 µg/plate	5000 µg/plate	240 µg/mL	80 µg/mL
	Negative	Negative	Negative	Negative

Fig. 2. Genetic Toxicology results. Ames test and MLA +/- S9 mix

Vehicle	Concentrations (µM)	Lethality	Embryo morphology	Yolk sac morphology
0.04% DMSO	0 (vehicle)			
	0.01			
	0.1			
	1			
	10			
	10†			
	25			
	50			
	100			

† repeated doses

Fig. 3 Reproductive Toxicology results. Whole Embryo Culture from rat

Duration	Vehicle	Doses (mg/Kg)	Parameters		
			Blood Pressure	Heart Rate	QA interval
1 day	1% MC	10			
		30	Increase		
		100	Increase	Increase	Increase

Fig. 5 Cardiovascular Toxicology results. Rat study

Conclusions

The predicted human whole blood C_{max} for a 33mg/day dose is 149ng/mL and AUC is 3481ng.h/mL. The NOEL in the *in vitro* WEC test was 10uM which equates to 2760ng/mL and provides an 18-fold cover from predicted hC_{max}. Systemic exposure of dose with no relevant sings, 30 mg/Kg, in CV study was 115000 ng.h/mL (AUC_{0-t}), providing a 33-fold cover to the hAUC. And after 7 days the systemic exposure was 164000ng.h/mL, which provides an exposure margin of 47-fold.

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

References

•Ward SA, et al. Lancet of Infectious Diseases. 2007;2:136-144
•Greaves P. *Histopathology of Preclinical Toxicity in Studies.* 3rd ed; page 126. London:Elsevier Academic Press; 2007.
•ICH S2(R1) (2011) Adopted EMA/CHMP/ICH/126642/2008. December 2011.

uM	ECG and TdP Score (0.5 Hz / 1 Hz)									
	QRS (ms) %		QT (ms) %		Tp-e (ms) %		Ratio Tp-e/QT		TdP score	
1	2.21	-0.45	-0.17	0.00	-9.13	-5.52	0.19	0.2	0.3	0.3
10	4.64	4.74	1.03	2.37	-13.20	-3.97	0.2	0.2	0.7	0
30	7.28	6.32	1.79	5.77	-18.06	-7.24	0.21	0.21	1.3	0.7
100	9.49	6.77	2.31	2.89	-10.68	-1.38	0.2	0.2	0.7	0.3

Tp-e Score < 2.5

Fig. 4 Cardivascular toxicology results. Rabbit Ventricular Wedge

Duration	Vehicle	Doses (mg/Kg)	Parameters		
			Clinical observations	Clinical chemistry & Haematology	Histopathology
7 days	1% MC	30			
		100			Spleen, Liver, Hematopoietic
		300	No tolerated	Decrease on Reticulocytes	Spleen, Liver, Hematopoietic

Fig. 6 General Toxicology results. 7 days rat study

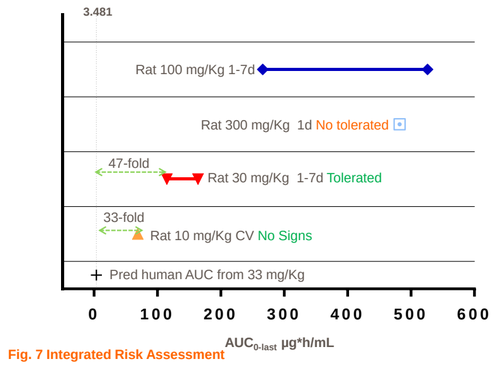


Fig. 7 Integrated Risk Assessment

Acknowledgements

All studies were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals and were reviewed the Institutional Animal Care and Use Committee either at GSK or by the ethical review process at the institution where the work was performed