In vivo antitubercular activity of GSK070, a Mycobacterium tuberculosis leucyl-tRNA synthetase inhibitor

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Introduction

Tuberculosis (TB) is a chronic, air-borne infectious disease caused by *Mycobacterium tuberculosis* (Mtb). According to the WHO, one-third of the world population is currently infected with TB. The prevalence of multi-drug resistant TB (MDR-TB) is very high in underdeveloped nations due to lack of adherence to therapy. Consequently, there is an urgent need to develop novel, fast acting anti-TB drugs with high potency that can provide treatment options for MDR-TB and reduce the duration of therapy to improve adherence.

Protein synthesis inhibitors play an important role in the treatment of tuberculosis. Parenteral aminoglycosides form a key part of the treatment of MDR-TB and currently the oxazolidinones are the only class of protein synthesis inhibitors that are orally bioavailable and are effective against TB. The rise of resistance including extensively (XDR) and totally resistant (TDR) TB demands the need for new oral frontline drugs. Here, we show the excellent in vivo profile of GSK070, a new Mycobacterium tuberculosis leucyl-tRNA synthetase inhibitor (LeuRS).

Methods

Laboratory Animals. Female C57BL/6 mice were used in acute and chronic assay. Female BALB/c mice were used for combo studies.

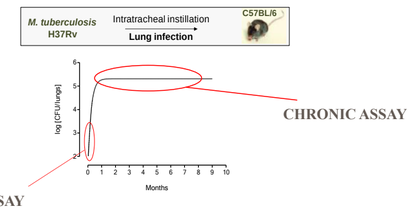
All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals.

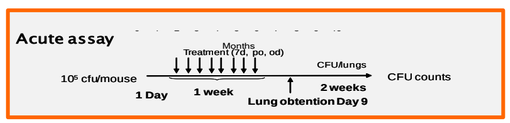
Sampling, quantification and efficacy data analysis

- Administration schedule: once a day (7/7 for 7days in acute assay, 7/7 for 8 weeks for chronic assay and 5/7 for 4 weeks in combo studies), oral route for every product.
- Data analysis: Non linear fitting to logistic equation of log10 (logCFU in lungs).Parameters of efficacy:
  - 1-ED_{99}: Dose in mg/kg that reduced bacterial burden by two logCFU with respect to untreated mice.
  - 2-EDmax: Dose in mg/kg that shows a reduction of 90% of the total logCFU reduction
  - 3-Maximum effect: Maximum reduction of logCFU

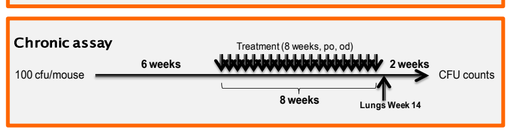
Software: GraphPadPrism 5.0

Experimental designs :





Exponential growth
Intracellular
No evidence of granulomas



No net growth
Intracellular
Presence of granulomas

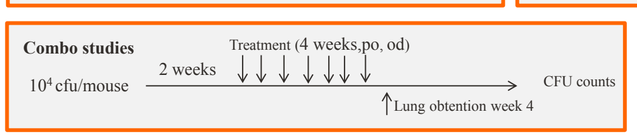


Figure 1.- Design and general characteristics of the Acute and Chronic assays and Combo study design.

Objective:

1.-To evaluate the antimycobacterial activity of GSK070 in monotherapy in the standard acute and chronic murine assays.

2.-To evaluate the effect of the addition of GSK070 provides to a combination with emerging anti-TB agents including Bedaquiline, PA-824 and Linezolid.

Results:

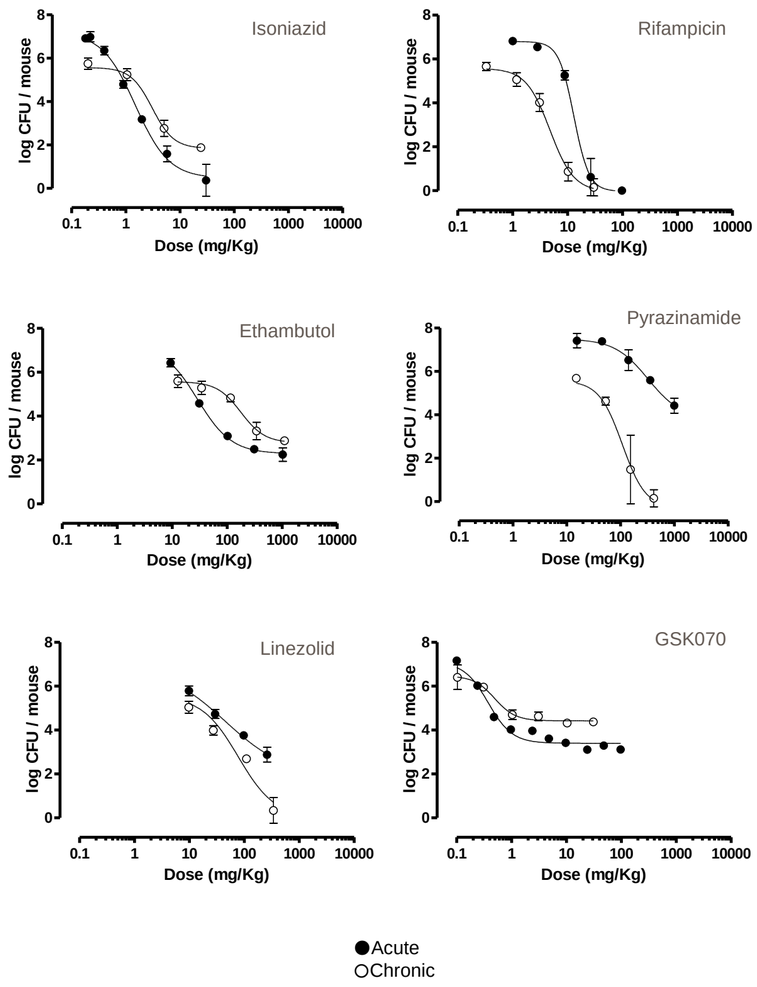
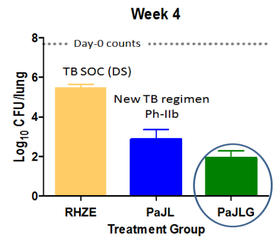


Figure 2.-Pattern of efficacy of GSK070 in the acute and chronic murine models. Dose response curves of antituberculars against *M. tuberculosis* in the acute (solid symbols) and chronic (open symbols) models.



R: Rifampicin 10 mg/kg
H: Isoniazid 10 mg/kg
Z: Pyrazinamide 150mg/kg
E: Ethambutol 100 mg/kg
Pa: Protomanid (PA-824) 100 mg/kg
J: Sirturo (Bedaquiline) 25 mg/kg
L:Linezolid 100 mg/kg
G: GSK070 10 mg/kg

Figure 3.-Decline in lung CFU counts in a chronic mouse model after 4 weeks of dosing with combos containing GSK070

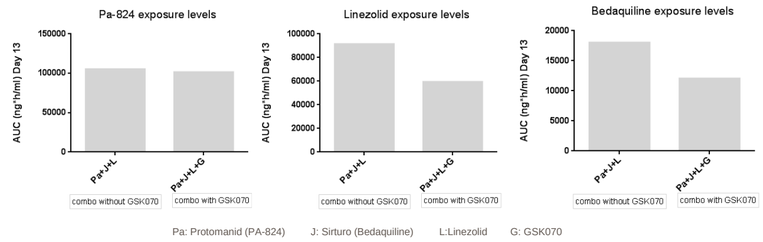


Figure 4.-Exposure levels in a chronic mouse model after 13 days of dosing in combination with GSK070 or without

References

For the acute and combination studies have been previously described by Rullas et al. (AAC 2010; 54:2262) for the acute assay and Nuermberger et al. (AAC 2008; 52:1522) for the model used for the combinations.

Conclusions

-GSK070 is our most potent compound tested so far in the acute or chronic models in terms of administered dose.

-GSK070 has shown excellent in vivo antitubercular activity with demonstrated efficacy in both the standard acute and chronic murine assays. The EDmax is around 1m/kg in both assays, this dose were used for human dose projection.

-The combination of GSK070 with J, Pa, and L (emerging anti-TB agents) demonstrated a more rapid reduction in logCFU when compared to the standard of care (RHZE).

-No significant changes were observed in exposure levels of PA-824, Linezolid and Bedaquiline when administered in combination with GSK070.The greater efficacy observed by adding GSK070 to the PaJL combination cannot be explained by an increase in PA-824, Bedaquiline, or Linezolid exposures.

Acknowledgements

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