Long-Acting Injectable Rifapentine With Activity in a Mouse Model of Tuberculosis Preventive Therapy

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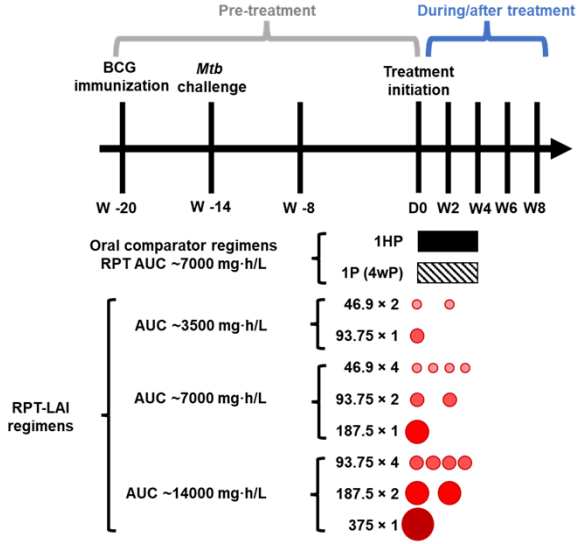
BACKGROUND

- Use of long-acting injectables (LAIs) has the potential to simplify tuberculosis preventive therapy (TPT) addressing issues such as pill burden and adherence.
- Rifapentine (RPT) is a key component of shorter TPT regimens and has physicochemical and pharmacokinetic (PK) properties amenable to LAI formulation.
- The aim of this work was to characterize preclinical performance of a new LAI RPT formulation prepared by nanoprecipitation spray drying for use in TPT.

METHODS

- Single intramuscular dose PK profiles were first characterized in mice at doses of 187.5 and 375 mg/kg.
- Based on the mouse PK, 8 RPT-LAI regimens as outlined in Fig. 1 (1, 2 or 4 injections, doses in mg/kg), were designed in expectation of clearing a 0.6 µg/mL plasma concentration target[1] and used to evaluate bactericidal activity in a validated paucibacillary mouse model of TPT.
- With 3 control groups [untreated negative control; positive control daily oral isoniazid and RPT (1HP); 4 weeks of oral RPT], a total of 186 adult female BALB/c mice were used.

Fig. 1: TPT Model, Drug administration and CFU sampling



[1]*Initial estimate for Day 28 C_{trough} after single LAI dose in human (Rajoli et al. 2018)*

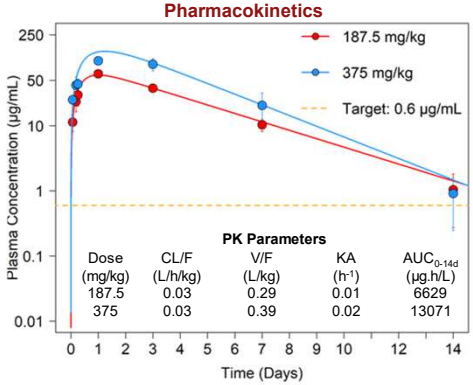
A long-acting injectable formulation for rifapentine demonstrates encouraging exposure profiles and efficacy in a mouse model of tuberculosis preventive therapy

- Lung bacterial colony-forming units (CFU) counts and plasma RPT exposures were measured 0-8 weeks after the start of treatment at timepoints indicated (Fig. 1), with sparse PK sampling weeks 2-8.
- Group mean CFU counts were analyzed using 1-way ANOVA and plasma exposure (determined by LC-MS) with compartmental PK analysis.

RESULTS – Pilot Pharmacokinetic Study

- RPT-LAI in mice demonstrated dose-linear PK for single injection doses of 187.5 and 375 mg/kg.
- PK disposition parameter estimates were in keeping with reported RPT values in mouse and a release-dependent, "flip-flop" terminal phase (Fig. 2).
- As for other successful LAIs which demonstrate longer half-lives in larger species, longer exposure durations were observed in rats *(data not shown)*.

Fig. 2: RPT Mouse Intramuscular LAI Plasma Pharmacokinetics



RESULTS –TPT Efficacy Study

Fig. 3: CFU Data x1 Injection Groups

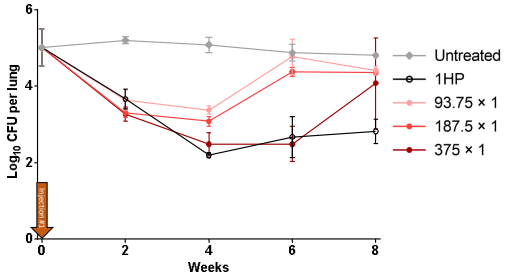


Fig. 4: CFU Data x2 Injection Groups

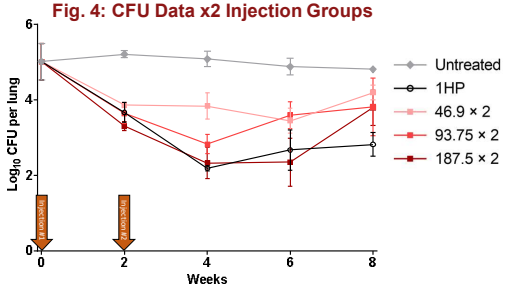
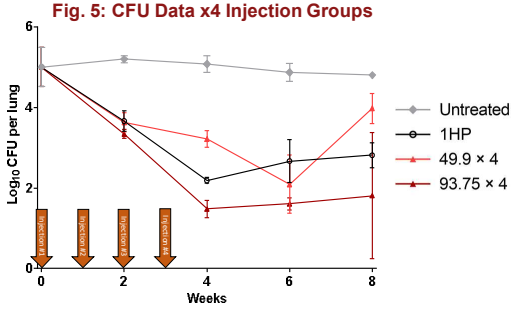


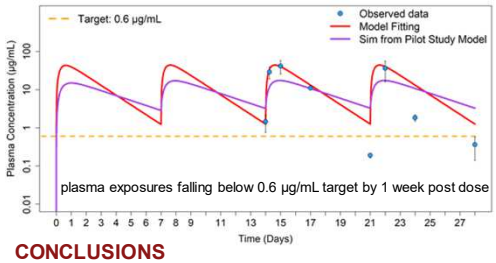
Fig. 5: CFU Data x4 Injection Groups



RESULTS –TPT Efficacy Study (continued)

- All RPT-LAI regimens had dose-dependent bactericidal activity in mice (Fig. 3 – 5).
- Several regimens had bactericidal activity equal to or greater than the 1HP control regimen: 375 mg/kg x 1, 93.75 mg/kg x 2, 187.5 mg/kg x 2, 93.75 mg/kg x 4, and 46.9 mg/kg x 4 injections.
- Multiple regimen variations for a given total dose resulted in efficacy, including a single administration of 375mg (Fig.3) vs e.g. 187.5 mg/kg x 2 (Fig. 4).
- PK exposure in infected animals after 2nd, 3rd or 4th dose in multiple injection regimens was inconsistent with single injection pilot PK (e.g. Fig. 3 for 46.9 mg/kg x 4 regimen).

Fig. 6: RPT-LAI Mouse Plasma PK in TPT model mice
46.9 mg/kg x4 injections regimen



CONCLUSIONS

- These data provide proof-of-concept for RPT-LAI to achieve efficacy comparable to 1HP in a validated mouse TPT model.
- Cross-species PK data suggest efficacious RPT exposures should be achievable in humans and do not preclude a single shot intervention option.
- Further work to characterize the impact of repeat dosing on PK and conduct GLP toxicology studies to support first in human evaluation are underway.

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