Thursday, December 18, 2025

Poster abstract submission

Approval Status Not Started

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Type of organization

Academic / research institution

Poster title

Assessment of feasibility of the hollow-fiber system for PKPD studies of diarylquinolines

Poster abstract

The hollow-fiber system for tuberculosis (HFS-TB) is a preclinical in vitro pharmacokinetic/pharmacodynamic (PKPD) tool endorsed by the European Medicines Agency to underpin anti-TB drug development. It can inform the design of Phase II/III clinical trials by mimicking in vivo PKPD parameters of anti-TB compounds, which may feed ulterior in silico models. The diarylquinoline bedaquiline (BDQ) belongs to the WHO essential antimicrobials list to treat drug-resistant TB. However, its adverse effects restrict its use. In contrast, TBAJ-587 is a next-generation diarylquinoline with enhanced anti-TB activity and safer properties. To implement the use of TBAJ-587 in the HFS-TB, we evaluated the compatibility of both diarylquinolines with two types of fibers, finding that both molecules displayed a high degree of unspecific binding to most materials in the model. To optimize the protocol, we performed a set of proof-of-concept assays with BDQ, including different infusion ports, high concentrations to overcome the binding, and saturation procedures. In light of these tests, we designed a strategy to mimic total lung [TBAJ-587]median derived from 100 mg or 200 mg quaque die (QD; once daily), built on a physiologically-based pharmacokinetic (PBPK) model that enabled the extrapolation of lung pharmacokinetics from mice to humans. Then, a PKPD assay with M. tuberculosis H37Ra strain against 100 mg, 200 mg and 400 mg QD of TBAJ-587 for 7 and 14 days, and with non-replicating Ss18b strain against 100 mg and 200 mg QD of TBAJ-587 for 7 days; was carried out. Bacterial dynamics were monitored by colony forming units (CFU)/mL, most probable number (MPN), ribosomal RNA synthesis (RS) ratio and molecular bacterial load assay (MBLA). Results showed that 200 mg QD and 400 mg QD of TBAJ-587 eradicated H37Ra strain at day 2, whereas 100 mg QD-treated bacteria relapsed. Conversely, both 100 and 200 mg QD of TBAJ-587 eradicated Ss18b strain at day 10. Target [TBAJ-587]median was successfully imitated against H37Ra, while in Ss18b drug levels were below the expected threshold, likely because medium composition for this strain affects TBAJ-587's stability. Hence, the compound behaviour in the system should be taken into account when interpreting the results. To sum up, we have developed a method to mimic total drug concentrations of diarylquinolines in the lung against various M. tuberculosis strains, which, along with PK modelling, can provide useful data on TBAJ-587 monotherapy.

Research topic

PK/PD