Toxicological assessment of TBAJ-876, a second-generation diarylquinoline anti-tubercular drug, in rats and dogs.

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Type selection
Category: Scientific research
Prefered presentation type: Oral abstract presentation

Track selection
Track: A2: Drug and vaccine development, including for COVID-19

Title

Scientific Research Abstract Text
Background: TBAJ-876 is a second generation diarylquinoline under development for treatment of pulmonary tuberculosis (TB) and was selected for its reduced QT prolongation risk compared with the first generation diarylquinoline, bedaquiline (BDQ), based on in vitro (hERG assay) results and absence of adverse effects on electrocardiograms in safety pharmacology and toxicology studies.
Design/Methods: The toxicological profile of TBAJ-876 was characterized in GLP repeat-dose oral toxicity studies of 13-weeks duration in rats and dogs.
Results: Both studies identified no-observed-adverse effect levels (NOAELs) in terms of dose level and systemic exposure to TBAJ--876 and its major metabolite. All findings were either reversible or showed evidence of reversing after a 13-week treatment-free period and are clinically monitorable. Dose limiting toxicities included diarrhea, histopathologic findings of degeneration/necrosis and/or hyperplasia in the stomach mucosa, elevated serum transaminase activities in both species, and skeletal muscle myopathy in rats. At higher doses and exposures in the toxicology studies, findings also included hepatocellular necrosis in rats and elevated serum amylase activity without histopathologic findings in the pancreas, decreased bone marrow cellularity, and myocardial muscle fiber necrosis/infiltrate accompanied by an increase in serum troponin I concentrations in dogs. At the NOAELs, daily plasma exposure for TBAJ-876 and its major metabolite, as assessed by area under the concentration-time curve ($AUC_{0\text{-}24h}$), were higher or approximately comparable to the NOAEL exposure for similar duration studies with BDQ in rats and dogs, respectively. However, TBAJ-876 has an approximately 10-fold greater anti-mycobacterial activity in vitro and faster time to sterilization in relapsing mouse models.
Conclusions: Taken together, these nonclinical data suggest that TBAJ-876 has a larger therapeutic index than BDQ and has the potential to enable safer and shorter TB treatment regimens that could be used for all forms of pulmonary TB.

Summary
Summary: TBAJ-876 is being developed for pulmonary tuberculosis (TB). Selected for its reduced QT prolongation risk and superior anti-mycobacterial activity and time to sterilization in animal models versus bedaquiline, TBAJ-876 results from 13-week toxicology studies in rats and dogs support its potential to enable safer, shorter treatment regimens for pulmonary TB.

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