A study of the drug interaction potential of TBAJ-876 on CYP3A4 and P-gp substrates in healthy adults

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Background

TBAJ-876 is a drug candidate from the TB Alliance's efforts to develop a safer diarylquinoline with the potential to deliver superior efficacy to bedaquiline as part of novel TB treatment regimens. In vitro studies of TBAJ-876 identified the potential for CYP3A4 induction and P-gp inhibition. NC-009 is a planned phase 2 study with TBAJ-876 that will allow participation of patients with TB and HIV coinfection who will receive tenofovir, a P-gp substrate, and dolutegravir, a P-gp and CYP3A4 substrate. The primary objective of this study was to evaluate the effects of TBAJ-876 on the probe substrates midazolam of CYP3A4 and digoxin of P-gp.

Methods

Twenty-eight healthy subjects were enrolled in a phase-1 clinical unit in Fair Lawn, NJ, U.S.A. Treatment was 2 mg of midazolam syrup on Day 1 and Day 20, a 0.25 mg digoxin tablet on Day 2 and Day 21, and daily doses of 150 mg – 200 mg TBAJ-876 from Days 6 through 24 in a schedule designed to quickly reach and maintain anticipated therapeutic clinical exposure. Plasma concentrations of midazolam were measured for 24 hours following each dose and of digoxin for 96 hours. Pharmacokinetic parameters of midazolam and digoxin were compared between co-administration with TBAJ-876 versus alone by analysis of variance of log-transformed values, from which geometric mean ratios (GMRs) and 95% confidence intervals (CIs) were calculated for C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}last}$.

Results

Twenty-six subjects completed the study and contributed to the pharmacokinetic analysis. GMRs (90% CIs) of midazolam C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$, and were 0.86 (0.76 – 0.98), 0.94 (0.84 – 1.06), and 1.00 (0.88 – 1.12). For C_{max} and $AUC_{0\text{-}last}$ of digoxin they were 1.18 (0.91 – 1.53) and 1.51 (1.13 – 2.03). $AUC_{0\text{-}inf}$ could not be computed for most digoxin profiles.

Conclusions

Based on these results, no changes may be needed to dosages of substrates of CYP3A4 and P-gp co-administered with TBAJ-876. Tenofovir and dolutegravir will be required without dose adjustment as antiretroviral therapy of TB-HIV-coinfected participants in NC-009. Confirmation of observations in this study is intended in the NC-009 study.