BTZ-043 shows good safety and strong bactericidal activity in a seamless phase 1b/2a study in patients with pulmonary TB

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Background: New TB drugs are needed to shorten treatment durations and to counteract rising resistance against most recent drugs, especially bedaquiline. BTZ-043 is a first-in-class benzothiazinone and inhibitor of the essential cell-wall target DprE1 with potent activity and lesion penetration in mice.

Design/Methods: PanACEA-BTZ-043-02 was an adaptive seamless phase 1b/2a study performed at two South African sites. In phase 1b, doses were escalated by increments of 250 mg with pre-specified decision-rules for seamless transition; in phase 2a, patients were randomised to receive one of three different doses BTZ-043, or standard treatment. Bacterial killing was assessed in liquid culture from overnight pooled sputum samples. Food effect on BTZ-043 exposure was assessed in phase 1b, drug-drug-interaction potential by a probe drug cocktail or dolutegravir in phase 2a.

Results: 78 participants were enrolled and hospitalized for 14 days of treatment. Doses up to 1750 mg were studied in phase 1b and doses of 250mg, 500mg and 1000mg were advanced to phase 2a. Safety was not dose-limiting. Mild and moderate nausea were the most frequent AEs and no toxicity signals were found; transaminases rose transiently and later declined despite continued dosing. BTZ-043 pharmacokinetics were dose-proportional up to 1000mg. Under fed conditions AUCs increased by a factor of 2.99. Probe drug evaluations suggested a moderate inhibition of CYP2C9/OAT2 with a 1.7-2.5-fold increase in tolbutamide exposure. Other potential interactions were not considered clinically significant. The bactericidal activity was found in the same range as rifampicin doses of 10mg/kg, with –0.115 (95%CI:-0.162;-0.069) $\log_{10}$CFU/(ml*d) at the highest dose.

Conclusions: To our knowledge, this was the first adaptive seamless phase 1/2 trial in TB patients accelerating bactericidal activity and safety evaluation, assessment of food effect and drug-drug-interactions. BTZ-043 was safe and efficacious over 14 days of dosing. BTZ-043 should be administered with food, and can safely be co-administered with important TB drugs and dolutegravir.