Pharmacokinetics and pharmacodynamics of BTZ-043 in patients with pulmonary tuberculosis

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UNITE 4TB — Part of IMI AMR Accelerator

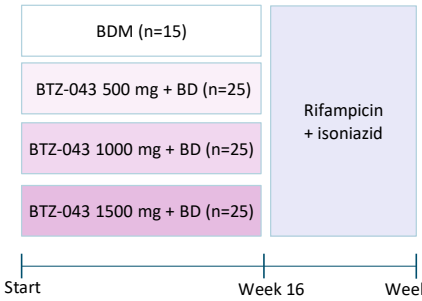
Introduction

- **BTZ-043**
  - Drug in development for treatment of tuberculosis (TB)
  - Inhibits mycobacterial cell wall synthesis by blocking enzyme DprE1
  - Two major metabolites
    - Amine derivative M1
    - Meisenheimer complex M2, which is converted back into parent
- The **DECISION** study was performed to evaluate **safety, efficacy, tolerability, pharmacokinetics and exposure-response relationship** of different doses of BTZ-043

Methods

Study design

- **Phase 2b controlled dose-ranging trial** in South Africa and Tanzania.



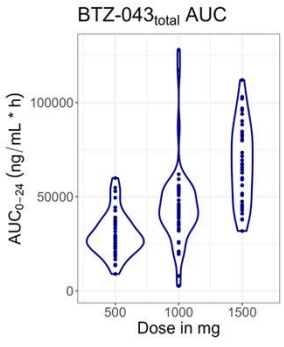
- BTZ-043 administered in combination with standard-dose **bedaquiline** and **delamanid (BD)**
- Control arm received **moxifloxacin (M)** instead of BTZ-043
- 90 participants planned, 92 included, 83 in PKPD analysis (68 receiving BTZ-043)

- **Population** 70 men & 13 women, median age 35 years (18-55), median weight 51 kg (36-76) at start treatment, 9.6% living with HIV
- **PK sampling**
  - Day 28 at 0 (pre-dose) and 0.25, 0.5, 1, 1,5, 2, 3, 4, 6, 8, 12, 24 hrs postdose
  - Day 56 at 0 (pre-dose) and 1, 2, 4, 6 hrs postdose
- Concentrations of BTZ-043, B and D in plasma determined with LC-MS/MS
- Sputum samples collected every week during treatment period.
- **BTZ-043 efficacy** evaluated by measuring change in mycobacterial load in sputum over time, quantified by **time to positivity (TTP)**
- **BTZ-043 population PK-PD model** was developed using nonlinear mixed-effects methodology implemented in NONMEM

Results

BTZ-043 population PK

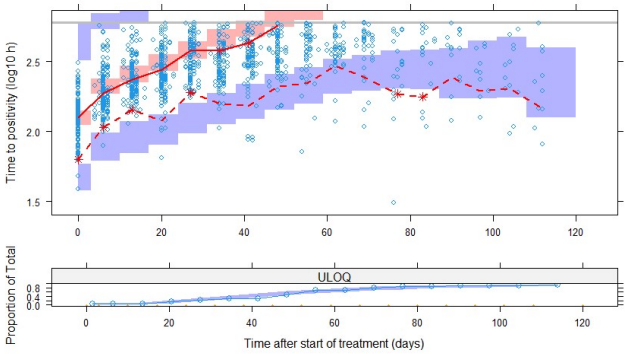
- 1209 samples from 68 participants
- M2 concentrations calculated by subtracting BTZ-043 from BTZ-043_{total} concentrations
- Below limit of quantification data ignored (BTZ-043_{total} 5.29%, BTZ-043 11.1%, M1 1.07%)
- In total 1075 BTZ-043, 1196 M1 ,795 M2 concentrations used in PK modelling

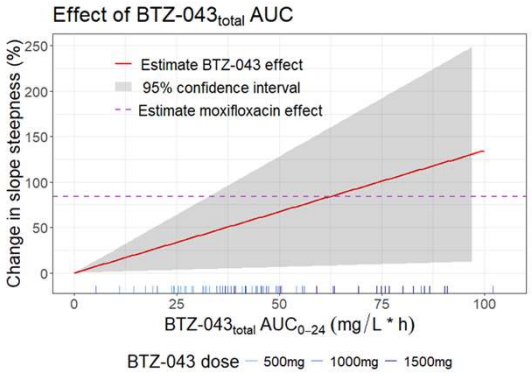


- BTZ-043, M1 and M2 were PK well-described by **a pre-existing PK model** (1) with some adaptations
  - Significant effect of **BTZ-043 dose on bioavailability**, which was 28% (95% CI 13-46%) higher for 500mg than 1000mg & 1500mg
- BTZ-043_{total} and BTZ-043 AUC_{0-24} and C_{max} derived from PK model

Population PD

- 2986 TTP observations (1227 quantitative) from 83 participants
- **Linear model** described log_{10}-transformed TTP data well
  - Upper Limit of Quantification (ULOQ) of 25 days (2)
  - **Scaling effect on baseline** representing difference before and after start of treatment
  - ***Exposure-response***: Significant linear effect of **BTZ-043_{total} AUC_{0-24}** on slope (*p=0.0009*)
    - Estimated effect **39.6% steeper slope** (95% CI 5.05 – 103%) for median AUC_{0-24} of 44100 ng/mL*h compared to only **BD**
  - ***Covariates***: Significant negative linear effect of X-ray AI severity (CAD4TB) score on slope (*p=0.0008*)





Conclusion

- Results indicate that **BTZ-043 adds efficacy on top of bedaquiline and delamanid** in persons with pulmonary TB
- As no maximal effect was observed, **highest BTZ-043 dose of 1500mg is expected to be most effective**
- Individuals with higher pulmonary lung involvement have slower decrease in bacterial load during treatment

References

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