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

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FACTS & FIGURES

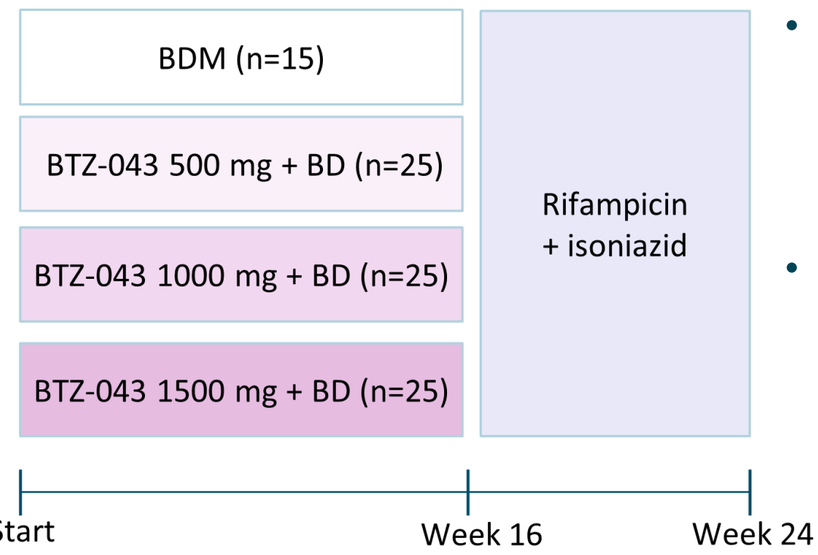
Start date:	01/06/2021
End date:	31/05/2028
IMI funding:	92,500,000 €
EFPIA in kind:	62,364,744 €
Other:	30,135,256 €
Total Cost:	185,000,000 €
Project website:	unite4tb.org
Social media:	linkedin/company/unite4tb

CHALLENGE

- Tuberculosis (TB) caused an estimated 1.3 million deaths in 2024
- Many factors complicate the worldwide eradication of TB, including but not limited to fast spread, stigma in society and the emergence of resistance against TB drugs
- New regimens are urgently needed to ensure effective treatment for all people living with TB

APPROACH & METHODOLOGY

- DECISION trial: Phase 2B controlled trial to evaluate safety, efficacy, tolerability, pharmacokinetics and exposure-response relationship of different doses of BTZ-043

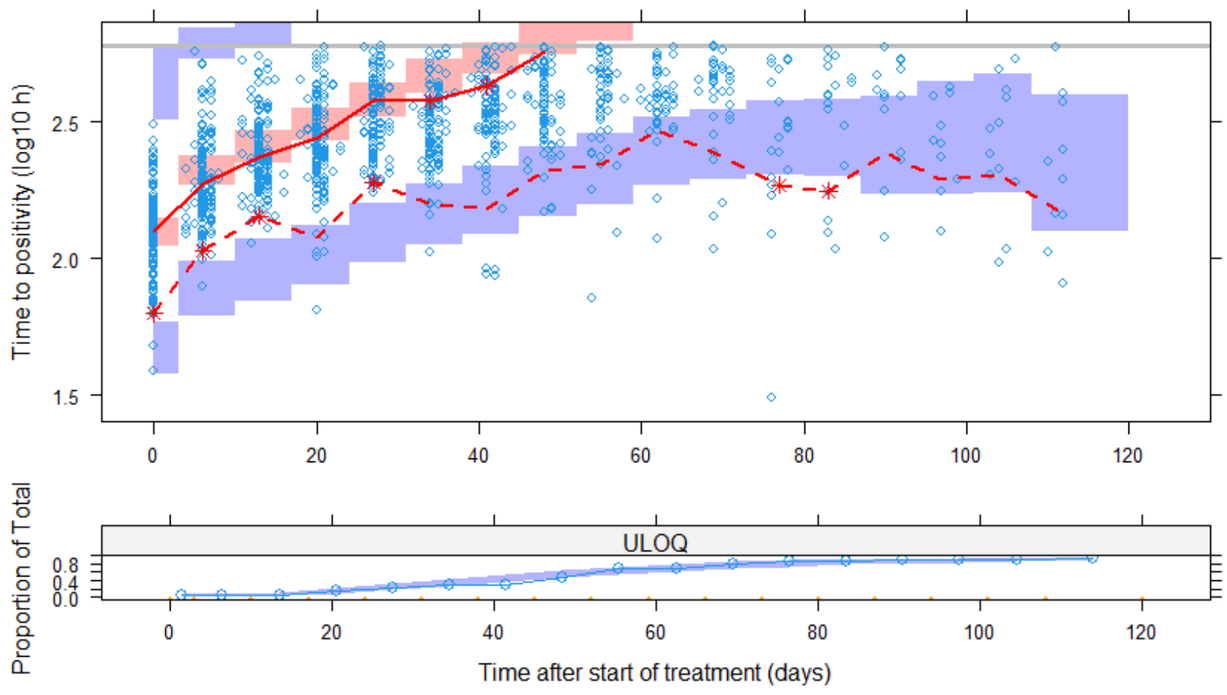


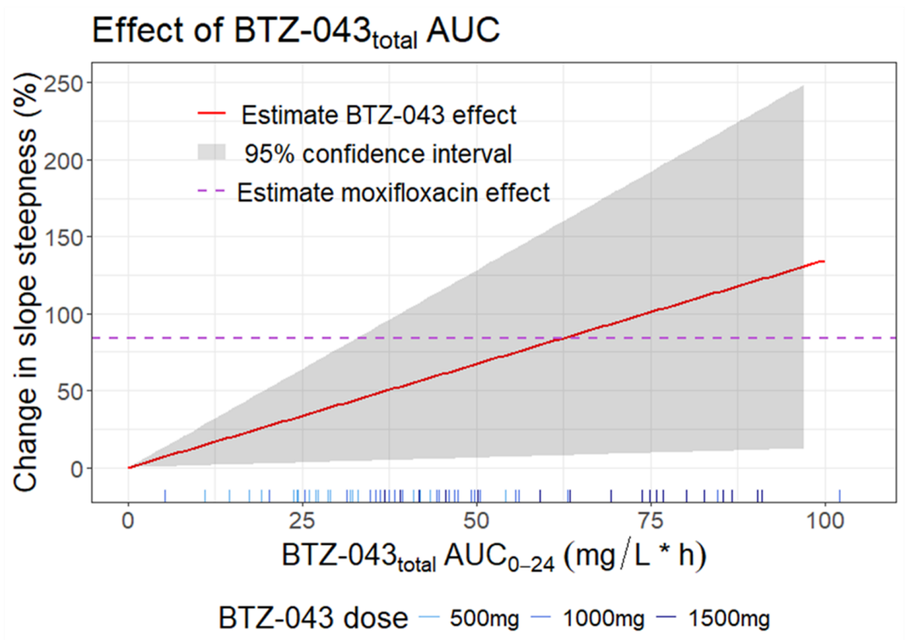
- BTZ-043 administered in combination with standard-dose bedaquiline and delamanid (BD)
- Control arm moxifloxacin (M) instead of BTZ-043
- PK sampling week 4 (intensive) and week 8 (sparse)
- Plasma BTZ-043, B and D concentrations determined with LC-MS/MS
- Sputum samples collected every week during 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 developed using non-linear mixed-effects methodology implemented in NONMEM

RESULTS

Population PD

- 2986 TTP observations from 83 participants
- Linear model described log_{10}-transformed TTP data well
- Upper Limit of Quantification (ULOQ) of 25 days
- 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*)





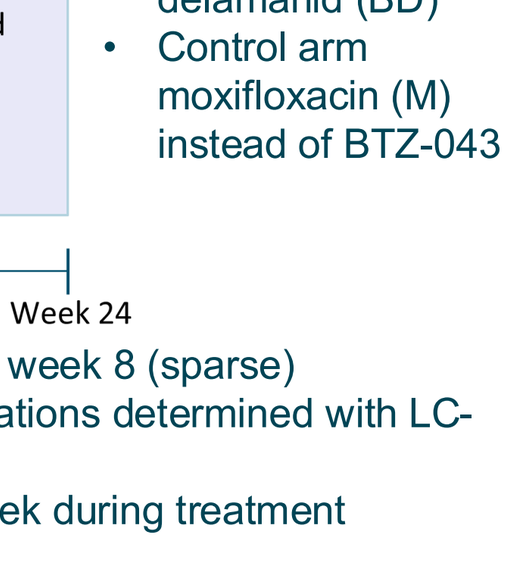
VALUE OF IMI COLLABORATION

- Collaboration between private and public organizations in the large-scale UNITE4TB consortium is accelerating the development of more effective and safe regimens for the treatment of pulmonary TB
- Results of the DECISION study are used to inform dose selection and support decision-making processes for novel regimens including BTZ-043

RESULTS

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



CAREER IMPACT

- The UNITE4TB consortium provided me with opportunities to present my research at the UNITE4TB Annual Meeting
- Collaboration in international teams expanded my professional network
- The experience of a PhD within the UNITE4TB consortium has prepared me for a career in model-informed drug development

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