

Delpazolid population pharmacokinetics and pharmacodynamics in patients with pulmonary tuberculosis

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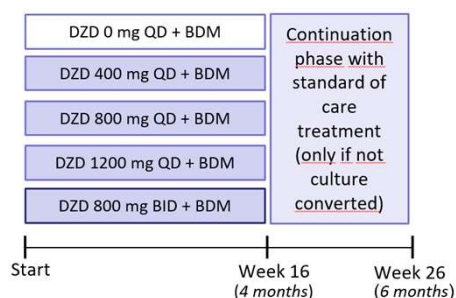
Introduction

- **Linezolid** (oxazolidinone)
 - recommended for treatment multi-drug resistant tuberculosis (MDR-TB)
 - effective, but causes severe adverse effects
 - e.g. myelosuppression, peripheral neuropathies
- **Delpazolid (DZD)** (new oxazolidinone)
 - has been shown to be effective and safe in tuberculosis (TB) patients up to 14 days (1)
 - could be **promising alternative** for linezolid in MDR-TB treatment
- **Objectives** of the PanACEA Delpazolid dose-finding and Combination DEvelopment (**DECODE**) study
 - evaluation of DZD safety, tolerability, **pharmacokinetics** (PK), **pharmacodynamics** (PD) in drug-sensitive pulmonary TB patients over a longer treatment period.

Methods

Study design

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



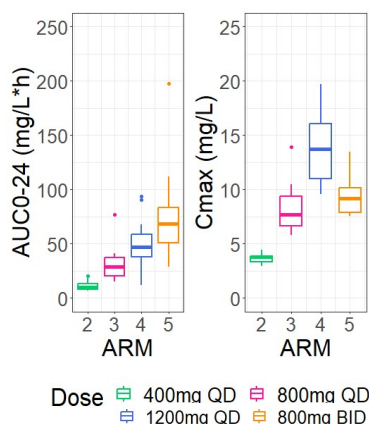
- DZD administered in combination with standard-dose **bedaquiline, delamanid and moxifloxacin** (BDM)
- **5 arms with 15 participants** (75 planned, 76 included)
- **Population** 60 men & 16 women, median age 34 years (20-57), median weight 53 kg (40-84), HIV positive 14.5%

- **PK sampling** on day 14 at 0 (pre-dose) and 1, 2, 4, 8, 12, 24 hrs after dosing
- Drug concentrations in plasma determined with LC-MS/MS
- Sputum samples collected every week during treatment period.
- **DZD efficacy** evaluated by measuring change in mycobacterial load in sputum over time, quantified by **time to positivity (TTP)**
- **DZD population PK-PD model** was developed using nonlinear mixed-effects methodology implemented in NONMEM

Results

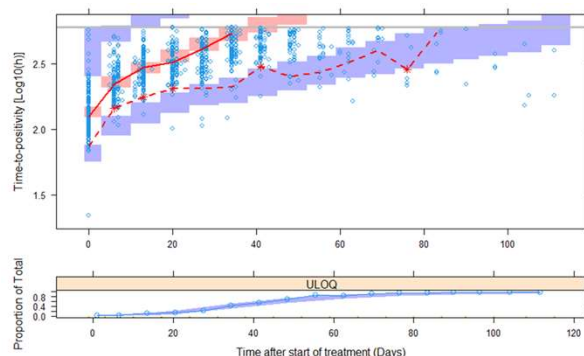
Population PK

- 402 plasma concentrations from 60 participants
- 18.6% of observations below limit of quantification
 - Included as censored (M3 method)
- **Two-compartment model** with first-order absorption and first-order elimination, proportional residual error and allometric scaling based on fat-free mass (FFM) described DZD PK well.

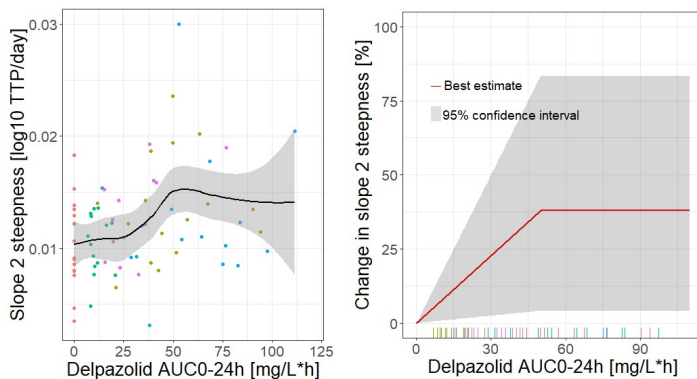


Population PD

- 2312 TTP results from 75 participants
- **Bi-linear model with upper limit of quantification at 25 days** described log-transformed TTP data well (2)
 - Node point estimated at **7-8 days**



- The effect of various predictors on exposure-response was tested
- There was a significant **linear effect of DZD AUC₀₋₂₄ on second slope** with maximum effect at **50 mg/L*h** ($p=0.025$)
- Estimated maximal effect was 38% steeper second slope, but 95% confidence interval was wide (4.2 – 83%)
- Observed **median AUC₀₋₂₄ of 1200 mg DZD dose** (47.0 mg/L*h) close to exposure estimated to generate **maximum effect**.



Delpazolid dose • 0 • 1200mgQD • 400mgQD • 800mgQD • 800mgBID

Conclusion and discussion

- **Delpazolid exposure increased linearly with dose**
- **Results indicate that delpazolid adds efficacy on top of bedaquiline, delamanid and moxifloxacin.**
- **From an efficacy standpoint, a dose of 1200 mg is reasonable to move forward in development.**

References

1. Kim JS et al. Early Bactericidal Activity of Delpazolid (LCB01-0371) in Patients with Pulmonary Tuberculosis. Antimicrob Agents Chemother. 2022 Feb 15;66(2):e0168421..
2. Dufault SM et al. Analysis of time-to-positivity data in tuberculosis treatment studies: Identifying a new limit of quantification. medRxiv [Preprint]. 2024 May 7:2024.05.06.24306879.



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