Delamanid or Pretomanid for Drug-Resistant TB: No evidence of a difference in efficacy or safety

- Dominic Wakerley[1], Iman Raza[1], Angela Crook[1], Derek Sloan[2], David Fisher[1], Christoph Lange[3], Hanif Esmail[1]

[1]University College London
[2]Radboudumc
[3]Research Center Borstel

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

World Health Organisation recommendations for the treatment of drug-resistant tuberculosis include two different 6-month regimens, each containing a nitroimidazole, either delamanid or pretomanid; no published trials have directly compared the two.

To inform decision-making within the PARADIGM4TB trial, we performed an individual participant data meta-analysis comparing their efficacy and safety.

APPROACH & METHODOLOGY

A systematic review identified BEAT-TB and TB-PRACTECAL as clinical trials comparing delamanid- or pretomanid-containing regimens to a WHO-approved standard of care. The TB-IPD platform provided the data.

BEAT-TB provided the delamanid arms:



TB-PRACTECAL provided pretomanid arms:



A one stage individual participant data meta-analysis was then performed with trial ID included as a factor. A series of sensitivity analyses were then performed in increasingly harmonised populations:

1. Rifampicin resistance confirmed on DST
2. Restriction to sites using BDQ-based SOC
3. Restriction to South Africa alone
4. Exclusion of pregnant women, children
5. Restriction to FQ-sensitive TB
6. Exclusion of clofazimine arms

Primary outcome: favourable status at 72 weeks in TB-PRACTECAL and 76 weeks in BEAT-TB,

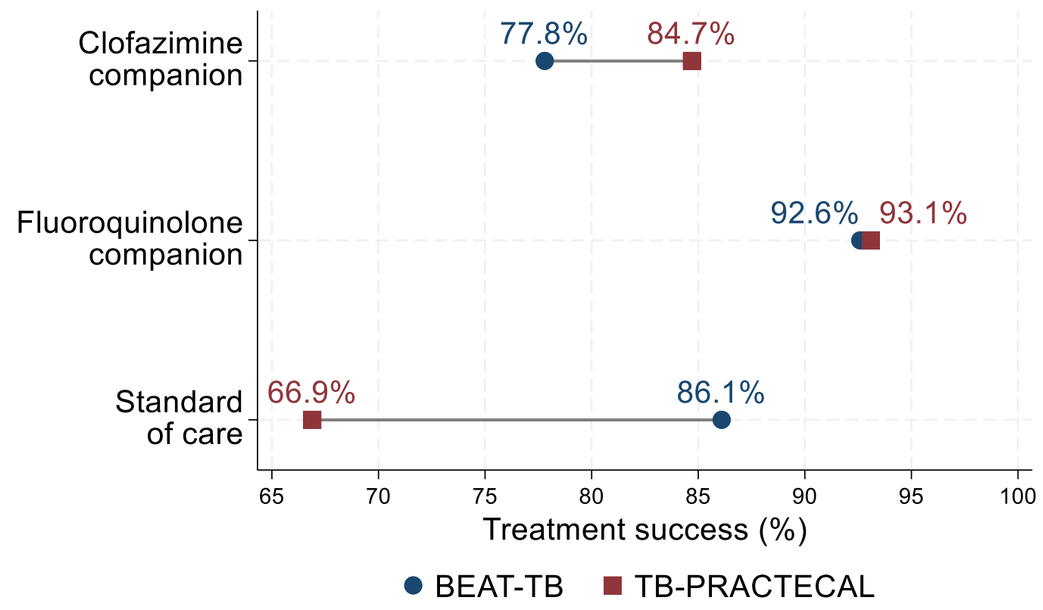
Secondary outcome: favourable status at 24 weeks.

Safety outcomes: proportion of participants developing QTcF >450ms, >500ms and ALT >120 IU/L.

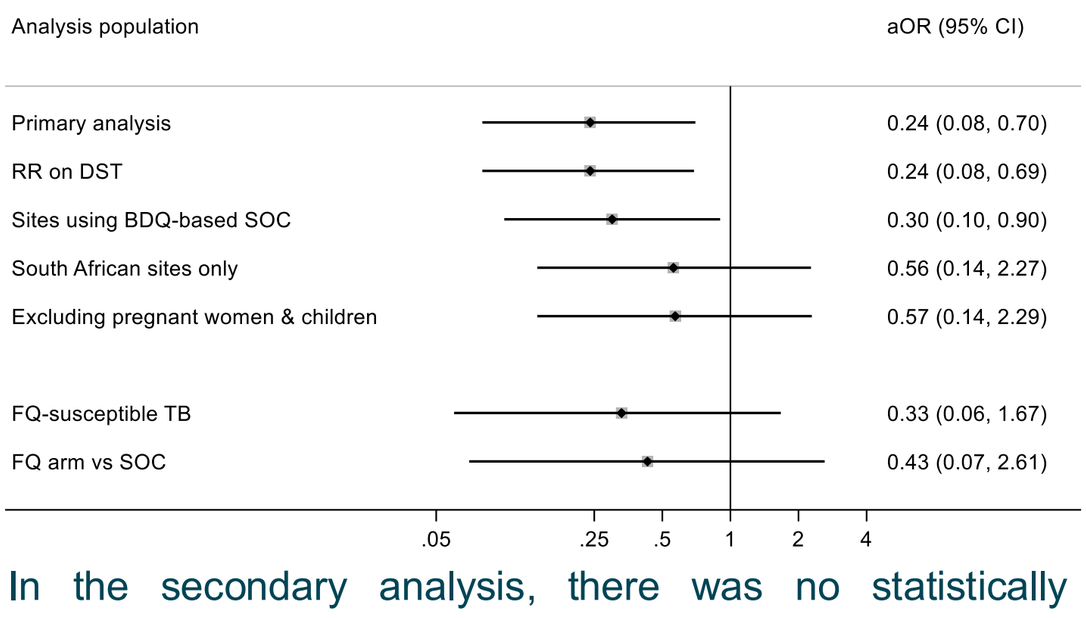
The performance of each nitroimidazole arm was compared with standard of care, with the odds ratio generated from that forming the basis for comparison.

RESULTS

While the investigational arms performed comparably, the standard of care performed worse in TB-PRACTECAL than in BEAT-TB (66·9% versus 86·1%):



The primary analysis, favourable status at 72/76 weeks, showed a significant difference in favour of pretomanid (aOR 0·24, 0·08 - 0·70). However, as the populations became harmonised in sensitivity analyses, the effect size reduced and became non-significant:



In the secondary analysis, there was no statistically significant difference at any level of analysis. Safety analyses did not show any difference between the drugs.

Overall, there was insufficient evidence to show that one drug is superior to the other in either efficacy or safety.

VALUE OF IMI COLLABORATION

Combined expertise from the UNITE4TB consortium has helped this project considerably, from the inception of the research question and analysis plan through to the presentation and dissemination of results.

This in turn has supported a key aim of UNITE4TB: accelerating the development of new regimens.

CAREER IMPACT

Working in UNITE4TB has had a significant aid to my career:

- Experience working in a large international research consortium.
- Opportunity to present results at UNITE4TB meetings, including the annual meeting.
- Expansion of my professional network.
- Contributed to research dissemination through posters and manuscripts.

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