Early termination of randomisation into TB-PRACTECAL, a study examining novel six month, all-oral regimens for treatment of drug-resistant tuberculosis

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Introduction

Almost 500,000 people worldwide develop multidrug-resistant tuberculosis (MDR-TB) annually, with a treatment success rate of around 60%. Current treatment consists of up to 20 pills per day taken for a duration of between nine and 24 months. TB-PRACTECAL is a multi-arm multi-stage, randomised controlled, open-label phase II/III clinical trial, evaluating the safety and efficacy of regimens containing bedaquiline, pretomanid, and linezolid for the treatment of MDR-TB. On 18th March, 2021, randomisation into the trial was terminated early following recommendations from the trial's Data and Safety Monitoring Board (DSMB). We present the trial design, rationale for this decision and the planned next steps.

Methods

Adults and children aged from 15 years were enrolled into the trial's six sites based in Uzbekistan, Belarus, and South Africa. An adaptive phase IIB/III design was chosen to accelerate the trial. Stage 1, corresponding to the phase IIB component of the trial, comprised three investigational arms compared to a locally-approved standard of care (SoC). The best performing arm in this phase was then selected for stage 2. In Stage 2 of the trial, corresponding to a phase III trial, patients were randomised to either the SoC, or the PRACTECAL-1 arm, in which patients would receive bedaquiline 400mg daily for 2 weeks followed by 200mg three times a week for 22 weeks, pretomanid 200mg daily for 24 weeks, tapered dose linezolid 600mg daily for 16 weeks then 300mg for 8 weeks, and moxifloxacin 400mg daily for 24 weeks (B-Pa-Lzd-Mfx). The primary outcome measure was the proportion of patients with an unfavourable outcome (treatment failure, death, treatment discontinuation, recurrence, or loss to follow-up) at 72 weeks post-randomisation. The target sample size was 201 per arm.

Ethics

This study was approved by the London School of Hygiene and Tropical Medicine Ethics Review Board (ERB) and the MSF Ethics Review Board, as well as national or regional ERB's at each trial site. Clinicaltrials.gov registry number, NCT02589782.

Results

The decision to terminate recruitment was made based on 120 patients having been randomised to the PRACTECAL-1 arm, and 120 to the SoC arm. 31 patients in the PRACTECAL-1 arm and 33 patients in the SoC arm could have reached 108 weeks of follow-up. Data from another 229 patients in PRACTECAL arms 2 and 3 were also available. For the interim analysis on the primary outcome measure (percentage of study participants with an unfavourable outcome), there was a difference of at least three standard deviations favouring PRACTECAL-1 when compared to the SoC. The difference in the proportion of unfavourable outcomes was primarily driven by a higher rate of treatment discontinuations in the SoC arm. For both arms, there were no TB treatment failure or recurrence events. There were five deaths in the SoC arm, versus none in the PRACTECAL-1 arm. The final number of patients randomised into the trial at termination of randomsation was 552.

Conclusion

The results of the interim analyses convinced the DSMB and the trial steering committee that equipoise between the two arms no longer existed, with further recruitment unlikely to change the conclusion. Accumulated data from all 552 patients will be analysed and submitted to answer specific questions for the World Health Organization's guidelines development process for management of rifampicin-resistant TB. A manuscript for publication in a peer reviewed journal will be prepared and results will be communicated to communities that participated in the trial by the end of the year. All patients in the trial will be followed up to at least 72 weeks post-randomisation. Given the positive findings, MSF is currently developing guidance and collaborations to scale up the regimen.

Conflicts of interest

None declared.

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