POTENTIAL IMPACT ON ANTI-MYCOBACTERIAL STUDY DESIGN AND TUBERCULOSIS TREATMENT LANDSCAPE

Innovative Design of the TBAJ876 Phase 2 NC-009 Study

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BACKGROUND AND OBJECTIVES

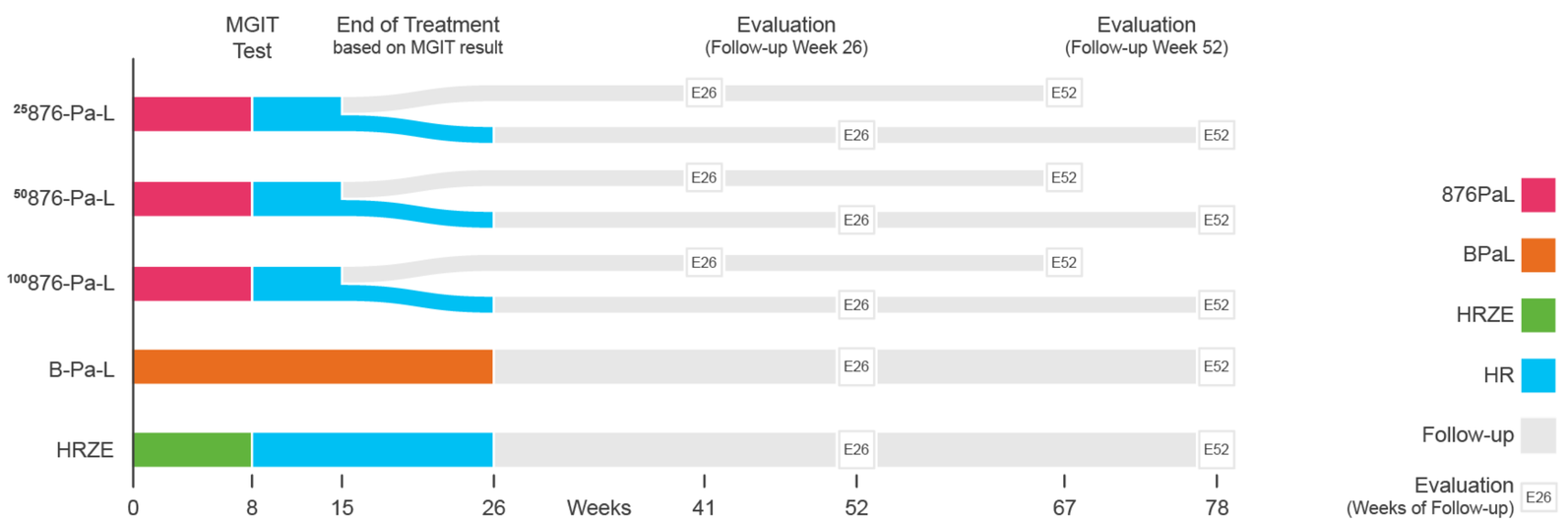
Preclinical studies have shown that TBAJ876 (a second generation diarylquinoline) has greater antimycobacterial activity and a potentially better safety profile than bedaquiline.[a b c]

In addition, bedaquiline resistance is fast becoming a public health challenge.[d]
Pre-clinical studies have shown that TBAJ876 has improved antimycobacterial activity on Rv0678 resistance-associated variants (RAVs) of mycobacterium tuberculosis – the most common mutant strain conferring resistance to bedaquiline. Phase 1 data supports the advancement of TBAJ876 into Phase 2.[e]
The NC-009 study is an ongoing, first-in-patient, dose-ranging, Phase 2 trial of TBAJ876, with an innovative design combining Ph2a, Ph2b, and Ph2c elements.

STUDY DESIGN

Approximately 300 drug-sensitive TB participants randomized to one of five regimens

- Nos per arm = at least 60
- Newly diagnosed DS-TB
- HIV allowed
- Equally randomized
- Stratified by country, disease severity
- Biomarkers



METHODS

At least 300 newly-diagnosed, drug-sensitive TB participants will be randomized in equal ratios to 5 treatment arms: HRZE for 8 weeks, followed by HR for 18 weeks; B-Pa-L for 26 weeks; or one of three arms combining 25, 50, or 100mg of TBAJ876 with pretomanid, and linezolid 600mg (TBAJ876-Pa-L) for 8 weeks, followed by HR for up to 18 weeks.
Randomization is stratified by country and severity of disease (AFB 3+ and/or bilateral cavitation). The diarylquinoline arms are blinded during the first 8 weeks, after which only the TBAJ876 dose remain blinded.
Both pretomanid and linezolid are open-label, and linezolid dose modifications are allowed for management of potential adverse events.
Participants randomized to the three TBAJ876 arms will be able to stop treatment at week 15, based on week 8 MGIT results and absence of symptoms indicative of active TB. If the week 8 MGIT result is negative and no active TB symptoms, participant can stop HR at week 15. If either of the two criteria are present, participant will complete full 18 weeks of HR.
All participants will be followed for 52 weeks after end of treatment. This study is being conducted in South Africa, Tanzania, Uganda, Georgia, and Philippines.

RESULTS

The primary objective is to evaluate the efficacy of 3 doses of TBAJ876 in combination with pretomanid and linezolid, relative to HRZE/HR at week 8 using the endpoint of time to stable sputum culture conversion. The primary endpoint will be used in combination with other efficacy and safety analyses to identify the optimal TBAJ876 dose for use in subsequent studies. The proportion of participants who stopped treatment at week 15, in combination with demonstrated sustainability of response during 52-week follow-up, will provide insight into the potential for shorter than 4-month treatment duration of TBAJ876-Pa-L. The efficacy and safety of TBAJ876 will also be compared to bedaquiline.
The study will also allow the evaluation of 6-months of B-Pa-L regimen in DS-TB participants to confirm if similar efficacy and safety profile is observed as established in drug-resistant TB patients.

A special thanks to the investigators, site staff, and – most importantly – the participants.

CONCLUSION

The design of NC-009 may allow for the acceleration of development of a promising second-generation diarylquinoline by simultaneously allowing dose-ranging exploration and evaluation of its treatment-shortening potential. Successful completion and positive results from these studies can potentially lead to a reshaping of the treatment landscape for DS-TB with a shorter and safer regimen.

LEARN MORE

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NC-009

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