month optimized background regimen. Results are expected in 2017 for a primary outcome of distribution of time to sputum culture conversion during the 6-month period of delamanid or placebo treatment, along with multiple secondary outcomes including survival, 2-month culture conversion, and 30-month treatment success. Another phase III randomized trial is evaluating delamanid for treatment of MDR-TB in multiple combination regimens with other newer TB drugs such as bedaquiline, linezolid, and clofazimine (endTB; clinical trial NCT02754765).

Phase I and phase II pediatric trials are in progress (clinical trials NCT01856634 and NCT01859923), and an additional phase II trial in adults is scheduled to evaluate the safety, tolerability, and pharmacokinetics of delamanid and bedaquiline in combination, with a focus on QT prolongation and cardiac safety (clinical trial NCT02583048). For treatment of latent tuberculosis infection, a trial comparing delamanid to isoniazid for preventing TB disease in high-risk contacts of MDR-TB cases is expected to begin enrollment in 2017 (PHOENix, ACTG A5300B).

7b. Use of pretomanid in treatment of tuberculosis

Whereas delamanid has been evaluated only for treatment of MDR-TB (in combination with an optimized background regimen), pretomanid is being evaluated for the treatment of both MDR-TB and drug-susceptible (non-MDR) TB, in combinations with two or more other active tuberculosis drugs.

In completed 2-week trials in patients with drug-susceptible pulmonary tuberculosis, pretomanid alone had significant early bactericidal activity that appeared to plateau at doses ≥ 100 mg daily (Diacon *et al.*, 2010; Diacon *et al.*, 2012). A subsequent 8-week phase IIb trial (Study NC-002) evaluated pretomanid (100 mg or 200 mg daily) in combination with moxifloxacin 400 mg daily and pyrazinamide 1500 mg daily (the "PaMZ" regimen), compared to the standard (isoniazid, rifampin, pyrazinamide, and ethambutol) regimen for drug-susceptible tuberculosis. The primary outcome considered was the mean daily rate of reduction in *M. tuberculosis* colony-forming units (CFUs) measured in weekly sputum specimens. Patients receiving the PaMZ regimen containing 200 mg pretomanid had significantly more rapid declines in sputum CFU counts than the control group, and compared to control subjects, larger fractions of both pretomanid-treated groups achieved culture negativity in liquid media by 8 weeks. In addition, in a non-randomized group of MDR-TB patients treated with the PaMZ regimen (with a 200-mg pretomanid dose) within the same trial, the rate of CFU reduction was comparable to the rate observed in drug-susceptible patients treated with the standard regimen (Dawson *et al.*, 2015).

A phase subsequent III trial of the PaMZ regimen has begun enrollment (STAND; clinical trial NCT02342886) is evaluating 12-month outcomes of the PaMZ regimen for in drug-susceptible tuberculosis two different pretomanid doses (100 mg daily and 200 mg daily) and two different treatment durations (17 weeks and 26 weeks), with controls receiving 26 weeks of the standard regimen. The study also includes a non-randomized MDR-TB arm. This trial was temporarily on clinical hold due to concerns about possible hepatotoxicity but was allowed to resume.

Additional phase II and phase III trials are evaluating pretomanid as part of other tuberculosis drug combinations. The 8-week NC-005 study (clinical trial NCT02193776) is evaluating the bactericidal activity of the combination of pretomanid 200 mg daily with bedaquiline and pyrazinamide for drug-susceptible tuberculosis compared to standard regimen controls, and of pretomanid 200 mg daily with bedaquiline, pyrazinamide, and moxifloxacin for MDR-TB without a comparator arm. The phase III NiX-TB trial (clinicaltrials.gov NCT02333799) is evaluating 6 months of pretomanid 200 mg daily plus bedaquiline and linezolid for the treatment of XDR-TB or treatment-intolerant MDR-TB.

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