ORIGINAL ARTICLE

Assessing Multiple Treatment Regimens for Tuberculosis

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ABSTRACT

BACKGROUND

Ganfeborole and BTZ-043 are new drugs that may improve tuberculosis treatment.

METHODS

In this phase 2, randomized, controlled trial, we assigned participants with rifampin-susceptible pulmonary tuberculosis to receive the standard four-drug combination (isoniazid–rifampin–pyrazinamide–ethambutol; HRZE) for 24 weeks; bedaquiline–delamanid–moxifloxacin for 16 weeks; or one of 10 new four-drug combinations for 16 weeks. The new regimens contained ganfeborole, BTZ-043, or both, with combinations of bedaquiline, delamanid, moxifloxacin, pyrazinamide, pretomanid, and linezolid. The primary end point was the $\log_{10}$(time to positivity) slope (rate of change from baseline to week 12 in the time to *Mycobacterium tuberculosis* growth in a positive sputum culture). The treatment effect was assessed as the Bayesian posterior probability of superiority of each new regimen to HRZE with respect to the primary end point (results were used to select regimens for further evaluation, rather than for characterization of efficacy).

RESULTS

A total of 401 participants underwent randomization; 371 were included in the modified intention-to-treat population and 400 in the safety population. We identified two promising regimens for further evaluation: ganfeborole–bedaquiline–pretomanid–moxifloxacin (BPMG) and BTZ-043–bedaquiline–delamanid–moxifloxacin (BDMT). The $\log_{10}$(time to positivity) slope was 0.129 $\log_{10}$(days) per week (95% Bayesian credible interval, 0.112 to 0.146) with BPMG and 0.142 $\log_{10}$(days) per week (95% Bayesian credible interval, 0.126 to 0.160) with BDMT, as compared with 0.118 $\log_{10}$(days) per week (95% Bayesian credible interval, 0.105 to 0.131) with HRZE, for a relative difference of 9.1% (95% Bayesian credible interval, −8.6 to 29.0) and 20.5% (95% Bayesian credible interval, 2.7 to 41.1), respectively, and a posterior probability of superiority of 0.83 and 0.99. The incidence of adverse events of grade 3 or higher was 38% in the BPMG group (none of the participants discontinued), 28% in the BDMT group (one discontinued because of a drug reaction with eosinophilia and systemic symptoms), and 24% in the HRZE group (none discontinued). Bedaquiline–moxifloxacin–pyrazinamide–BTZ-043 was discontinued because of hepatotoxic effects.

CONCLUSIONS

In this trial, two four-drug regimens, one with ganfeborole and one with BTZ-043, showed evidence of potential efficacy and a safety profile that did not preclude progression to further evaluation. (Funded by Innovative Medicines Initiative 2 Joint Undertaking and others; PARADIGM4TB ClinicalTrials.gov number, NCT06114628.)

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*A complete list of the members of the PARADIGM4TB (UNITE4TB-01) trial team is provided in the Supplementary Appendix, available at NEJM.org.

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The global standard of care for rifampin-resistant pulmonary tuberculosis is a 6-month regimen consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin.[1-3] Additional development of antituberculosis drugs is needed to improve safety, reduce treatment duration, and diversify treatment options for both drug-resistant *Mycobacterium tuberculosis* strains and drug-susceptible strains.[4]

The pipeline of antituberculosis drugs contains many new agents with promising activity against complementary bacterial targets, offering multiple potential drug combinations.[5] Substantial new investments have expanded the capacity to evaluate antituberculosis regimens in phase 2 clinical trials. The UNITE4TB consortium, a public–private partnership funded by the European Union Innovative Health Initiative, was created to develop and conduct innovative phase 2 trials that can speed up the development of new antituberculosis drugs and regimens.[6]

Ganfeborole is a selective inhibitor of mycobacterial leucyl–tRNA synthetase, an essential enzyme in protein synthesis.[7] Ganfeborole has activity against drug-susceptible *M. tuberculosis* strains and resistant strains and has a low potential for drug–drug interactions and for toxic effects that overlap with those of other antituberculosis drugs; adverse effects on embryofetal development were observed in preclinical studies.[8] BTZ-043 is a covalent, irreversible inhibitor of decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1), an essential enzyme in mycobacterial cell-wall synthesis.[9] BTZ-043 has activity against drug-susceptible *M. tuberculosis* strains and resistant strains, with no phenotypic DprE1 resistance detected in clinical isolates, although low-level mmpR5 efflux-pump–mediated resistance is described.[10]

Both ganfeborole and BTZ-043 have shown dose-dependent activity in animal models,[7,11,12] safety in healthy volunteers, and safety and efficacy over 14 days in patients with drug-susceptible tuberculosis[13-16]; safety and efficacy over 16 weeks were shown with a three-drug regimen that included BTZ-043.[17] Here, we report results for the first group of regimens tested in the PARADIGM-4TB (Platform Assessing Regimens and Durations in a Global Multisite Consortium for TB) trial (also known as UNITE4TB-01), an adaptive platform trial that is simultaneously assessing the 10 new 16-week combination regimens built around ganfeborole, BTZ-043, or both drugs.

Methods

Trial Design and Oversight

The current trial is an ongoing phase 2, prospective, multinational, open-label, randomized, controlled platform trial. Stage one involves evaluation of the efficacy and safety of new antituberculosis regimens (efficacy comparison within a superiority framework for regimen selection). Stage two involves assessment of the duration of response to regimens selected in stage one (efficacy comparison within a noninferiority framework for duration selection) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Here we report findings from the assessment of 10 new regimens in stage one.

An independent data and safety monitoring committee reviewed interim safety and efficacy data. An independent trial steering committee (which included a community member) made decisions about the cessation of the trial regimens and the progression of regimens to stage two. National and local ethics committees and regulatory agencies approved the trial. All the participants provided written informed consent. GSK provided ganfeborole, Ludwig Maximilians Universität München provided BTZ-043, Otsuka provided delamanid, and Johnson & Johnson provided bedaquiline. Details on trial oversight and author responsibilities are provided in the Supplementary Appendix.

Trial Population

Participants with rifampin-susceptible pulmonary tuberculosis were enrolled at 14 clinical sites in South Africa, Tanzania, Uganda, Vietnam, and Moldova (countries are listed in order of highest to lowest enrollment size). Participants were at least 18 years of age, had symptoms or evidence of tuberculosis on chest radiography, and had a semiquantitative result of medium or high, without rifampin resistance, on the Xpert MTB/RIF Ultra assay (Cepheid). Complete eligibility criteria are provided in the protocol (available at NEJM.org) and in Section S1 of the Supplementary Appendix.

Randomization and Treatment

Using an online system, we randomly assigned participants in a 1:1 ratio to the regimen groups that were open for enrollment. A minimization algorithm with a random element was used to bal-

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ance the groups according to trial site and risk of relapse (assigned on the basis of semiquantitative results on the Xpert MTB/RIF Ultra assay and findings on chest radiography at screening) (Section S2).

Treatment regimens and doses are shown in Section S3. A 24-week regimen consisting of isoniazid and rifampin plus pyrazinamide and ethambutol during the first 8 weeks (HRZE) was included as a control for all efficacy and safety comparisons. A 16-week regimen consisting of bedaquiline, delamanid, and moxifloxacin (BDM) was included to provide context for interpreting efficacy (but not as a candidate for progression to stage two) and as an additional comparator for assessing the safety of the new regimens. HRZE is the standard treatment for drug-susceptible tuberculosis, and bedaquiline, delamanid, and moxifloxacin are used in the treatment of drug-resistant tuberculosis.

We assessed 10 new 16-week, four-drug regimens that contained ganfeborole, BTZ-043, or both drugs. Three regimens contained ganfeborole, bedaquiline, delamanid, and moxifloxacin (BDMG), pyrazinamide (BDZG), or linezolid (BDLG); one contained ganfeborole, bedaquiline, pretomanid, and moxifloxacin (BPMG); three contained BTZ-043, bedaquiline, delamanid, and moxifloxacin (BDMT), pyrazinamide (BDZT), or linezolid (BDLT); two contained BTZ-043, bedaquiline, moxifloxacin, and pretomanid (BPMT) or pyrazinamide (BMZT); and one contained ganfeborole, BTZ-043, bedaquiline, and delamanid (BDGT). Participants in the BDLG and BDLT groups received linezolid (administered at a dose of 600 mg) during the first 8 weeks only.

Regimens could be extended for up to 7 days for missed doses, or they could be switched to HRZE in the event of an unacceptable side effect, poor response, or other reasons. Treatment adherence was monitored with pill counts and an electronic pill box. Additional measures to support adherence, including directly observed therapy, were implemented when appropriate. Treatment completion was defined as taking at least 100 of the daily doses within the 16-week regimens and at least 120 of the daily doses within the HRZE regimen (≥89% of the total daily doses within the assigned regimen). Adequate adherence was defined as taking at least 100 daily doses within the assigned regimen (84% of the total daily doses) in the first 119 days, without an interruption lasting more than 10 consecutive days. Adequate treatment was defined as treatment completion with adequate adherence.

Symptom assessment and sputum culture were performed at each visit, and additional tests were conducted for participants who had suspected relapse. Participants who met the criteria for disease recurrence were retreated with a 24-week course of standard treatment, with adjustment for the *M. tuberculosis* resistance profile.

ASSESSMENTS

Participants attended clinic visits weekly through week 8 and then every 2 to 8 weeks through week 72, with additional monthly visits by telephone (Section S4). Adverse events (graded according to the Division of AIDS [DAIDS] Table for Grading the Severity of Adult and Pediatric Adverse Events) and adherence were assessed at all visits. Blood tests for the assessment of safety and electrocardiography were performed every 1 to 2 weeks during treatment; chest radiography was performed every 4 to 8 weeks during treatment and if relapse was suspected.

At least two sputum samples were collected at every visit for testing; the number of samples collected at each visit varied because some tests were not performed at all visits. Sputum assessments included *M. tuberculosis* liquid culture with the Mycobacteria Growth Indicator Tube (MGIT) system (Becton Dickinson); drug-susceptibility testing, in which susceptibility to first-line drugs was assessed with MGIT-based methods and the minimum inhibitory concentration of experimental drugs was assessed according to European Committee on Antimicrobial Susceptibility Testing standards; and by genome sequencing to identify reinfection and interpret susceptibility findings.

END POINTS

The primary efficacy end point was the $\log_{10}$(time to positivity) slope, assessed as the rate of change from baseline to week 12 in the time to *M. tuberculosis* growth in a positive MGIT culture. This end point is commonly used in phase 2 tuberculosis trials.[18] The main secondary efficacy end point was a favorable outcome status, defined as a negative culture status without treatment failure, retreatment (unless used to treat reinfection), relapse, or death related to tuberculosis at week 48 (Section S5).

Additional secondary efficacy end points included the time to culture conversion (the time

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from baseline to negative cultures for *M. tuberculosis* at two consecutive visits, without an intervening positive culture) and culture status at weeks 4, 8, 12, and 16. Safety end points were assessed from the start of the assigned treatment through day 30 after the last dose of any drug in the assigned treatment and included severe (grade ≥3) adverse events, serious adverse events, adverse events of special interest (i.e., prolongation of the QT interval [corrected by Fridericia's formula] and hepatotoxic effects), adverse events that were considered by the investigator to be related to the trial treatment, and adverse events that led to discontinuation of the trial treatment or withdrawal from the trial.

STATISTICAL ANALYSIS

The intention-to-treat population included all the participants who had undergone randomization. All efficacy analyses were performed in the modified intention-to-treat population, which included all the participants in the intention-to-treat population who had received at least one dose of the assigned treatment and excluded those who did not have a positive sputum culture by week 4 or who were later identified to have had resistance to at least one trial drug at baseline. Safety analyses were conducted in the safety population, which included all the participants who had undergone randomization and received at least one dose of the assigned treatment.

For each new regimen, we used a Bayesian linear mixed-effects model with a noninformative prior distribution to estimate the posterior distribution of the $\log_{10}$(time to positivity) slope over 12 weeks and the posterior probability that the $\log_{10}$(time to positivity) slope over 12 weeks with the new regimen was superior to that with HRZE (Sections S6 and S7). Sensitivity analyses included an analysis restricted to data from baseline through week 8, an analysis accounting for culture results from multiple samples that had been collected at the same visit, and an analysis using alternative prior probability distributions. The time to culture conversion was analyzed with a Cox proportional-hazards model. The difference between each new-regimen group and the HRZE group with respect to the percentage of participants with a favorable outcome at week 48 was analyzed with logistic regression. Safety analyses were descriptive.

After all the participants had completed 16 weeks of follow-up, an interim analysis was performed to select new regimens for progression to stage two of the trial. A probability of at least 0.975 for a better $\log_{10}$(time to positivity) slope than HRZE and at least 0.025 for a 20% better slope than HRZE was provided as guidance to the independent data and safety monitoring committee for recommending new regimens for progression (Section S8).

Using simulations of decision probabilities for progression to stage two, we estimated that 33 participants per group would be sufficient to correctly identify and no select 99% of the regimens that would ultimately be unsuitable for progression to stage two (on the basis of long-term favorable outcome) and incorrectly identify and not select 1% of the regimens that would ultimately be suitable for progression, assuming that relapse would occur in 5% of the participants in the HRZE group and allowing for 10% attrition (Section S9).

Analyses were performed with Stata, version 19.5 (StataCorp), and R, version 4.4.2 (R Foundation for Statistical Computing). Additional details about the statistical methods are provided in the statistical analysis plan, available with the protocol.

RESULTS

PARTICIPANTS

From January 23, 2024, through July 21, 2025, we screened 723 participants. A total of 401 participants were randomly assigned to the HRZE group (46 participants), the BDM group (34 participants), or one of the 10 new-regimen groups (31 to 35 participants per regimen) (intention-to-treat population). The safety population included 400 participants (1 participant in the intention-to-treat population did not start the assigned treatment), the modified intention-to-treat population included 371 participants (29 participants in the safety population had shown resistance to a trial drug at baseline), and the per-protocol population included 331 participants (39 participants in the modified intention-to-treat had inadequate treatment, and 1 participant had a major protocol deviation) (Fig. 1 and Table S1).

Baseline characteristics were generally similar across the trial groups (Table 1). Overall, 53% of the participants were considered to be at higher risk for relapse on the basis of a semiquantitative

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result of high on the Xpert MTB/RIF Ultra assay and the presence of cavities on a chest radiograph. The representativeness of the trial population is described in Table S2; no participants living with human immunodeficiency virus (HIV) were enrolled.

Overall, 327 of 371 participants (88%) in the intention-to-treat population completed the assigned regimen with adequate adherence (Table S3). Assignment to the BMZT regimen was stopped because of hepatotoxic effects after 31 participants had started the treatment; 6 of these participants were switched to standard treatment.

EFFICACY

The $\log_{10}$(time to positivity) slope in the HRZE group was 0.118 $\log_{10}$(days) per week (95% Bayesian credible interval, 0.105 to 0.131). Among the four groups that received ganfeborole but not BTZ-043, the slope was best with BPMG (0.129 $\log_{10}$[days] per week; 95% Bayesian credible interval, 0.112 to 0.146). The relative difference in slope between the BPMG group and the HRZE group was 9.1% (95% Bayesian credible interval, −8.6 to 29.0), resulting in a probability of superiority of 0.83 (Table 2 and Fig. 2). The slopes in the BDMG and BDZG groups were similar to the slope in the HRZE group, and the slope in the BDLG group was worse than that in the HRZE group (relative difference, −34.7%; 95% Bayesian credible interval, −48.4 to −19.7).

Among the five groups that received BTZ-043 but not ganfeborole, the $\log_{10}$(time to positivity) slope was best with BDMT (0.142 $\log_{10}$[days] per week; 95% Bayesian credible interval, 0.126 to 0.160). The relative difference in slope between the BDMT group and the HRZE group was 20.5% (95% Bayesian credible interval, 2.7 to 41.1), resulting in a probability of superiority of 0.99 (Table 2 and Fig. 2). The BMZT group also had a favorable slope (relative difference vs. HRZE, 18.6%; 95% Bayesian credible interval, 0.6 to 39.2; probability of superiority, 0.98). The slopes in the BDZT and BPMT groups were similar to the slope in the HRZE group, and the slope in the BDLT group was worse than that in the HRZE group (relative difference, −30.5%; 95% Bayesian credible interval, −45.0 to −14.0).

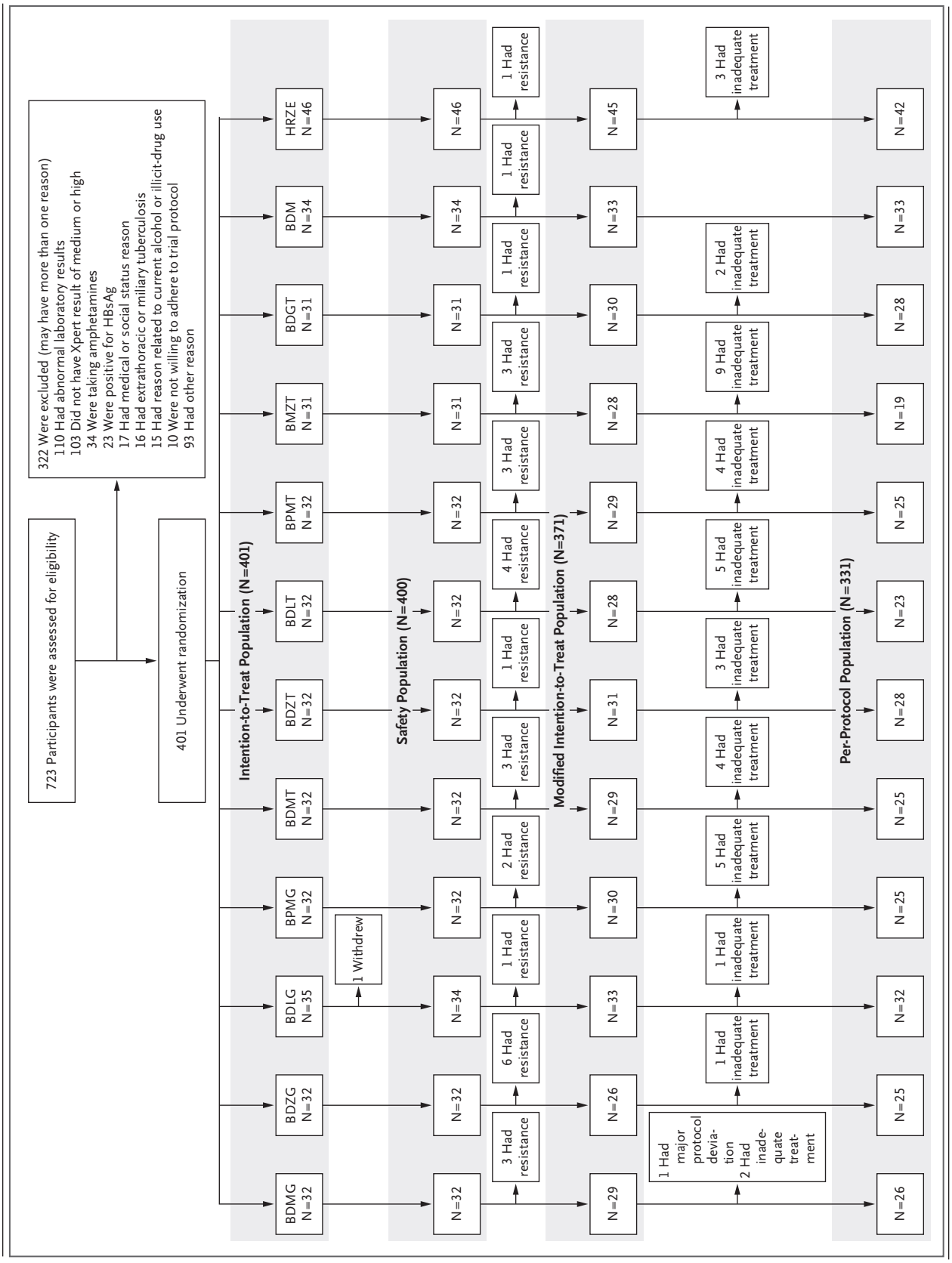
In the group that received both ganfeborole and BTZ-043 (BDGT), the $\log_{10}$(time to positivity) slope was 0.09 $\log_{10}$(days) per week. This slope was worse than that in the HRZE group (relative difference, −24.1%; 95% Bayesian credible interval, −39.3 to −6.6).

In a supportive analysis in which data on the $\log_{10}$(time to positivity) slope were censored for participants with a change in regimen, results were similar to those of the primary efficacy analysis (Table S4). Results of sensitivity analyses were also similar to those of the primary efficacy analysis (Table S5 and Figs. S2 and S3).

Hazard ratios for the time to culture conversion (calculated for each new-regimen group vs. the HRZE group) showed that the relative magnitude of treatment effects across the new regimens was similar to those for the primary efficacy analysis. The BPMG group had the best performance among the groups that received a regimen containing ganfeborole (adjusted hazard ratio, 1.10; 95% confidence interval [CI], 0.61 to 2.00), and the BDMT group had the best performance among the groups that received a regimen containing BTZ-043 (adjusted hazard ratio, 1.51; 95% CI, 0.83 to 2.76); findings for the BMZT group were similar to those for the BDMT group (Table 3). No participants had a positive culture status at weeks 12 and 16 in the BDMT group or at week 16 in the BPMG group (Table 3). The results of a per-protocol analysis were similar.

The interim analysis to select regimens for assessment in stage two was performed after a median follow-up of 43 weeks. At the time of the analysis, incident treatment failure or relapse had occurred in none of 30 participants in the BPMG group and in 1 of 28 participants (4%) in the BDMT group (Table S6). At week 48, a favorable-outcome status was present in 24 of 30 participants (80%) in the BPMG group and in 27 of 29 participants (93%) in the BDMT group, as compared with 40 of 45 participants (89%) in the HRZE group (difference, −8.2 percentage points [95% CI, −26.2 to 9.7] and 4.9 percentage points [95% CI, −9.4 to 19.1], respectively) (Table 3 and Table S7). In a planned supportive analysis that was limited to participants who had an assessable outcome, a favorable-outcome status was present in 24 of 25 participants (96%) in the BPMG group and in 27 of 28 participants (96%) in the BDMT group, as compared with 40 of 42 participants (95%) in the HRZE group (difference, 2.2 percentage points [95% CI, −9.1 to 13.6] and 2.7 percentage points [95% CI, −8.2 to 13.5], respectively) (Table 3). The results of a per-

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Figure 1 (facing page). Screening, Randomization, and Analysis.

The trial assessed 10 new 16-week, four-drug regimens that contained ganfeborole, BTZ-043, or both drugs. Three regimens contained ganfeborole, bedaquiline, delamanid, and moxifloxacin (BDMG), pyrazinamide (BDZG), or linezolid (BDLG); one contained ganfeborole, bedaquiline, pretomanid, and moxifloxacin (BPMG); three contained BTZ-043, bedaquiline, delamanid, and moxifloxacin (BDMT), pyrazinamide (BDZT), or linezolid (BDLT); two contained BTZ-043, bedaquiline, moxifloxacin, and pretomanid (BPMT) or pyrazinamide (BMZT); and one contained ganfeborole, BTZ-043, bedaquiline, and delamanid (BDGT). Included as comparators were the 24-week standard regimen of isoniazid and rifampin, plus pyrazinamide and ethambutol during the first 8 weeks (HRZE), and a 16-week regimen consisting of bedaquiline, delamanid, and moxifloxacin (BDM). Screening may have identified multiple reasons for ineligibility. Enrollment in the BDGT group commenced later than enrollment in other groups and continued for 16 days after the completion of enrollment in the other new-regimen groups and the BDM group. Enrollment in the HRZE group continued contemporaneously with enrollment in the BDGT group; 11 and 6 participants, respectively, were in enrolled in these groups during this period. One participant withdrew before starting treatment; all other participants were included in the safety analysis population, which included all the participants who had undergone randomization and received at least one dose of the assigned treatment. Resistance was defined as resistance to any of the trial drugs at baseline and was assessed later during the trial. Inadequate treatment was defined by incomplete treatment (taking <89% of the total doses of the assigned regimen) or inadequate adherence (taking <84% of the daily doses during the first 119 days or treatment interruption lasting >10 consecutive days); 5 additional participants had inadequate treatment but also had an unfavorable outcome during treatment (4 participants died, and 1 participant had a clinical nonresponse [signs and symptoms of tuberculosis did not resolve]) and were retained in the per-protocol population. One participant had a major protocol deviation that led to exclusion from the per-protocol population; this participant took HRZE together with the assigned treatment for 1 week. Xpert denotes Xpert MTB/RIF Ultra assay. HBsAg denotes hepatitis B virus surface antigen.

protocol analysis were consistent with those of this supportive analysis (Table S8).

SAFETY

A severe (grade ≥3) adverse event during treatment was reported in 24% of the participants in the HRZE group and in 21% of those in the BDM group. One participant in each group had a serious adverse event; the event in the HRZE group was fatal (Table 4).

A severe adverse event occurred in 38% of the participants in the BPMG group and in 25 to 31% of the participants across the remaining three groups that received ganfeborole but not BTZ-043 (Table 4 and Table S9). Five participants in these groups had a serious event; the events were fatal in two of the participants. The serious adverse events were distributed across the four groups, and none were considered by the investigator to be related to the assigned treatment. The percentage of participants with an adverse event of any grade that was considered by the investigator to be related to treatment was generally similar between these four groups and the HRZE and BDM groups. One participant (who was in the BDMG group) discontinued treatment because of an adverse event (psychotic disorder).

A severe adverse event occurred in 28% of the participants in the BDMT group and in 25 to 38% of the participants across the remaining four groups that received BTZ-043 but not ganfeborole (Table 4). Eight participants in these groups had a serious event; the events were distributed across the groups, and none were fatal. Serious events in 5 participants were considered by the investigator to be related to the assigned treatment; a hepatic adverse event occurred in 3 participants in the BMZT group and in 1 participant in the BPMT group, and drug reaction with eosinophilia and systemic symptoms that was related to moxifloxacin (as assessed with patch testing) occurred in 1 participant in the BDMT group. Adverse events of any grade that were related to the trial treatment appeared to be more common in the BTZ-043 groups than in the other treatment groups; this difference was driven mainly by excess gastrointestinal events (predominantly vomiting [median duration, 2 days] and nausea), of which none were severe (Table 4 and Table S10). Ten participants discontinued treatment because of an adverse event, including the 3 participants in the BMZT group who had a hepatic adverse event (Table 4 and Fig. S4).

A severe adverse event occurred in 39% of the participants in the BDGT group (Table 4). Two participants had a serious event; neither event was considered by the investigator to be related to the treatment, and both events were fatal. One participant discontinued treatment because

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Table 1. Baseline Characteristics of the Participants (Intention-to-Treat Population).*

Characteristic	BDMG (N=32)	BDZG (N=32)	BDLG (N=35)	BPMG (N=32)	BDMT (N=32)	BDZT (N=32)	BDLT (N=32)	BPMT (N=32)	BMZT (N=31)	BDGT (N=31)	BDM (N=34)	HRZE (N=46)	Total (N=401)
Median age (IQR) — yr	28 (25–37)	32 (28–41)	29 (23–38)	34 (23–44)	30 (26–34)	32 (24–42)	35 (24–40)	30 (24–44)	30 (25–39)	27 (22–38)	33 (27–42)	29 (25–41)	30 (24–40)
Female sex — no. (%)†	5 (16)	4 (12)	8 (23)	4 (12)	7 (22)	8 (25)	3 (9)	8 (25)	5 (16)	5 (16)	3 (9)	6 (13)	66 (16)
Trial site — no. (%)													
South Africa	13 (41)	13 (41)	14 (40)	14 (44)	11 (34)	14 (44)	13 (41)	11 (34)	12 (39)	11 (35)	12 (35)	19 (41)	157 (39)
Tanzania	9 (28)	10 (31)	9 (26)	10 (31)	10 (31)	9 (28)	9 (28)	9 (28)	8 (26)	9 (29)	10 (29)	12 (26)	114 (28)
Uganda	8 (25)	8 (25)	11 (31)	6 (19)	9 (28)	6 (19)	8 (25)	8 (25)	10 (32)	7 (23)	8 (24)	9 (20)	98 (24)
Vietnam	1 (3)	0	0	1 (3)	2 (6)	2 (6)	1 (3)	2 (6)	0	3 (10)	3 (9)	5 (11)	20 (5)
Moldova	1 (3)	1 (3)	1 (3)	1 (3)	0	1 (3)	1 (3)	2 (6)	1 (3)	1 (3)	1 (3)	1 (2)	12 (3)
BMI‡													
Median (IQR)	19 (17–20)	19 (17–21)	19 (17–21)	19 (18–21)	19 (18–21)	19 (17–20)	18 (17–19)	20 (18–22)	19 (18–22)	19 (17–21)	19 (17–20)	19 (18–21)	19 (17–21)
<18.5 — no. (%)	16 (50)	14 (44)	16 (46)	13 (41)	13 (41)	14 (44)	22 (69)	13 (41)	11 (35)	13 (42)	15 (44)	21 (46)	181 (45)
Current alcohol use — no. (%)	14 (44)	18 (56)	17 (49)	13 (41)	6 (19)	10 (31)	5 (16)	13 (41)	12 (39)	12 (39)	13 (38)	18 (39)	151 (38)
Previous tuberculosis — no. (%)	2 (6)	4 (12)	4 (11)	6 (19)	3 (9)	1 (3)	0	4 (12)	6 (19)	2 (6)	4 (12)	6 (13)	42 (10)
Smear grade of 3+ — no. (%)§	19 (59)	15 (47)	27 (77)	14 (44)	20 (62)	13 (41)	16 (50)	16 (50)	20 (65)	16 (52)	20 (59)	19 (41)	215 (54)
Bacterial load¶													
Medium — no. (%)	12 (38)	10 (31)	10 (29)	11 (34)	9 (28)	12 (38)	10 (31)	10 (31)	11 (35)	9 (29)	9 (26)	16 (35)	129 (32)
High — no. (%)	20 (62)	22 (69)	25 (71)	21 (66)	23 (72)	20 (62)	22 (69)	22 (69)	20 (65)	22 (71)	25 (74)	30 (65)	272 (68)
Median Ct (IQR)	16.3 (16.2–16.9)	16.2 (16.1–16.9)	16.4 (16.2–17.2)	16.4 (16.1–17.0)	16.3 (16.2–16.7)	16.3 (16.2–16.6)	16.3 (16.1–16.6)	16.3 (16.2–16.6)	16.3 (16.2–16.8)	16.3 (16.1–16.7)	16.3 (16.2–16.7)	16.3 (16.2–16.7)	16.3 (16.2–16.7)

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Cavitation on chest radiograph — no. (%)	28 (88)	24 (75)	23 (66)	25 (78)	26 (81)	27 (84)	25 (78)	25 (78)	24 (77)	22 (71)	22 (65)	37 (80)	308 (77)
Risk of relapse — no. (%)‖													
Lower	2 (6)	3 (9)	4 (11)	3 (9)	2 (6)	3 (9)	2 (6)	3 (9)	4 (13)	2 (6)	4 (12)	3 (7)	35 (9)
Moderate	12 (38)	12 (38)	14 (40)	12 (38)	11 (34)	11 (34)	13 (41)	11 (34)	10 (32)	14 (45)	13 (38)	19 (41)	152 (38)
Higher	18 (56)	17 (53)	17 (49)	17 (53)	19 (59)	18 (56)	17 (53)	18 (56)	17 (55)	15 (48)	17 (50)	24 (52)	214 (53)

* This randomized, controlled platform trial assessed 10 new 16-week, four-drug regimens that contained ganfeborole, BTZ-043, or both drugs. Three regimens contained ganfeborole, bedaquiline, delamanid, and moxifloxacin (BDMG), pyrazinamide (BDZG), or linezolid (BDLG); one contained ganfeborole, bedaquiline, pretomanid, and moxifloxacin (BPMG); three contained BTZ-043, bedaquiline, delamanid, and moxifloxacin (BDMT), pyrazinamide (BDZT), or linezolid (BDLT); two contained BTZ-043, bedaquiline, moxifloxacin, and pretomanid (BPMT) or pyrazinamide (BMZT); and one contained ganfeborole, BTZ-043, bedaquiline, and delamanid (BDGT). Included as comparators were the 24-week standard regimen of isoniazid and rifampin, plus pyrazinamide and ethambutol during the first 8 weeks (HRZE), and a 16-week regimen consisting of bedaquiline, delamanid, and moxifloxacin (BDM). Enrollment in the BDGT group commenced later in the trial. Enrollment in the HRZE group was extended to provide contemporaneously enrolled controls for comparison with participants in the BDGT group. Enrollment in the BMZT group was discontinued prematurely because of excess hepatotoxic events. The intention-to-treat population included all the participants who had undergone randomization. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Sex was reported by the participant.

‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ Sputum smear grading on microscopy was based on World Health Organization guidelines, with a grade of 3+ defined by more than 10 acid-fast bacilli per high-power field. Results were not available for 2 participants (1 each in the BDLG and BDLT groups).

¶ The bacterial load is shown as the semiquantitative result on the Xpert MTB/RIF Ultra assay, which assigns a categorical result on the basis of the cycle threshold (Ct).

‖ Lower risk of relapse is defined by a semiquantitative result of medium on the Xpert MTB/RIF Ultra assay and the absence of cavities on a chest radiograph, moderate risk by a semiquantitative result of medium and the presence of cavities or by a result of high and the absence of cavities, and higher risk by a semiquantitative result of high and the presence of cavities.

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Table 2. Primary Efficacy End Point.*

End Point	BDMG (N=29)	BDZG (N=26)	BDLG (N=33)	BPMG (N=30)	BDMT (N=29)	BDZT (N=31)	BDLT (N=28)	BPMT (N=29)	BMZT (N=28)	BDGT (N=30)	BDM (N=33)	HRZE (N=45)
Log_{10}(TTP) slope†												
Overall (95% CrI) — log_{10}(days) per wk	0.103 (0.088 to 0.119)	0.115 (0.098 to 0.132)	0.077 (0.062 to 0.092)	0.129 (0.112 to 0.146)	0.142 (0.126 to 0.160)	0.124 (0.109 to 0.140)	0.082 (0.066 to 0.098)	0.122 (0.106 to 0.139)	0.140 (0.123 to 0.157)	0.09 (0.074 to 0.106)	0.111 (0.096 to 0.126)	0.118 (0.105 to 0.131)
Difference vs. HRZE (95% CrI)												
Absolute — log_{10}(days) per wk	−0.015 (−0.035 to 0.006)	−0.003 (−0.024 to 0.018)	−0.041 (−0.060 to −0.021)	0.011 (−0.011 to 0.0320)	0.024 (0.003 to 0.046)	0.006 (−0.014 to 0.027)	−0.036 (−0.057 to −0.016)	0.004 (−0.017 to 0.025)	0.022 (0.000 to 0.043)	−0.028 (−0.050 to −0.008)	−0.007 (−0.027 to 0.013)	—
Relative — %	−12.4 (−27.9 to 4.9)	−2.7 (−19.5 to 16.6)	−34.7 (−48.4 to −19.7)	9.1 (−8.6 to 29.0)	20.5 (2.7 to 41.1)	5.3 (−11.2 to 23.8)	−30.5 (−45.0 to −14.0)	3.6 (−13 to 23)	18.6 (0.6 to 39.2)	−24.1 (−39.3 to −6.6)	−6.1 (−21.2 to 11.6)	—
Probability of better slope than for HRZE	0.08	0.38	0	0.83	0.99	0.73	0	0.65	0.98	0	0.24	—
Probability of ≥20% better slope than for HRZE	0	0.01	0	0.14	0.52	0.06	0	0.05	0.44	0	0	—

* Data are for the modified intention-to-treat population, which included all the participants who had undergone randomization, received at least one dose of the assigned treatment, and had a culture positive for *Mycobacterium tuberculosis* up to week 4; participants who were later found to have resistance at baseline to any of the trial drugs were excluded. Pairwise comparisons between the new-regimen groups and the HRZE group were performed with data from the subgroup of participants in the HRZE group who had undergone randomization contemporaneously with the participants in each new-regimen group. CrI denotes Bayesian credible interval.

† Data are presented as the posterior estimate of the log_{10}(time to positivity [TTP]) slope, assessed as the rate of change from baseline to week 12 in the time to *M. tuberculosis* growth in liquid culture with the Mycobacteria Growth Indicator Tube system. Estimates were calculated with the use of a Bayesian linear mixed-effects model with a noninformative prior, with adjustment for risk of relapse (fixed effect) and trial site (random effect). For the primary analysis, shown here, changes in treatment from the assigned regimen or cessation of treatment were ignored; missing values after death from any cause were censored. One participant (in the BDLT group) did not have usable data on the time to positivity and was not included in the analysis.

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of an adverse event (progression of pulmonary tuberculosis).

Of the 118 participants with a severe adverse event, 53 (45%) had a decrease from baseline in creatinine clearance, which contributed to excess severe adverse events in some new-regimen groups. In most of these participants, creatinine clearance had decreased by more than 30% from the baseline value (the DAIDS criterion for grade 3 relative decreases), but few values had decreased to less than 60 ml per minute (1 ml per second) (Table 4 and Table S11).

DISCUSSION

In this phase 2, open-label, randomized, platform trial, we assessed 10 new 16-week, four-drug antituberculosis regimens containing ganfeborole, BTZ-043, or both drugs. Two promising regimens, one containing ganfeborole and one containing BTZ-043, were selected for further clinical evaluation.

The best ganfeborole-containing regimen, BPMG (which also included bedaquiline, pretomanid, and moxifloxacin), had a probability of superiority to HRZE of 0.83 with respect to the primary end point of $\log_{10}$(time to positivity) slope, a bacteriologic surrogate end point that was assessed from baseline to week 12. A favorable-outcome status at week 48 was reported in a high percentage of participants in the BPMG group, and there were no major safety concerns precluding further evaluation. In addition to its shorter duration than the standard regimen for rifampin-resistant tuberculosis (16 weeks vs. 6 months), BPMG is appealing for clinical development because it replaces linezolid with ganfeborole, potentially minimizing linezolid use and its associated toxic effects.[2,19]

The best BTZ-043–containing regimen, BDMT (which included bedaquiline, delamanid, and moxifloxacin), had a probability of superiority to HRZE of 0.99 with respect to the bacteriologic surrogate end point, and a high percentage of the participants who received BDMT had a favorable outcome at week 48. There were no major safety concerns precluding further evaluation. Although some participants reported vomiting during BDMT use, the episodes were nonsevere and led to discontinuation in only one participant. Anecdotal reports suggest that vomiting was related to unpalatability of the BTZ-043 pill; the pill is currently being reformulated, with a reduced size (half the pill size used in our trial) and the addition of a coating to improve palatability. A high percentage of severe adverse events

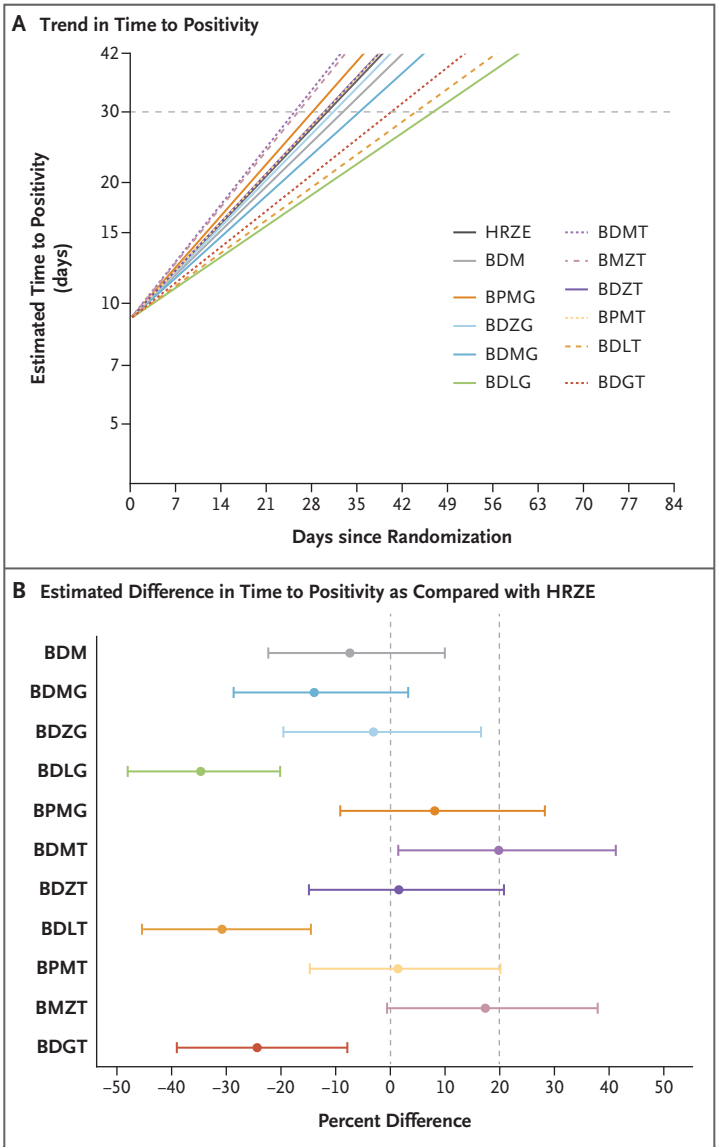


Figure 2. Time to a Positive Sputum Culture.

Panel A shows estimated trends in the time to *Mycobacterium tuberculosis* positivity on sputum culture, presented on a $\log_{10}$ scale, from baseline to week 12 in the trial groups. Data are from the intention-to-treat population and were assessed with a Bayesian linear mixed-effects model adjusted for risk of relapse (fixed effect) and trial site (random effect). Culture was performed with the Mycobacteria Growth Indicator Tube (MGIT) system. One participant (in the BDLT group) did not have usable data on the time to positivity and was not included in the analysis. Panel B shows the median estimated relative difference in the $\log_{10}$(time to positivity) slope as compared with the HRZE group. The vertical dashed lines indicate 0% improvement (left) and 20% improvement (right) from the HRZE group.

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Table 3. Secondary Efficacy End Points.*

End Point	BDMG (N=29)	BDZG (N=26)	BDLG (N=33)	BPMG (N=30)	BDMT (N=29)	BDZT (N=31)	BDLT (N=28)	BPMT (N=29)	BMZT (N=28)	BDGT (N=30)	BDM (N=33)	HRZE (N=45)
Time to culture conversion†												
Adjusted hazard ratio (95% CI)	0.68 (0.38 to 1.24)	0.94 (0.49 to 1.79)	0.18 (0.09 to 0.35)	1.10 (0.61 to 2.00)	1.51 (0.83 to 2.76)	1.12 (0.62 to 2.04)	0.32 (0.16 to 0.64)	0.75 (0.41 to 1.35)	1.54 (0.81 to 2.91)	0.30 (0.15 to 0.58)	0.67 (0.37 to 1.23)	—
Median (IQR) — wk	8.0 (7.0 to 10.0)	6.9 (5.0 to 10.0)	10.3 (9.9 to 13.9)	7.7 (5.0 to 10.0)	6.9 (5.0 to 7.9)	7.0 (6.0 to 8.0)	9.9 (7.0 to 14.0)	8.0 (6.0 to 10.0)	6.0 (5.0 to 8.0)	10 (8.0 to 12.1)	9.9 (5.9 to 10.0)	7.0 (6.0 to 8.0)
Culture status — no. %‡												
Positive at wk 4	29 (100)	21 (81)	33 (100)	22 (73)	23 (79)	27 (87)	24 (86)	24 (83)	22 (79)	25 (83)	31 (94)	37 (82)
Positive at wk 8	12 (41)	11 (42)	26 (79)	9 (30)	4 (14)	7 (23)	14 (50)	12 (41)	4 (14)	18 (60)	17 (52)	7 (16)
Positive at wk 12	1 (3)	2 (8)	10 (30)	1 (3)	0	3 (10)	9 (32)	2 (7)	1 (4)	6 (20)	4 (12)	2 (4)
Positive at wk 16	0	1 (4)	1 (3)	0	0	2 (6)	5 (18)	0	0	2 (7)	3 (9)	0
Outcome status§												
Favorable												
No. of participants (%)	23 (79)	22 (85)	24 (73)	24 (80)	27 (93)	27 (87)	18 (64)	23 (79)	26 (93)	20 (67)	29 (88)	40 (89)
Difference vs. HRZE (95% CI) — percentage points	−8.9 (−27.2 to 9.4)	−3.6 (−21.2 to 14.0)	−15.5 (−34.2 to 3.2)	−8.2 (−26.2 to 9.7)	4.9 (−9.4 to 19.1)	−1.1 (−17.2 to 14.9)	−23.9 (−44.7 to −3.2)	−8.9 (−27.2 to 9.4)	7.1 (−9.0 to 23.2)	−24.5 (−43.9 to −5.1)	−0.4 (−15.9 to 15.2)	—
Unfavorable — no. (%)	2 (7)	2 (8)	8 (24)	1 (3)	1 (3)	3 (10)	7 (25)	2 (7)	1 (4)	7 (23)	4 (12)	2 (4)
Unassessable — no. (%)	4 (14)	2 (8)	1 (3)	5 (17)	1 (3)	1 (3)	3 (11)	4 (14)	1 (4)	3 (10)	0	3 (7)
Favorable: assessable population¶												
No./total no. (%)	23/25 (92)	22/24 (92)	24/32 (75)	24/25 (96)	27/28 (96)	27/30 (90)	18/25 (72)	23/25 (92)	26/27 (96)	20/27 (74)	29/33 (88)	40/42 (95)
Difference vs. HRZE (95% CI) — percentage points	−1.8 (−15.3 to 11.8)	−2.1 (−16.0 to 11.8)	−18.8 (−35.9 to −1.6)	2.2 (−9.1 to 13.6)	2.7 (−8.2 to 13.5)	−3.7 (−17.4 to 9.9)	−21.8 (−41.2 to −2.3)	−1.8 (−15.3 to 11.8)	4.0 (−8.5 to 16.5)	−19.9 (−38.3 to −1.4)	−5.9 (−19.8 to 8.1)	—

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* Unless otherwise indicated, data are for the modified intention-to-treat population. Pairwise comparisons between the new-regimen groups and the HRZE group were performed with data from the subgroup of participants in the HRZE group who had undergone randomization contemporaneously with the participants in each new-regimen group. CI denotes confidence interval.
† The time to culture conversion was defined as the time from randomization to the first visit at which a negative culture status was defined by two negative sputum cultures on consecutive visits without an intervening positive culture. The culture result assigned at each visit was based on culture of all sputum samples collected at the visit; the culture result was recorded as negative if a sputum specimen could not be provided, and the culture result was considered to be missing if the culture was contaminated. The time to culture conversion was analyzed with a Cox proportional-hazards model adjusted for trial site and risk of relapse. Proportional-hazards assumptions were tested with Schoenfeld residuals and found to hold ($P>0.05$).
‡ A positive culture status indicates the absence of two consecutive negative sputum cultures without an intervening positive culture in participants who remained in follow-up at the indicated week.
§ A favorable outcome was defined by a negative culture status without treatment failure, retreatment (unless used to treat reinfection), relapse, or death related to tuberculosis at week 48. An unfavorable outcome was defined by treatment failure (the absence of a negative culture status at week 48 or noncompletion of treatment owing to clinical nonresponse [signs and symptoms of tuberculosis did not resolve] or deterioration), retreatment (including extending initial treatment for reasons other than to make up missed doses, changing treatment because of treatment failure, or restarting treatment without evidence of reinfection), or relapse (two consecutive positive cultures after the end of treatment in participants who previously had a negative culture status or one positive culture that met criteria for retreatment). Reinfection with a different strain, as detected on genome sequencing, was not counted as retreatment or relapse. The difference between each new-regimen group and the HRZE group with respect to the percentage of participants with a favorable outcome at week 48 was estimated with logistic regression. Unadjusted estimates are shown because data were too sparse to fit the adjusted model. Reasons for classification of the outcome status as unfavorable or unassessable are shown in Table S7.
¶ The assessable population comprises the modified intention-to-treat population, with the additional exclusion of participants with an unassessable outcome status. This analysis is supportive and includes the unverified assumption that the percentage of participants with a favorable outcome is the same among those with an unassessable outcome status and those with an assessable outcome status.

across all the trial groups were due to a decrease from baseline in creatinine clearance, which remained within the normal range; this finding has been reported in previous trials.[20]

The trial also has findings relevant to registered drugs in current clinical use. First, whether pretomanid and delamanid — the two nitroimidazoles recommended by the World Health Organization for rifampin-resistant tuberculosis — are interchangeable has been unclear. Only one previous trial has evaluated both agents in combination with identical companion drugs, but the trial did not compare the regimens formally.[21] The relative difference between the two drugs appeared to change direction when they were assessed in otherwise identical regimens containing ganfeborole or BTZ-043. An exploratory investigation with a factorial design in which participants are randomly assigned to receive BDMT or BPMT is planned for stage two of the current trial. Second, although high bacteriologic efficacy was observed in the BMZT group, the hepatotoxic effects observed with this regimen resemble those reported in previous trials in which promising pyrazinamide-containing regimens were terminated because of these adverse events.[22,23] Hepatotoxic effects have previously been attributed to combination regimens containing pyrazinamide, pretomanid, and moxifloxacin, but the results of our trial suggest that the risk of pyrazinamide-associated hepatotoxic effects extends beyond these combinations.[24] Third, we limited the duration of linezolid therapy to 8 weeks to minimize the risk of toxic effects in this population with drug-susceptible tuberculosis. The poor performance of both linezolid-containing regimens that were included the trial suggests that the 8-week duration is insufficient and is consistent with results of a previous trial involving short-duration linezolid.[19]

This trial, in its design and scale, represents an efficient strategy for early-phase evaluation of new antituberculosis drug regimens. The treatment period ended when administration of the drugs in the new regimens ended at week 16. This approach is in contrast to the common practice in past trials of antituberculosis drugs, in which the total treatment duration was extended to 24 weeks by adding an additional course of HRZE. Ending treatment in the new-regimen groups at 16 weeks permitted the comparison of the trial regimens on the basis of both the

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Table 4. Adverse Events during the Treatment Period (Safety Population).*

Event	BDMG (N=32)	BDZG (N=32)	BDLG (N=34)	BPMG (N=32)	BDMT (N=32)	BDZT (N=32)	BDLT (N=32)	BPMT (N=32)	BMZT (N=31)	BDGT (N=31)	BDM (N=34)	HRZE (N=46)	Overall (N=400)
	number of participants (percent)												
Adverse event of grade ≥3	8 (25)	10 (31)	9 (26)	12 (38)	9 (28)	8 (25)	11 (34)	12 (38)	9 (29)	12 (39)	7 (21)	11 (24)	118 (29)
Serious adverse event†	1 (3)	1 (3)	1 (3)	2 (6)	2 (6)	1 (3)	0	2 (6)	3 (10)	2 (6)	1 (3)	1 (2)	17 (4)
Prespecified adverse events of special interest													
QTcF prolongation‡	4 (12)	2 (6)	2 (6)	2 (6)	3 (9)	1 (3)	2 (6)	1 (3)	1 (3)	0	5 (15)	0	23 (6)
Hepatotoxic effects§	3 (9)	1 (3)	3 (9)	3 (9)	2 (6)	3 (9)	0	3 (9)	3 (10)	5 (16)	3 (9)	5 (11)	34 (8)
Treatment-related adverse event	18 (56)	20 (62)	20 (59)	17 (53)	22 (69)	23 (72)	20 (62)	21 (66)	21 (68)	20 (65)	19 (56)	28 (61)	249 (62)
Adverse event leading to discontinuation of treatment¶	1 (3)	0	0	0	2 (6)	0	2 (6)	3 (9)	3 (10)	1 (3)	0	0	12 (3)

* The safety population comprised all participants who had undergone randomization and received at least one dose of the assigned trial treatment. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.0. Severity was graded with the use of the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Participants with multiple adverse events in each category were counted only once in each category. Adverse events were counted if they started between the administration of the first dose of any drug in the assigned regimen and day 30 after the last administration of any drug in the assigned regimen.

† Serious adverse events included pneumonia (resulting in death) in one participant in the HRZE group; complicated malaria in one participant in the BDM group; dengue fever in one participant in the BDMG group; chemical poisoning (resulting in death) in one participant in the BDZG group; constipation in one participant in the BDLG group; hyperglycemia and respiratory failure (resulting in death) in one participant and road traffic accident in one participant in the BPMG group; anal fistula in one participant and drug reaction with eosinophilia and systemic symptoms (DRESS) related to treatment in one participant in the BDMT group; head injury in one participant in the BDZT group; lower respiratory tract infection in one participant and abnormal hepatic function related to treatment in one participant in the BPMT group; abnormal hepatic function related to treatment in one participant, drug-induced liver injury related to treatment in one participant, and hepatic enzyme increased related to treatment in one participant in the BMZT group; and progression of tuberculosis (resulting in death) in one participant and respiratory distress (resulting in death) in one participant in the BDGT group.

‡ Prolongation of the QT interval corrected by Fridericia's formula (QTcF) was defined as an adverse event of any DAIDS grade that was identified on the basis of a standardized MedDRA query with the preferred term torsade de pointes/QT prolongation (narrow scope).

§ Hepatotoxic effects were defined as adverse events of any DAIDS grade that were identified on the basis of a standardized MedDRA query with the preferred term hepatic disorders (broad scope).

¶ Adverse events leading to discontinuation of treatment were brief psychotic disorder in one participant in the BDMG group; vomiting in one participant and DRESS (also classified as a severe adverse event) in one participant in the BDMT group; peripheral neuropathy in one participant and QTcF prolongation in one participant in the BDLT group; hypersensitivity in one participant, brain fog in one participant, and abnormal hepatic function in one participant in the BPMT group; abnormal hepatic function in one participant, drug-induced liver injury in one participant, and increased hepatic enzyme levels in one participant in the BMZT group; and progression of pulmonary tuberculosis in one participant in the BDGT group. There were no adverse events in any of the treatment groups that led to withdrawal of consent from the trial.

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$\log_{10}$(time to positivity) slope and favorable outcome. The $\log_{10}$(time to positivity) slope is the microbiologic end point of choice for phase 2 trials of antituberculosis drugs, although it is an imperfect surrogate (previous studies have shown an uneven predictability of eventual cure),[25] and favorable outcome is the definitive indicator of cure.

At the time of the interim analysis, the trial steering committee selected BPMG and BDMT as the primary regimens for progression to stage two. This decision was made on the basis of data that included the accumulated percentage of participants with incident treatment failure or relapse, the $\log_{10}$(time to positivity) slope, culture conversion, and safety. The probability of superiority of BPMG was 0.83, which is below the threshold for progression that was specified in guidance provided to the independent data and safety monitoring committee, but greater value was assigned to the absence of treatment failure or relapse with this regimen. BPMT was also selected for progression to stage two as a comparator to BDMT in order to explore the effects of nitroimidazoles. The trial illustrates how differences in incident treatment failure or relapse (the main cause for not meeting criteria for a favorable outcome) may strengthen confidence in (and most likely the accuracy of) early clinical development decisions. The low percentage of participants with early treatment failure or relapse in some groups at the time of the interim analysis had a substantive effect on decisions regarding progression to stage two, and the paucity of unfavorable outcomes in the selected regimens was sustained at the definitive analysis of favorable-outcome status at 48 weeks.

The current trial assessed a large number of new regimens, which is unprecedented for a tuberculosis trial and has advantages beyond the simple additive value of multiple pairwise control comparisons. Evaluating multiple regimens that differ with respect to a single drug may suggest possible contributions of individual drugs to the performance of the regimen, although informal comparisons between small groups warrant cautious interpretation. The scale and platform design of our trial minimize the risk of trial termination if one or two candidate regimens cease to be viable[21,26] and thereby enhance trial continuity and efficiency — factors that are important for accelerating regimen evaluation. In due course, model-based selection may result in accurate predictions of efficacy, reducing the number of regimens considered to be priority candidates for testing in early-phase trials.[27] However, the results of our trial suggest that extensive testing of regimens in early-phase trials currently represents a more secure basis for selection because it allows decisions to be made on the basis of a range of efficacy and safety end points. Such large-scale clinical trials may accelerate the validation of model-based predictions.

Limitations of our trial include the open-label administration of drugs, but the use of multiple placebos was not feasible for several reasons, including the added pill burden. However, the laboratory-based primary end point ($\log_{10}$[time to positivity] slope), which was analyzed with standardized methods with blinding to regimen, reduces the chance of bias. Time to positivity is a surrogate end point, rather than a clinical end point, and has not always predicted clinical end points.[25] The small sample sizes in each trial group limit the precision of the findings. The trial enrolled relatively few female or non-African participants and no participants living with HIV. Participants had rifampin-susceptible tuberculosis, whereas the target clinical population includes persons with rifampin-resistant tuberculosis. However, the relative efficacy of the new regimens should not differ if rifampin-resistant strains retain susceptibility to all drugs in these regimens. The assessment of regimen safety was performed with traditional approaches to adverse-event reporting, which consider the totality of the data, including data on low-grade events. Nevertheless, the effect of adverse events on treatment experience and acceptability may not have been fully captured. A greater role of participant-reported outcomes is planned in subsequent studies.

In this randomized, controlled, platform trial involving participants with rifampin-susceptible pulmonary tuberculosis, we identified two promising 16-week regimens, each containing a drug with a new mechanism of action, for further clinical development. Our findings show the potential of large-scale, early-phase clinical trials for evaluating multiple regimens simultaneously with a design that permits the use of early data on treatment failure or relapse to inform selection of regimens for further evaluation.

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