ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch., Timothy D. McHugh, Ph.D., Melvin Spigelman, M.D., David A.J. Moore, M.D., Koert Ritmeijer, Ph.D., Philipp du Cros, M.B., B.S., and Katherine Fielding, Ph.D., for the TB-PRACTECAL Study Collaborators*

ABSTRACT

BACKGROUND

In patients with rifampin-resistant tuberculosis, all-oral treatment regimens that are more effective, shorter, and have a more acceptable side-effect profile than current regimens are needed.

METHODS

We conducted an open-label, phase 2–3, multicenter, randomized, controlled, noninferiority trial to evaluate the efficacy and safety of three 24-week, all-oral regimens for the treatment of rifampin-resistant tuberculosis. Patients in Belarus, South Africa, and Uzbekistan who were 15 years of age or older and had rifampin-resistant pulmonary tuberculosis were enrolled. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) was compared with a 9-to-20-month standard-care regimen. The primary outcome was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks after randomization. The noninferiority margin was 12 percentage points.

RESULTS

Recruitment was terminated early. Of 301 patients in stage 2 of the trial, 145, 128, and 90 patients were evaluable in the intention-to-treat, modified intention-to-treat, and per-protocol populations, respectively. In the modified intention-to-treat analysis, 11% of the patients in the BPaLM group and 48% of those in the standard-care group had a primary-outcome event (risk difference, –37 percentage points; 96.6% confidence interval [CI], –53 to –22). In the per-protocol analysis, 4% of the patients in the BPaLM group and 12% of those in the standard-care group had a primary-outcome event (risk difference, –9 percentage points; 96.6% CI, –22 to 4). In the as-treated population, the incidence of adverse events of grade 3 or higher or serious adverse events was lower in the BPaLM group than in the standard-care group (19% vs. 59%).

CONCLUSIONS

In patients with rifampin-resistant pulmonary tuberculosis, a 24-week, all-oral regimen was noninferior to the accepted standard-care treatment, and it had a better safety profile. (Funded by Médecins sans Frontières; TB-PRACTECAL ClinicalTrials.gov number, NCT02589782.)

From the Public Health Department, Operational Center Amsterdam (OCA), Médecins sans Frontières, Amsterdam (B.-T.N., K.R.); the Public Health Department, OCA, Médecins sans Frontières (C.B., E.K., I.M.), the London School of Hygiene and Tropical Medicine (B.-T.N., M.D., D.A.J.M., K.F.), and University College London (T.D.M.) — all in London; the Republican Specialized Scientific and Practical Medical Center of Phthisiology and Pulmonology, Tashkent (N.P., I.L.), and the Republican Phthisiological Hospital No. 2, Nukus (Z.T.) — both in Uzbekistan; the Republican Scientific and Practical Center for Pulmonology and Tuberculosis, Minsk, Belarus (V.S.); THINK TB and HIV Investigative Network, Durban (R.M.), and Wits Health Consortium, Johannesburg (N.N., M.R.) — both in South Africa; the Global Alliance for TB Drug Development, New York (M.S.); and the Burnet Institute, Melbourne, VIC, Australia (P.C.). Dr. Nyang'wa can be contacted at bern.nyangwa@london.msf.org or at Médecins sans Frontières, Operational Center Amsterdam, Plantage Middenlaan 14, 1018 DD Amsterdam, the Netherlands.

*A complete list of the TB-PRACTECAL study collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

In 2019, approximately 465,000 patients had rifampin-resistant tuberculosis worldwide.[1] A total of 59% of the patients with rifampin-resistant tuberculosis who began receiving treatment in 2018 have had successful outcomes, and this incidence has not improved much in the past 5 years.[2]

The recommended duration of treatment for rifampin-resistant tuberculosis in programmatic care settings is 9 to 20 months[3] and involves up to 20 tablets per day. Cost,[4] adverse events,[5] and social disruption are prominent challenges. More effective, shorter treatments with a more acceptable side-effect profile are needed.[6] In a two-stage, phase 2–3 clinical trial (Pragmatic Clinical Trial for a more Effective, Concise and Less Toxic Regimen [TB-PRACTECAL]), we evaluated the safety and efficacy of 24-week, all-oral regimens for the treatment of rifampin-resistant tuberculosis.

In stage 1 of the trial, the primary objective was to identify regimens containing bedaquiline, pretomanid, and linezolid (BPaL) for evaluation in stage 2 on the basis of safety and efficacy at 8 weeks after randomization. The primary objective in stage 2 was to evaluate the safety and efficacy of a 24-week regimen containing BPaL plus moxifloxacin (BPaLM) for the treatment of rifampin-resistant tuberculosis. We report the outcomes of both stages of the trial as well as the results of additional analyses involving the groups that were not included in stage 2 of the trial.

Methods

Trial Design and Oversight

We conducted an open-label, phase 2–3, multicenter, randomized, controlled noninferiority trial to compare the safety and efficacy of three investigational 24-week regimens with those of the accepted 9-to-20-month standard-care treatment for rifampin-resistant pulmonary tuberculosis. The trial was designed to seamlessly transition from a phase 2b trial to a phase 3 trial with one or two investigational groups. Further details are provided in Section S4 in the Supplementary Appendix and the protocol, both of which are available with the full text of this article at NEJM.org. The trial was approved by institutional ethics boards as well as local ethics committees and national regulatory authorities in the countries where the trial was conducted.

The trial was designed by the protocol development team (Section S1.1 in the Supplementary Appendix). The data were collected by the site investigators, and the statistical analysis was performed by the tenth and last authors and interpreted by all the authors. The first draft of the manuscript was written by the first four authors and the last author. All the authors participated in revision of the manuscript, approved the submitted versions, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients 15 years of age or older who had rifampin-resistant pulmonary tuberculosis were enrolled at seven sites in Belarus, South Africa, and Uzbekistan. The investigators were notified of new cases of laboratory-diagnosed rifampin-resistant tuberculosis from within the catchment areas.

The major inclusion criterion was *Mycobacterium tuberculosis* infection (as confirmed by a positive sputum smear) with resistance to rifampin. Patients were included irrespective of fluoroquinolone resistance, human immunodeficiency virus (HIV) status, or CD4 count. Patients were excluded if they were pregnant or if they had an alanine aminotransferase level or an aspartate aminotransferase level higher than 3 times the upper limit of the normal range, a corrected QT interval calculated with the use of Fridericia's formula (QTcF) greater than 450 msec, structural heart disease, or suspected resistance to bedaquiline, pretomanid, or linezolid. All the patients provided written informed consent.

Treatment

In stage 1 of the trial, enrolled patients were randomly assigned to the locally accepted standard-care treatment or to one of three investigational regimens. The standard-care regimen consisted of locally accepted treatment regimens. These regimens were closely aligned with the World Health Organization (WHO) guidelines for treatment of drug-resistant tuberculosis,[3] and the agents (some oral and some intravenous) were administered at least 6 days per week with food and under observation (see Section S5).

All the investigational agents were administered orally, with food and under observation, 7 days per week. The BPaL regimen consisted of the following: bedaquiline at a dose of 400 mg daily for 2 weeks, followed by 200 mg three

times per week for 22 weeks; pretomanid at a dose of 200 mg daily for 24 weeks; and linezolid at a dose of 600 mg daily for 16 weeks, followed by 300 mg daily for 8 weeks. The BPaLM regimen included BPaL plus moxifloxacin at a dose of 400 mg daily for 24 weeks, and the BPaLC regimen included BPaL plus clofazimine at a dose of 100 mg daily (or 50 mg if the patient weighed <30 kg) for 24 weeks. In stage 2 of the trial, patients were enrolled either into the standard-care group or into one of two investigational groups.

PROCEDURES

Patients were randomly assigned in a 1:1:1:1 ratio in stage 1 of the trial and in a 1:1 ratio in stage 2 of the trial (see the Supplementary Appendix). Randomization lists were prepared by the trial statisticians, and randomization was stratified according to trial site.

The trial schedule (see the protocol) included weekly visits for the first 2 weeks, monthly visits until week 24, and then visits every 2 months until week 108. Each visit included laboratory tests, three electrocardiographic assessments, and a physical examination that included a neurologic assessment. Assessments of visual acuity and color blindness and audiometric testing were also performed according to the schedule. The investigators assessed adverse events at each visit. Serious adverse events, adverse events of special interest, pregnancies, and overdoses that were identified were reported to the pharmacovigilance officer within 24 hours.

At inclusion and at scheduled time points, two sputum samples were obtained for smear microscopy and culture in liquid medium with the use of the Mycobacteria Growth Indicator Tube (MGIT) system (Becton Dickinson). Drug-susceptibility testing was performed in *M. tuberculosis* isolates that were obtained at baseline and in any samples that were culture positive at week 16 or later. Culture conversion was defined as at least one positive culture at baseline and at least two consecutive negative cultures obtained at least 2 weeks apart. Paired whole-genome sequencing was conducted in the event of treatment failure or recurrence of tuberculosis.

OUTCOMES

In stage 1 of the trial, the primary efficacy outcome was culture conversion in MGIT liquid medium at 8 weeks after randomization. The primary safety outcome was the incidence of death or discontinuation of treatment for any reason by week 8.

In stage 2 of the trial, the primary outcome was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks after randomization. The secondary efficacy outcomes were culture conversion at 12 weeks, time to culture conversion, composite unfavorable outcomes at 24 weeks and 108 weeks after randomization, and recurrence of tuberculosis by week 48 after randomization (in the investigational groups only).

The safety outcomes in stage 2 of the trial were at least one serious adverse event or an adverse event of grade 3 or higher at 72 and 108 weeks after randomization and at the end of treatment and the incidence of prolongation of the QTcF interval at week 24. Deaths and adverse events of special interest were also reported.

ANALYSIS POPULATIONS

In the efficacy analyses, the intention-to-treat population included all patients who had undergone randomization. In the safety analyses, the as-treated population comprised all patients who had undergone randomization and received at least one dose of trial medication, and the patients were evaluated according to the regimen they received. The modified intention-to-treat population included patients in the intention-to-treat population who had received at least one dose of trial medication and excluded patients who did not have microbiologically proven rifampin-resistant tuberculosis. The per-protocol population included patients in the modified intention-to-treat population except those who did not complete a protocol-adherent course of treatment (>80% of doses within 120% of the prescribed duration) for any reason other than treatment failure or death and for those who discontinued treatment early because after they had received the first dose of trial treatment it was discovered that they had not met the inclusion or exclusion criteria.

Enrollment was terminated early for benefit, on March 18, 2021, in accordance with a recommendation from the data and safety monitoring board. We then performed an unplanned analysis, the results of which are presented here. In this analysis, the populations were restricted to include patients who could have had a prespecified

outcome event at a given time point (i.e., week 24, week 72, and week 108).

ADDITIONAL ANALYSES

After the stage 1 analysis, no analyses involving patients who were not included in stage 2 of the trial were planned. These patients were also followed to week 108, and these supportive data were viewed as important. All prespecified stage 2 analyses that involved the BPaLM group also were performed in the BPaLC and BPaL groups.

STATISTICAL ANALYSIS

The sample-size calculation is provided in the Supplementary Appendix. With the assumption that at 72 weeks after randomization 50% of the patients in the standard-care group and 45% of those in the investigational groups would have an unfavorable outcome event, we determined that a sample of 181 patients per group in trial stage 2 would provide the trial with approximately 85% power to detect a noninferiority margin of 12 percentage points. An alpha level of 1.7% (equivalent to a two-sided 96.6% confidence interval) was chosen to allow for both the adaptive nature of the design and the multiple comparisons of up to three groups. The estimated sample was increased to 201 patients per group to allow for patients who could not be evaluated. A noninferiority margin of 12 percentage points as the upper boundary of the confidence interval was determined to be a reasonable clinical and public health trade-off limit, given the benefits of a shorter treatment duration, decreased pill burden and regimen cost, and the all-oral nature of the investigational regimens. This noninferiority margin was congruent with that in recent trials involving patients with drug-resistant tuberculosis in which the noninferiority margin was 10 to 12 percentage points.[7,8]

The efficacy outcomes were analyzed in the intention-to-treat, modified intention-to-treat, and per-protocol populations, and the safety outcomes were analyzed in the as-treated population. Binary outcomes were summarized with absolute risk differences (with the use of a generalized linear model for a binomial outcome with an identity function) and risk ratios (with the use of a generalized linear model for a binomial outcome with a log-link function). Adjustment for randomization site was planned in all analyses. For the primary efficacy and safety outcomes, corresponding two-sided 96.6% confidence intervals were reported for effect estimates, and two-sided 95% confidence intervals were reported for secondary efficacy outcomes. The secondary outcomes were not adjusted for multiplicity. Prespecified subgroup analyses were conducted for the primary efficacy outcome. For binary safety outcomes, risk differences are reported with the use of the same approach as that described above. For the safety outcome of the QTcF value at 24 weeks, the difference in the mean value in each investigational group from the mean value in the standard-care group was assessed with adjustment for baseline QTcF values and with the use of linear regression.

Additional analyses of safety and efficacy were conducted in the BPaLC and BPaL groups with the use of the same approach but with two-sided 95% confidence intervals. Additional details are provided in the Supplementary Appendix.

Figure 1 (facing page). Trial Populations and Design.

Panel A shows the populations involved in the primary efficacy and safety analyses in stage 2 of the trial, including the patients who were excluded from the trial. Panel B shows the trial design. The trial was designed as a phase 2–3 clinical trial with a seamless transition from phase 2b to phase 3. Stage 1 included 240 patients with 60 patients in each group. A planned analysis involving the investigational groups only was then conducted to select groups for evaluation in stage 2. Evaluable patients included those who were enrolled in stage 1 and subsequently were included in the groups in stage 2. The first patient underwent randomization and the first visit occurred in January 2017, and stage 1 recruitment was completed in mid-2019. All three investigational groups met the eligibility criteria for progression to stage 2, but the trial steering committee elected to proceed with the BPaLM group only. Recruitment continued through the transition period across all four groups. This transition was delayed owing to the coronavirus disease 2019 pandemic. Recruitment was terminated for efficacy on March 18, 2021. Patients in all the groups underwent follow-up in accordance with the protocol for a minimum of 72 weeks after randomization. BPaL denotes bedaquiline, pretomanid, and linezolid; BPaLC bedaquiline, pretomanid, linezolid, and clofazimine; and BPaLM bedaquiline, pretomanid, linezolid, and moxifloxacin.

RESULTS

PATIENTS

The first patient underwent randomization in January 2017. A total of 552 patients were ran-

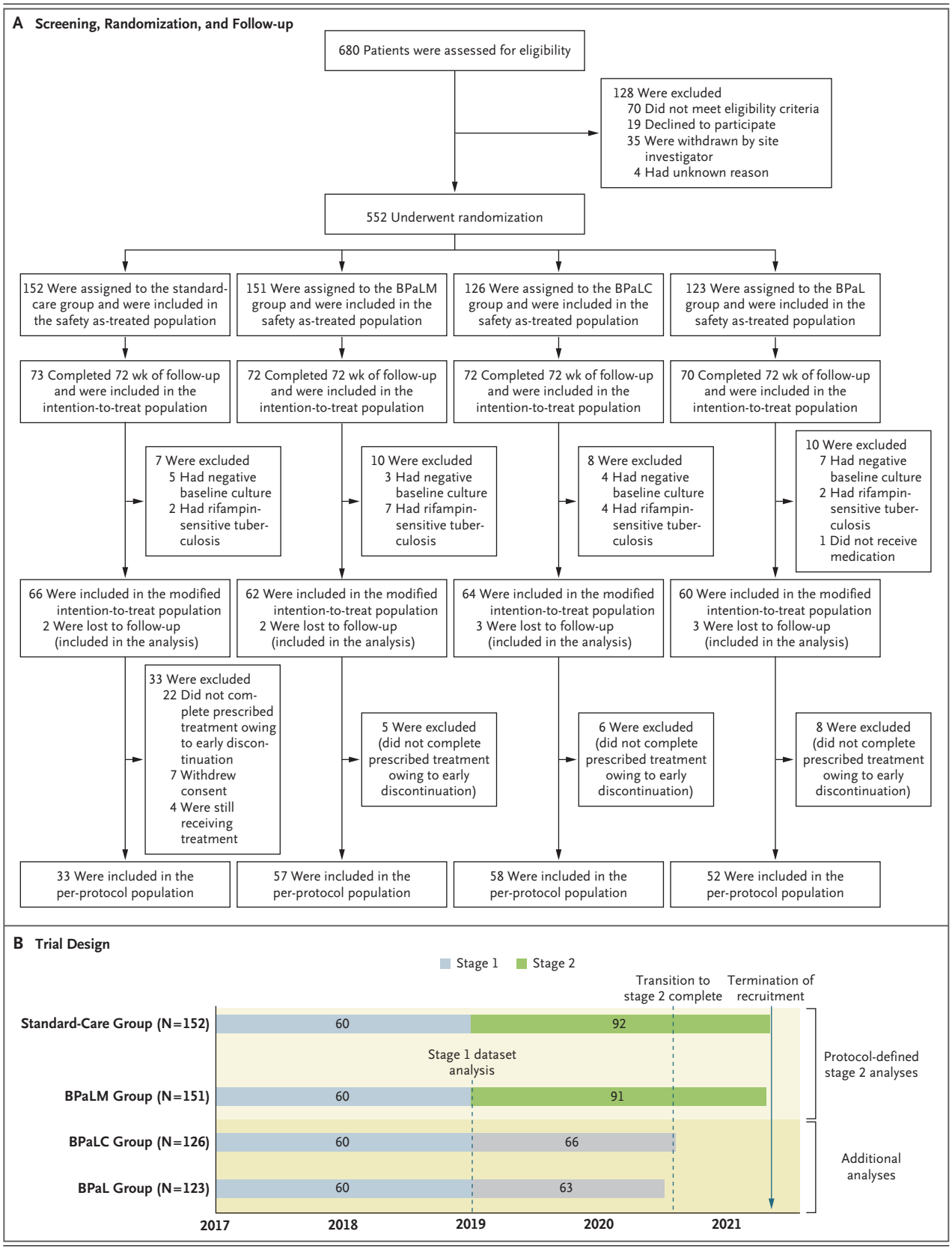

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Standard-Care Group	BPaLM Group	BPaLC Group	BPaL Group
Intention-to-treat population				
No. of patients	152	151	126	123
Geographic distribution — no. (%)				
Belarus	29 (19.1)	28 (18.5)	21 (16.7)	21 (17.1)
South Africa	54 (35.5)	56 (37.1)	48 (38.1)	47 (38.2)
Uzbekistan	69 (45.4)	67 (44.4)	57 (45.2)	55 (44.7)
Median age (range) — yr	37 (18–71)	35 (17–71)	32 (15–67)	35 (15–72)
Female sex — no. (%)	56 (36.8)	66 (43.7)	42 (33.3)	58 (47.2)
Median BMI (IQR)†	19.9 (17.3–22.8)	19.8 (17.7–22.7)	19.5 (17.7–22.2)	20.0 (18.1–22.4)
HIV-positive status — no. (%)	41 (27.0)	38 (25.2)	33 (26.2)	41 (33.3)
Median CD4 cell count (IQR) in HIV-infected patients — cells/mm^3‡	250 (132–460)	330 (209–547)	297 (114–481)	326 (153–550)
Smear positivity — no. (%)	98 (64.5)	91 (60.3)	84 (66.7)	77 (63)
Cavitation on chest radiography present — no. (%)	95 (62.5)	80 (53.0)	79 (62.7)	74 (60.2)
Fluoroquinolone-resistant tuberculosis — no./total no. (%)	32/131 (24.4)	32/134 (23.9)	22/118 (18.6)	25/104 (24.0)
QTcF interval — msec§	401±19	398±19	395±19	398±19
Median ALT level (IQR) — IU/liter¶	20 (15–28)	19 (14–28)	17 (14–26)	20 (14–31)
Modified intention-to-treat population with 72 wk of follow-up				
No. of patients	66	62	64	60
Geographic distribution — no. (%)				
Belarus	12 (18)	10 (16)	10 (16)	11 (18)
South Africa	18 (27)	16 (26)	19 (30)	16 (27)
Uzbekistan	36 (55)	36 (58)	35 (55)	33 (55)
Median age (range) — yr	36 (19–71)	34 (18–61)	29 (19–63)	34 (18–62)
Female sex — no. (%)	33 (50)	26 (42)	24 (38)	28 (47)
Median BMI (IQR)	19.2 (17.3–22.0)	19.8 (18.1–22.1)	18.8 (17.4–22.0)	20.5 (18.2–22.8)
HIV-positive status — no. (%)	15 (22.7)	14 (23)	14 (22)	14 (23)
Median CD4 cell count (IQR) — cells/mm^3‖	317 (154–383)	268 (182–364)	394 (112–511)	283 (153–424)
Smear positivity — no. (%)	50 (76)	40 (65)	43 (67)	45 (75)
Cavitation on chest radiography present — no. (%)	47 (71)	33 (53)	39 (61)	41 (68)
Fluoroquinolone-resistant tuberculosis — no./total no. (%)	18/65 (28)	17/60 (28)	16/62 (26)	19/56 (34)
QTcF interval — msec	398±18	396±18	393±20	398±18
Median ALT level (IQR) — IU/liter**	20 (15–27)	18 (14–27)	18 (15–27)	19 (14–27)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The intention-to-treat population included all patients who had undergone randomization, and the modified intention-to-treat population included all patients in the intention-to-treat population who had received at least one dose of trial medication and excluded those who did not have microbiologically proven rifampin-resistant tuberculosis. ALT denotes alanine aminotransferase; BPaL bedaquiline, pretomanid, and linezolid; BPaLC bedaquiline, pretomanid, linezolid, and clofazimine; BPaLM bedaquiline, pretomanid, linezolid, and moxifloxacin; HIV human immunodeficiency virus; IQR interquartile range; and QTcF corrected QT interval, calculated with Fridericia's formula.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Data on BMI were missing for one patient in the standard-care group.

‡ Data on CD4 cell count were missing for two patients each in the standard-care, BPaLM, and BPaL groups and for one patient in the BPaLC group.

§ Data on the QTcF interval were missing for one patient in the standard-care group.

¶ Data on the ALT level were missing for one patient each in the standard-care, BPaLM, and BPaLC groups.

‖ Data on the CD4 cell count were missing for one patient each in the standard-care, BPaLC, and BPaL groups.

** Data on the ALT level were missing for one patient in the BPaLM group.

Table 2. Primary Efficacy Analysis at 72 Weeks.

Variable	Intention-to-Treat Population		Modified Intention-to-Treat Population		Per-Protocol Population*	
	Standard-Care Group (N=73)	BPaLM Group (N=72)	Standard-Care Group (N=66)	BPaLM Group (N=62)	Standard-Care Group (N=33)	BPaLM Group (N=57)
Favorable outcome — no. (%)	34 (47)	55 (76)	34 (52)	55 (89)	29 (88)	55 (96)
Primary outcome: unfavorable status — no. (%)	39 (53)	17 (24)	32 (48)	7 (11)	4 (12)	2 (4)
Death — no. (%)	2 (3)	0	2 (3)	0	2 (6)	0
Early discontinuation — no. (%)	35 (48)	15 (21)	28 (42)	5 (8)	—	—
Adherence issues — no./total no. (%)	3/35 (9)	0	3/28 (11)	0	—	—
Adverse event — no./total no. (%)	17/35 (49)	5/15 (33)	17/28 (61)	5/5 (100)	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	10/15 (67)	0	0	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	6/28 (21)	0	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	2/28 (7)	0	—	—
Treatment failure — no.	0	0	0	0	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)	2 (3)	2 (3)	2 (6)	2 (4)
Recurrence — no.	0	0	0	0	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	−30 (−46 to −14)	—	−37 (−53 to −22)	—	−9 (−22 to 4)

* The per-protocol population included all patients in the modified intention-to-treat population with the exclusion of patients who did not complete a protocol-adherent course of treatment (>80% of doses within 120% of the prescribed duration), other than because of treatment failure or death, and patients who discontinued treatment early because they did not meet the inclusion or exclusion criteria.
† The "other outcome" category included one patient who could not be cared for at a trial site because of local regulations regarding infection control at the site and one patient who could not be cared for because the patient had acute behavioral challenges.
‡ The noninferiority margin was 12 percentage points on the difference scale.

domly assigned to one of the four groups; of these patients, 303 (54.9%) were included in the trial stage 2 groups (the standard-care group or the BPaLM group). On the date when enrollment was terminated, 145 patients (73 in the standard-care group and 72 in the BPaLM group) were included in the intention-to-treat population, 128 patients (66 in the standard-care group and 62 in the BPaLM group) were included in the modified intention-to-treat population, and 90 patients (33 in the standard-care group and 57 in the BPaLM group) were included in the per-protocol population. These patients could undergo 72 weeks of follow-up. In addition, of the patients who were originally assigned to one of four groups, 142 patients (72 in the BPaLC group and 70 in the BPaL group) in the intention-to-treat population, 124 patients (64 in the BPaLC group and 60 in the BPaL group) in the modified intention-to-treat population, and 110 patients (58 in the BPaLC group and 52 in the BPaL group) in the per-protocol population could undergo 72 weeks follow-up as well as additional evaluations (Fig. 1A and 1B).

The baseline demographic characteristics of the patients were generally balanced among the trial groups in the intention-to-treat, modified intention-to-treat, and per-protocol populations that underwent follow-up for 72 weeks. In the modified intention-to-treat analysis, the standard-care group had a higher proportion of female patients and patients with smear-positive and cavitary disease than the investigational groups (Table 1). Most patients in the standard-care group received at least two WHO group A drugs[3] as part of their regimen (Table S7); these drugs were fluoroquinolones (in 95%), linezolid (in 77%), and bedaquiline (in 76%).

EFFICACY OUTCOMES

In stage 1 of the trial, the percentages of patients with culture conversion in liquid medium at 8 weeks after randomization were 77%, 67%, and 46% in the BPaLM, BPaLC, and BPaL groups, respectively (Table S8 in the Supplementary Appendix); 8%, 6%, and 10% of the patients, respectively, discontinued treatment or died. The BPaLM regimen was selected for analysis in stage 2 of the trial.

In stage 2, by 72 weeks of follow-up in the intention-to-treat population, 39 of 73 patients in the standard-care group (53%) and 17 of 72 of

Table 3. Outcomes at 72 Weeks in the Standard-Care, BPaLC, and BPaL Groups.*

Variable	Intention-to-Treat Population			Modified Intention-to-Treat Population			Per-Protocol Population		
	Standard-Care Group (N=73)	BPaLC Group (N=72)	BPaL Group (N=70)	Standard-Care Group (N=66)	BPaLC Group (N=64)	BPaL Group (N=60)	Standard-Care Group (N=33)	BPaLC Group (N=58)	BPaL Group (N=52)
Favorable outcome — no. (%)	34 (47)	52 (72)	46 (66)	34 (52)	52 (81)	46 (77)	29 (88)	52 (90)	46 (88)
Primary outcome: unfavorable status — no. (%)	39 (53)	20 (28)	24 (34)	32 (48)	12 (19)	14 (23)	4 (12)	6 (10)	6 (12)
Death — no. (%)	2 (3)	1 (1)	0	2 (3)	1 (2)	0	2 (6)	1 (2)	0
Early discontinuation — no. (%)	35 (48)	14 (19)	18 (26)	28 (42)	6 (9)	8 (13)	—	—	—
Adherence issues — no./total no. (%)	3/35 (9)	2/14 (14)	2/18 (11)	3/28 (11)	2/6 (33)	2/8 (25)	—	—	—
Adverse event — no./total no. (%)	17/35 (49)	4/14 (29)	5/18 (28)	17/28 (25)	4/6 (67)	5/8 (62)	—	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	8/14 (57)	10/18 (6)	0	0	1/8 (12)	—	—	—
Did not receive at least one dose of trial medication — no./total no. (%)	0	0	1/18 (6)	—	—	—	—	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	0	6/28 (21)	0	0	—	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	0	2/28 (7)	0	0	—	—	—
Treatment failure — no. (%)	0	1 (1)	0	0	1 (2)	0	0	1 (2)	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	3 (4)	3 (4)	2 (3)	3 (5)	3 (5)	2 (6)	3 (5)	3 (6)
Recurrence — no. (%)	0	1 (1)	3 (4)	0	1 (2)	3 (5)	0	1 (2)	3 (6)
Risk difference for the primary outcome — percentage points (95% CI)	—	−26 (−41 to −10)	−19 (−36 to −2)	—	−30 (−45 to −14)	−25 (−41 to −9)	—	−2 (−15 to 12)	−1 (−15 to 14)

* Confidence intervals for the BPaLC group and BPaL group as compared with the standard-care group are two-sided and were not adjusted for multiplicity and should not be used to infer relative treatment effects.

† The "other outcome" category included one patient who could not be cared for at a trial site because of local regulations regarding infection control at the site and one patient could not be cared for because the patient had acute behavioral challenges.

patients in the BPaLM group (24%) had an unfavorable status (the primary composite outcome). In the modified intention-to-treat population, 32 of 66 patients in the standard-care group (48%) and 7 of 62 patients in the BPaLM group (11%) had an unfavorable status. The unadjusted risk difference was −37 percentage points (96.6% confidence interval [CI], −53 to −22), and the BPaLM regimen was both noninferior and superior to the standard regimen. In the per-protocol population, 4 of 33 patients in the standard-care group (12%) and 2 of 57 patients in the BPaLM group (4%) had an unfavorable status. No recurrences of tuberculosis or treatment failures were detected in either group (Table 2).

There was no evidence that treatment effects varied according to age, sex, HIV infection, sputum smear status, the presence of cavities on chest radiographs, fluoroquinolone resistance, or country of recruitment in the subgroup analyses. More details are provided in Table S22.

In stage 2, with regard to the secondary efficacy outcomes, the risk of a composite unfavorable outcome event at 24 and 108 weeks was broadly consistent with that with the primary outcome. In the modified intention-to-treat population, 78 of 99 patients in the standard-care group (79%) and 85 of 96 patients in the BPaLM group (88%) had culture conversion at 12 weeks; these results were similar in the per-protocol population. In a time-to-event analysis, the hazard ratio for culture conversion was 1.59 (95% CI, 1.18 to 2.14) in the modified intention-to treat population and 1.67 (95% CI, 1.14 to 2.45) in the per-protocol population (Table S13). At week 48, there were no recurrences of tuberculosis in the BPaLM group.

In additional efficacy analyses, by 72 weeks of follow-up in the modified intention-to-treat population, 12 of 64 patients in the BPaLC group (19%) and 14 of 60 patients in the BPaL group (23%) had an unfavorable composite outcome event. The unadjusted risk difference as compared with standard care was −30 percentage points (95% CI, −45 to −14) in the BPaLC group and −25 percentage points (95% CI, −41 to −9) in the BPaL group. In the per-protocol population, 6 of 58 patients in the BPaLC group (10%) and 6 of 52 patients in the BPaL group (12%) had an unfavorable composite outcome event. The unadjusted risk difference as compared with the standard of care was −2 percentage points (95% CI, −15 to 12) in the BPaLC group and −1 percentage point (95% CI, −15 to 14) in the BPaL group. In the per-protocol population, one treatment failure and one tuberculosis recurrence were observed in the BPaLC group; in the BPaL group, three tuberculosis recurrences were observed (Table 3).

SAFETY OUTCOMES

By 72 weeks of follow-up, 43 of 73 patients in the standard-care group (59%) had a total of 69 events (at least one serious adverse event or an adverse event of grade ≥3), and 14 of 72 patients in the BPaLM group (19%) had a total of 16 events (risk difference, −40 percentage points; 96.6% CI, −55 to −24). At least one serious adverse event or an adverse event of grade 3 or higher occurred in 23 of 72 patients (32%; 32 events) in the BPaLC group and 15 of 69 patients (22%; 24 events) in the BPaL group (Table 4).

By 72 weeks, the most frequently observed serious or grade 3 or higher adverse events were hepatic disorders. These affected 8 of 73 patients in the standard-care group (11%), 3 of 72 patients in the BPaLM group (4%), 3 of 72 patients in the BPaLC group (4%), and 2 of 69 patients in the BPaL group (3%). None of the patients in any of the groups met the Hy's law criteria for drug-induced liver injury (Fig. S4).

QTcF prolongation, the second most frequent serious or grade 3 or higher adverse event, affected 14 patients: 10 of 73 patients in the standard-care group (14%), 1 of 72 patients in the BPaLM group (1%), 3 of 72 patients in the BPaLC group (4%), and none of the patients in the BPaL group. QTcF prolongation for more than 500 msec led to early discontinuation of treatment in 6 patients in the standard-care group and in 1 patient in any of the investigational groups (the BPaLC group). At 24 weeks after randomization, the mean difference in a QTcF from the standard-care group, with adjustment for baseline QT, was −18.1, −5.4, and −20.0 msec in the BPaLM group, BPaLC group, and BPaL group, respectively.

Peripheral neuropathy (any grade) was seen in 28 of 150 patients in the standard-care group (19%; a total of 33 events), in 14 of 151 patients in the BPaLM group (9%; a total of 15 events), in 10 of 126 patients in the BPaLC group (8%; a total of 10 events), and in 16 of 122 patients in the BPaL group (13%; a total of 19 events). A

Table 4. Safety Outcomes (As-Treated Population).*

Variable	Standard-Care Group	BPaLM Group	BPaLC Group	BPaL Group
QTcF interval at 24 wk				
No. of patients with data†	71	98	92	92
QTcF interval at 24 wk — msec	441.8±18.0	423.5±18.5	435.7±17.6	423.1±18.5
Mean difference (CI) — msec‡§	—	−18.1 (−23.4 to −12.8)	−5.4 (−10.3 to −0.6)	−20.0 (−25.1 to −14.9)
Serious adverse event or grade ≥3 adverse event within 108 wk after randomization				
Patients with at ≥1 event — no./total no. (%)	26/43 (60)	10/40 (25)	18/43 (42)	11/43 (26)
No. of events	48	11	22	21
Risk difference — percentage points CI)§	—	−36 (−57 to −14)	−19 (−39 to 2)	−35 (−54 to −15)
Serious adverse event or grade ≥3 adverse events during treatment and up to 30 days after treatment end date				to
Patients with ≥1 event — no./total no. (%)	25/43 (58)	7/40 (18)	11/43 (26)	10/43 (23)
No. of events	46	7	14	12
Risk difference — percentage points (CI)§	—	−41 (−61 to −20)	−33 (−52 to −13)	−35 (−54 to −16)
Serious adverse event or grade ≥3 adverse events within 72 wk after randomization				
Patients with at ≥1 event — no./total no. (%)	43/73 (59)	14/72 (19)	23/72 (32)	15/69 (22)
No. of events	69	16	32	24
Risk difference — percentage points (CI)§	—	−40 (−55 to −24)	−27 (−43 to −11)	−37 (−52 to −22)
Hepatic disorder, grouped				
No. of events	10	3	5	2
Patients with events — no./total no. (%)	8/73 (11)	3/72 (4)	3/72 (4)	2/69 (3)
QTcF prolongation¶‖				
No. of events	12	1	3	0
Patients with events — no./total no. (%)	10/73 (14)	1/72 (1)	3/72 (4)	0
Creatinine renal clearance decreased				
No. of events	7	1	0	2
Patients with events — no./total no. (%)	5/73 (7)	1/72 (1)	0	2/69 (3)
Anemia				
No. of events	6	2	0	1
Patients with events — no./total no. (%)	6/73 (8)	2/72 (3)	0	1/69 (1)
Neutropenia				
No. of events	2	3	0	0
Patients with events — no./total no. (%)	2/73 (3)	3/72 (4)	0	0
Lipase level increased or pancreatitis				
No. of events	1	2	2	2
Patients with events — no./total no. (%)	1/73 (1)	2/72 (3)	2/72 (3)	2/69 (3)
Acute kidney injury				
No. of events	1	1	0	1
Patients with events — no./total no. (%)	1/73 (1)	1/72 (1)	0	1/69 (1)

Table 4. (Continued.)

Variable	Standard-Care Group	BPaLM Group	BPaLC Group	BPaL Group
Hemoptysis‖				
No. of events	2	0	1	0
Patients with events — no./total no. (%)	1/73 (1)	0	1/72 (1)	0
Vomiting				
No. of events	2	0	0	0
Patients with events — no./total no. (%)	2/73 (3)	0	0	0
Lymphocyte count decreased				
No. of events	0	1	1	1
Patients with events — no./total no. (%)	0	1/72 (1)	1/72 (1)	1/69 (1)
Pneumonia				
No. of events	1	0	2	1
Patients with events — no./total no. (%)	1/73 (1)	0	2/72 (3)	1/69 (1)
Other‖				
No. of events	25	2	18	14
Patients with events — no./total no. (%)	23/73 (32)	2/72 (3)	18/72 (25)	12/69 (17)

* Plus–minus values are means ±SD. The as-treated population included all patients who underwent randomization and received at least one dose of trial medication.
† This category excludes patients who were not participating in the trial at week 24, even if they discontinued owing to QTcF prolongation.
‡ The mean difference was adjusted for the baseline QTcF interval.
§ Confidence intervals for the BPaLM group group as compared with the standard-care group are two-sided 96.6% confidence intervals. Confidence intervals for the BPaLC group and BPaL group as compared with the standard-care group are two-sided 95% confidence intervals and are not adjusted for multiplicity.
¶ QTcF prolongation includes prolonged QT on electrocardiography and syncope.
‖ One patient had two events.

single event of grade 3 peripheral neuropathy occurred in a patient in the standard-care group 75 days after randomization. No episodes of optic neuropathy were observed.

Ten of the 549 patients (2%) in the as-treated population died; 7 of these patients were in the standard-care group. Four patients died during the treatment period, 3 died during follow-up, and 3 died after early withdrawal from the trial. Four of the deaths (all in the standard-care group) were considered by the investigators to be treatment-related. None of the deaths were attributed by the investigators to tuberculosis (Table S20).

DISCUSSION

In the modified-intention-to-treat population in this phase 2–3 trial, BPaLM was both noninferior and superior to the accepted standard care with respect to the primary composite outcome; 89% and 52% of the patients, respectively, had a favorable outcome. The percentages of patients with favorable outcomes in the BPaLC group (81%) and the BPaL group (77%) were also higher than the percentage in the standard-care group. The difference was principally driven by early discontinuation of treatment owing to adverse events in the standard-care group. The difference between the standard-care and investigational groups was less pronounced in the per-protocol analysis in which early discontinuations were excluded. These findings suggest that the standard-care treatment was similarly efficacious when patients could receive it without adverse effects.

The safety outcomes also favored BPaLM, with lower percentages of patients with adverse events of grade 3 or higher or serious adverse

events for all outcomes (at week 72, at week 108, and during treatment). In additional safety analyses, the BPaLC and BPaL regimens were also safer than the standard care. The QTcF interval at week 24 was lower in the BPaLM group than in the standard-care group and more closely resembled the QTcF in the BPaL group. The QTcF in the BPaLC group was similar to that in the standard-care group. This finding corroborates evidence suggesting that clofazimine is a primary driver of QTcF prolongation in bedaquiline-containing regimens.

These findings are generally consistent with those from other trials of shorter bedaquiline, pretomanid, and linezolid regimens.[9,10] In those trials, 84 to 93% of the patients had a successful outcome, percentages that were similar to those in trials involving patients with drug-sensitive tuberculosis.[11] In our trial, BPaL did not appear to perform as well as the regimen in the Nix-TB study,[9] with fewer successful outcomes and slower culture conversion. The trial design may explain this difference (Table S27).

These results are also consistent with data from trials of other shorter regimens. In the STREAM (Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB) trial, 78.8% of patients in the short-regimen group had a successful outcome.[7] A meta-analysis of the current 9-to-11-month all-oral regimen recommended by the WHO showed a successful outcome in 73% of patients.[12] A retrospective study of a shorter regimen including linezolid showed a successful outcome in 75.2% of patients.[13] Although the percentage of patients with unfavorable outcomes in the standard-care group in our trial is consistent with those reported worldwide,[1,2] it is lower than what has been reported in recent clinical trials involving patients with drug-resistant tuberculosis.[7] Enhanced monitoring and stringent discontinuation criteria in our trial probably explain this difference. The criteria for discontinuation were applied to all groups equally.

Our trial has several strengths. This randomized, controlled, regulatory-level trial enrolled patients who were broadly representative of patients in the epidemic of rifampin-resistant tuberculosis, with the inclusion of patients with fluoroquinolone-resistant tuberculosis and HIV coinfection (Table S2). The trial was patient-centered, with assistance in adherence to treatment adapted to the patients' circumstances. The safety of patients was paramount, with frequent visits to ensure that adverse events were identified and managed promptly. These visits were complemented by centralized safety oversight. TB-PRACTECAL substudies are also under way to provide explanatory data, specifically regarding the costs of new regimens for patients and providers, as well as their cost-effectiveness and effect on patients' poverty levels,[14] patient-reported outcomes,[15] and pharmacokinetics and pharmacodynamics.[16]

The TB-PRACTECAL trial was terminated for efficacy after recruitment of 75% of the planned sample. Trials that are terminated early for benefit have been suggested to overestimate treatment effects,[17] although it has been argued that this overestimation is limited.[18] Recruitment into our trial was terminated on the recommendation of the data and safety monitoring board after the prespecified stopping rule was triggered.[19] A study of follow-up data for at least 72 weeks after randomization in all patients who underwent randomization is under way.

The limitations of our trial include the open-label design. Poorer performance of the standard-care treatment was driven by early discontinuations in the modified intention-to-treat population, but the criteria for discontinuation owing to poor adherence to treatment or adverse events were prespecified (see the protocol). Although 17 of the 28 discontinuations in the standard-care group in the modified intention-to-treat population were due to adverse events, the remainder could have been subject to performance bias. Seven patients withdrew consent in the standard-care group while receiving treatment. Our inability to measure minimum inhibitory concentrations in all patients for this report limited the subgroup analyses. We were unable to perform whole-genome sequencing at the trial site where the recurrences of tuberculosis occurred, so we cannot rule out the possibility that these recurrences were caused by reinfection. The standard-care regimens were updated throughout the trial, in line with international recommendations. However, these changes meant that the standard care differed over time and according to trial site. Current standard-care regimens include less toxic drugs than those used earlier in the trial.[5] Of note, most patients in the standard-care group received at least two WHO

group A drugs[3] as part of their regimen, an approach consistent with current guidelines. As planned, the data and safety monitoring board reviewed summary data every 3 to 6 months to ensure adequate oversight. In November 2020, the data and safety monitoring board requested the treatment effect and confidence interval for the composite outcome; no adjustment in the alpha level was made for this analysis.

This multicountry, randomized, controlled trial of 24-week, all-oral regimens containing bedaquiline, pretomanid, and linezolid for the treatment of rifampin-resistant tuberculosis showed that treatment with BPaLM was more effective and had a better safety profile than standard care. BPaLC and BPaL were also highly efficacious.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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