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Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

ABSTRACT

BACKGROUND

Delamanid (OPC-67683), a nitro-dihydro-imidazooxazole derivative, is a new antituberculosis medication that inhibits mycolic acid synthesis and has shown potent in vitro and in vivo activity against drug-resistant strains of *Mycobacterium tuberculosis*.

METHODS

In this randomized, placebo-controlled, multinational clinical trial, we assigned 481 patients (nearly all of whom were negative for the human immunodeficiency virus) with pulmonary multidrug-resistant tuberculosis to receive delamanid, at a dose of 100 mg twice daily (161 patients) or 200 mg twice daily (160 patients), or placebo (160 patients) for 2 months in combination with a background drug regimen developed according to World Health Organization guidelines. Sputum cultures were assessed weekly with the use of both liquid broth and solid medium; sputum-culture conversion was defined as a series of five or more consecutive cultures that were negative for growth of *M. tuberculosis*. The primary efficacy end point was the proportion of patients with sputum-culture conversion in liquid broth medium at 2 months.

RESULTS

Among patients who received a background drug regimen plus 100 mg of delamanid twice daily, 45.4% had sputum-culture conversion in liquid broth at 2 months, as compared with 29.6% of patients who received a background drug regimen plus placebo (P=0.008). Likewise, as compared with the placebo group, the group that received the background drug regimen plus 200 mg of delamanid twice daily had a higher proportion of patients with sputum-culture conversion (41.9%, P=0.04). The findings were similar with assessment of sputum-culture conversion in solid medium. Most adverse events were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QT prolongation on electrocardiography were observed, QT prolongation was reported significantly more frequently in the groups that received delamanid.

CONCLUSIONS

Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. This finding suggests that delamanid could enhance treatment options for multidrug-resistant tuberculosis. (Funded by Otsuka Pharmaceutical Development and Commercialization; ClinicalTrials.gov number, NCT00685360.)

From the Makati Medical Center, Manila (M.T.G.), and the Tropical Disease Foundation, Makati City (M.T.G., T.T.) — both in the Philippines; the State Agency of Tuberculosis and Lung Diseases, Riga, Latvia (V.S.); Hospital Nacional Sergio E. Bernales (E.S.-G.), Unidad de Investigacion, Hospital Nacional Daniel A. Carrión (J.L.C.-R.), and Hospital Nacional Hipólito Unanue (D.E.V.-V.) — all in Lima, Peru; Shanghai Pulmonary Hospital, Shanghai (H.X.), and Beijing Chest Hospital, Beijing (M.G.) — both in China; Sadr Abassia Hospital, Cairo (M.A.); National Masan Hospital, Masan (S.-K.P.), Asan Medical Center, Seoul (T.S.S.), Samsung Medical Center, Seoul (G.Y.S., W.-J.K.), and Yonsei University Medical Center, Severance Hospital, Seoul (J.C.) — all in South Korea; Tartu University Lung Hospital, Tartu (M.D.), and North Estonian Medical Center Foundation, Center of Pulmonology, Tallinn (A.K.) — both in Estonia; Fukujuji Hospital, Tokyo (H.O.), and National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka (K.S.) — both in Japan; the University of Texas Health Center at Tyler, Tyler (B.S.); and Otsuka Pharmaceutical Development and Commercialization, Rockville, MD (L.J.G., C.D.W.). Address reprint requests to Dr. Geiter at Otsuka Novel Products/OPDC, 2440 Research Blvd., Rockville, MD 20850, or at lawrence.geiter@otsuka-us.com.

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The emergence over the past two decades of multidrug-resistant tuberculosis, or tuberculosis caused by strains of *Mycobacterium tuberculosis* that are resistant to isoniazid and rifampin, with or without resistance to other agents, has greatly complicated efforts to control the global tuberculosis epidemic. Approximately 440,000 cases of multidrug-resistant tuberculosis occur worldwide annually, accounting for nearly 5% of the global burden of tuberculosis.[1] Multidrug-resistant tuberculosis requires treatment with combination therapy consisting of four to six medications, including the more toxic and less potent second-line drugs, administered for up to 2 years. Cure rates are lower and mortality is higher with multidrug-resistant tuberculosis than with drug-susceptible tuberculosis, even with the most effective treatments.[2-6] As a result, the Global Plan to Stop TB, 2011 through 2015, calls for urgent development of new drugs involving new mechanisms to treat tuberculosis, including multidrug-resistant tuberculosis, as a key component of the response to the epidemic.[7]

Delamanid (OPC-67683), a new agent derived from the nitro-dihydro-imidazooxazole class of compounds that inhibits mycolic acid synthesis, has shown potent in vitro and in vivo activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis* in preclinical development.[8,9] In a subsequent assessment of the 14-day early bactericidal activity of the compound against *M. tuberculosis* in patients in South Africa, delamanid administered at doses of 200 and 300 mg daily resulted in a decrease in the sputum *M. tuberculosis* burden that was similar to that of the potent antituberculosis drug rifampin in previous studies of early bactericidal activity.[10,11]

On the basis of results from five decades of controlled trials showing the predictive value of status with respect to sputum-culture conversion at 2 months for disease relapse among patients with tuberculosis, as well as cohort studies showing its predictive value for treatment outcomes in multidrug-resistant tuberculosis, we conducted a multinational, randomized, double-blind, placebo-controlled trial to assess the safety, pharmacokinetic profile, and efficacy of delamanid in patients with multidrug-resistant tuberculosis.[12-14] We present the results for patients with sputum culture–positive multidrug-resistant pulmonary tuberculosis who received 2 months of treatment with delamanid, at a higher or lower dose, or placebo in combination with a background drug regimen developed according to World Health Organization (WHO) guidelines.[2]

Methods

Patients

This study included patients 18 to 64 years of age who had sputum culture–positive multidrug-resistant tuberculosis and chest radiographic findings consistent with tuberculosis. Patients with sputum smears that were positive for acid-fast bacilli and positive rapid tests for rifampin resistance were also enrolled, but they were excluded from the efficacy analysis if baseline cultures (i.e., results from cultures at day −1 and day 1) proved to be negative for multidrug-resistant tuberculosis. Patients were excluded from the trial if they had Karnofsky scores of less than 50%; those with human immunodeficiency virus (HIV) infection were excluded if they had a CD4 cell count of less than 350 per cubic millimeter or were receiving antiretroviral treatment. Patients who were receiving antiarrhythmic agents or who had clinically relevant cardiovascular disease or electrocardiographic (ECG) findings of conduction abnormalities or QT-interval prolongation (>450 msec in men or >470 msec in women) were also excluded, and the use of moxifloxacin was prohibited. Additional standard exclusion criteria were substance abuse, concomitant illness, drug hypersensitivity, abnormal renal and hepatic laboratory results, pregnancy, and breast-feeding. Women with childbearing potential were required to use birth control.

Trial Design

This multicenter, double-blind, stratified, randomized, placebo-controlled trial was conducted in 17 centers in nine countries: the Philippines, Peru, Latvia, Estonia, China, Japan, Korea, Egypt, and the United States. During the 8-week treatment period, all patients were hospitalized for intensive safety monitoring and weekly sputum-culture status assessments. The design included an additional 4-week period of patient monitoring to confirm the sputum-culture status while patients continued to receive the background drug regimen. The objective of the trial was to evaluate the safety, efficacy, and pharmacokinetics of two doses of delamanid (100 mg twice daily or 200 mg twice daily) plus the background drug regimen

for 2 months, as compared with placebo plus the standard drug regimen for 2 months.

Randomization was centralized, with patients stratified into two groups according to the extent of pulmonary tuberculosis (presence or absence of lung cavities) on baseline chest radiography as assessed by local radiologists. Patients were randomly assigned in a 1:1:1 ratio to receive the background drug regimen plus delamanid at a dose of 100 mg or 200 mg or placebo twice daily for 8 weeks.

The study drug, provided as delamanid in 50-mg tablets (Otsuka Pharmaceutical Development and Commercialization) or matching placebo, was administered with morning and evening meals 10 hours apart, since systemic exposure increases when delamanid is taken with food; ingestion of all doses was observed. For 12 weeks, all patients received the background drug regimen developed according to WHO guidelines for treating multidrug-resistant tuberculosis; this regimen generally consisted of four or five antituberculosis medications, including any first-line medications to which a patient's disease remained susceptible, an injectable antituberculosis medication (an aminoglycoside or capreomycin), a fluoroquinolone, and other medications.[2] The background drug regimen could be adjusted by the site investigators as needed. After 8 weeks of blinded treatment, patients could continue the background drug regimen as outpatients and were assessed weekly for 4 additional weeks for sputum-culture status and safety findings.

The trial protocol, available with the full text of this article at NEJM.org, was approved by independent ethics committees and institutional review boards for all sites. All patients provided written informed consent in their native language before enrollment occurred. The trial was performed in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization, adhered to the ethical principles of the Declaration of Helsinki, and was monitored by an independent data and safety monitoring committee. Otsuka sponsored the study, which was designed by employees of the sponsor with input from an academic author. Employees of the sponsor wrote the manuscript. All authors participated in the collection and analysis of the data and made the decision to submit the manuscript for publication. All authors vouch for the completeness and accuracy of the data presented and the fidelity of the study to the protocol.

STUDY PROCEDURES

Microbiologic Assessments

Morning sputum specimens were obtained during the 8-week treatment period and during the 4-week post-treatment period on days –1, 1, 8, 15, 22, 29, 36, 43 50, 57, 63, 70, 77, and 84. If patients were unable to expectorate sputum, attempts were made to induce sputum expectoration with the use of aerosol inhalation. Sputum samples were deemed unobtainable if no sputum could be obtained after induction. Samples were cultured in liquid broth medium (in an automated mycobacterial growth indicator tube [MGIT] system) (Becton Dickinson) and in solid mycobacteriologic culture medium (with the use of egg-based Löwenstein–Jensen medium for ≥90% of the patients). Mycobacterial cultures were identified according to the growth and morphologic characteristics of the colony and with the use of commercial identification methods, including DNA hybridization systems (e.g., Accuprobe), DNA amplification methods (e.g., INNO-LiPA Rif.TB [Innogenetics] and GenoType MTBDRplus [Hain Lifescience]), or other standardized methods. Microbiologic tests were performed in local laboratories in accordance with guidelines from the Clinical and Laboratory Standards Institute for sputum processing, smear microscopy, culture techniques, drug-susceptibility testing, and identification of mycobacteria.[15-17]

On the basis of previous studies showing that in 18% of patients with multidrug-resistant tuberculosis who received the background drug regimen, the initial monthly cultures reverted from being negative to positive for *M. tuberculosis*,[14] sputum-culture conversion was defined as five or more consecutive weekly cultures that were negative for growth of *M. tuberculosis* (without subsequent positive cultures). The time of sputum-culture conversion was defined as the day of sputum collection for the first of five cultures that were negative for *M. tuberculosis*. Meeting this criterion required patients to have a negative culture by the end of the treatment period with the investigational medication (day 57) and at all subsequent weekly assessments during the treatment period during which they received the background drug regimen alone (days 57, 63, 70, 77, and 84). In addition, since MGIT is automated, allowing for

standardization of processes across laboratories, and studies have shown that it is more sensitive than solid-culture media for detecting viable *M. tuberculosis* organisms,[18] assessment of sputum-culture conversion with the use of MGIT served as the primary efficacy analysis.

Pharmacokinetic Assessments

Serial blood samples were obtained over a 24-hour period on days 1, 14, 28, and 56. Plasma concentrations of delamanid were determined with the use of a validated liquid chromatography–mass spectrometry method at Tandem Labs, Salt Lake City. Summary tables were generated according to study-drug group for plasma concentrations per time point and for pharmacokinetic measures obtained with the use of WinNonlin software (Pharsight).

Safety Assessments

Safety tests included the following: monthly physical examinations, weekly assessment of vital signs, standard 12-lead ECG, clinical laboratory tests (including a hematologic profile, coagulation measurements, a urinalysis, and measurements of hepatic aminotransferase and thyroid and adrenal hormone levels), and baseline audiometry. The QT-interval duration for each ECG was corrected with the use of Fridericia's formula[19]: corrected QT interval = QT × (1000 ÷ RR interval in milliseconds)$^{0.33}$. Use of concomitant medications was recorded daily, and adverse events were documented; immediately reportable events and clinically significant abnormal laboratory results were evaluated as appropriate.

STATISTICAL ANALYSIS

Safety evaluations were performed in all patients who underwent randomization and who received at least one dose of study medication (the intention-to-treat population). Efficacy evaluations were performed in all patients who had positive multidrug-resistant tuberculosis cultures at baseline and who met no exclusion criteria (the modified intention-to-treat population). The primary efficacy end point was the proportion of patients in the modified intention-to-treat population who had sputum-culture conversion with the use of MGIT by 2 months (day 57) of treatment. Each of the delamanid groups was compared with the placebo group with the use of the Cochran–Mantel–Haenszel test, stratified according to randomization factor. The overall nominal significance level for testing the two pairwise comparisons was maintained at 0.05 (two-sided) with the use of the Hochberg multiple-testing procedure. Multiple secondary efficacy end points were also assessed, including sputum-culture conversion at 2 months, with the use of solid medium and time to sputum-culture conversion with the use of both medium types in a proportional-hazards model. We analyzed the results of the sensitivity data sets of both the MGIT and solid-medium cultures with the use of the last-observation-carried-forward, observed-cases, and per-protocol methods; the analysis was not controlled for site. A single-imputation method was used for any missing culture data. All end points were prespecified in a formal statistical analysis plan that was developed, finalized, and filed with regulatory authorities before database locking and unblinding. The Supplementary Appendix, including further details regarding study conduct and analyses, is available at NEJM.org.

RESULTS

STUDY POPULATION

Recruitment began in May 2008, and the last patient visit was in June 2010. A total of 611 patients with suspected multidrug-resistant tuberculosis were assessed for eligibility; 481 met eligibility requirements and were stratified into two groups according to the presence or absence of cavities observed in lung fields on chest radiography. Among the 481 patients in the intention-to-treat population, 402 (83.6%) met the criteria for the modified intention-to-treat population (positive sputum culture for multidrug-resistant tuberculosis at baseline) and were assessed for efficacy (141 patients who received delamanid at a dose of 100 mg twice daily, 136 who received delamanid at a dose of 200 mg twice daily, and 125 who received placebo) (Fig. 1). Of 402 patients who were assessed for efficacy, 217 were from Asia (54.0%), and 275 were men (68.4%); the median age was 35 years (range, 18 to 63) (Table 1). No significant differences in demographic or baseline clinical characteristics between the intention-to-treat and modified intention-to-treat populations or among the three study-drug groups were identified. Although lung cavities were identified on chest radiography at baseline in equal proportions of patients across the groups, slightly fewer pa-

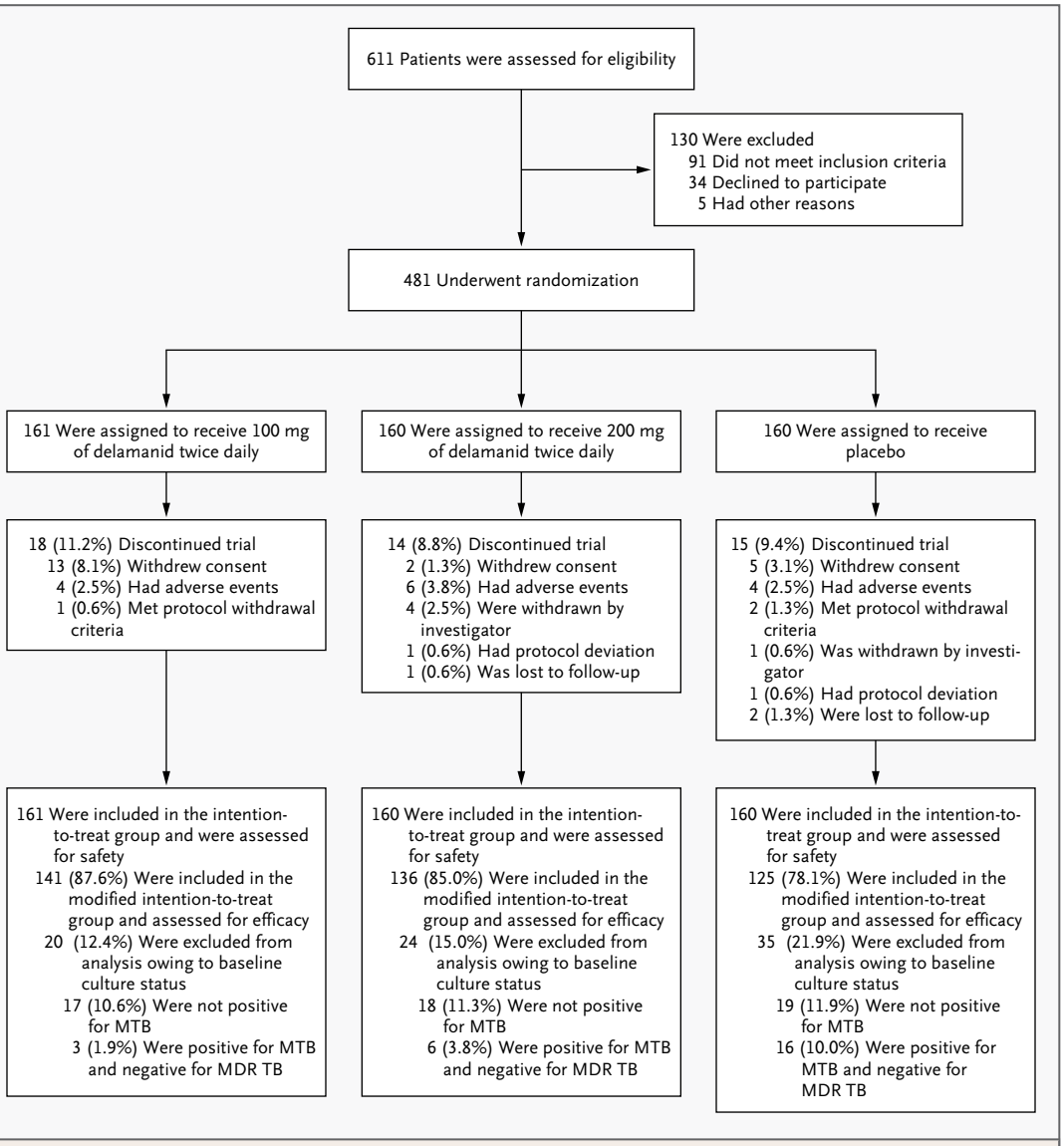

Figure 1. Enrollment, Study-Drug Assignments, Follow-up, and Assessment of Patients.
MDR TB denotes multidrug-resistant tuberculosis, and MTB *Mycobacterium tuberculosis*.

tients in the placebo group than in the two delamanid groups had bilateral cavities. More than 90% of patients had received treatment for tuberculosis before randomization; of these patients, more than 50% had received first-line antituberculosis drugs alone and nearly 40% had received a second-line or third-line antituberculosis drug. Details on the use of antituberculosis medication during the trial are included in the Supplementary Appendix. Four patients with HIV coinfection were enrolled, with at least one patient randomly assigned to each group. Approximately 85% of patients were fully adherent to the study-drug regimen; only 1% of patients had adherence of 80% or less, and the proportion did not differ among the groups.

SAFETY

The safety analysis included the 481 patients in the intention-to-treat population (Fig. 1). Similar proportions of patients in the three study-drug groups completed the 8-week drug regimen (≥89%); a total of 14 patients (2.9%), evenly distributed across the groups, discontinued the study

Table 1. Demographic and Baseline Clinical Characteristics of the Modified Intention-to-Treat Population for the Primary Efficacy Analysis.*

Characteristic	Delamanid, 100 mg Twice Daily (N=141)	Delamanid, 200 mg Twice Daily (N=136)	Placebo (N=125)	Total (N=402)
Age — yr				
Median	36	33	35	35
Range	19–63	18–63	18–63	18–63
Male sex — no. (%)	91 (64.5)	95 (69.9)	89 (71.2)	275 (68.4)
Body-mass index†				
Median	19.8	19.5	19.5	19.6
Range	12–31	12–40	12–31	12–40
Region — no. (%)‡				
Americas	39 (27.7)	38 (27.9)	39 (31.2)	116 (28.9)
Southeast Asia	43 (30.5)	47 (34.6)	45 (36.0)	135 (33.6)
Northeast Asia	29 (20.6)	28 (20.6)	25 (20.0)	82 (20.4)
Eastern Europe or Mediterranean	30 (21.3)	23 (16.9)	16 (12.8)	69 (17.2)
Lung cavities — no. (%)				
Absent	44 (31.2)	43 (31.6)	38 (30.4)	125 (31.1)
Unilateral	60 (42.6)	56 (41.2)	60 (48.0)	176 (43.8)
Bilateral	37 (26.2)	37 (27.2)	27 (21.6)	101 (25.1)
Previous treatment — no. (%)				
<30 days before randomization	11 (7.8)	14 (10.3)	12 (9.6)	37 (9.2)
≥30 days before randomization	130 (92.2)	122 (89.7)	113 (90.4)	365 (90.8)
First-line only	72 (51.1)	73 (53.7)	68 (54.4)	213 (53.0)
Second-line with or without first-line	40 (28.4)	27 (19.9)	23 (18.4)	90 (22.4)
Third-line with or without first-line or second-line	18 (12.8)	22 (16.2)	22 (17.6)	62 (15.4)

* The modified intention-to-treat population included patients with confirmed sputum-culture–positive multidrug-resistant tuberculosis at trial baseline. Differences among the groups were not significant.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The Americas region included Peru (98.3% of the patients) and the United States (1.7%). The Southeast Asia region consisted of the Philippines (100% of the patients). The Northeast Asia region included China (61.0% of the patients), Korea (29.2%), and Japan (9.8%). The Eastern Europe or Mediterranean region included Latvia (73.9% of the patients), Estonia (8.7%), and Egypt (17.4%).

drug because of adverse events (see the Supplementary Appendix for details).

Table 2 lists the adverse events that occurred in 10% or more of the patients in either or both of the delamanid groups and at a higher frequency than that in the placebo group. There were fewer adverse events in the group of patients who received delamanid at a dose of 100 mg twice daily than in the group that received delamanid at a dose of 200 mg twice daily; many of these events were of similar frequency to those in the placebo group. No episodes of a prolonged QT interval as measured on ECG were associated with clinical manifestations such as syncope or arrhythmias. However, the frequency of a prolonged QT interval was higher in the group that received 200 mg of delamanid twice daily (13.1%) than in the group that received 100 mg twice daily (9.9%), and both rates were higher than that in the placebo group (3.8%). Concomitant conditions that exacerbate QT-interval prolongation, particularly hypokalemia, which often result from the use of injectable antituberculosis medications, were noted.[20] The percentage of patients with

Table 2. Incidence of Adverse Events (Occurring in ≥10% of Patients in Either Delamanid Group and with Greater Frequency Than in the Placebo Group).*

Adverse Event	Delamanid, 100 mg Twice Daily (N=161)	Delamanid, 200 mg Twice Daily (N=160)	Placebo (N=160)
		number of patients (percent)	
Hematopoietic			
Anemia	18 (11.2)	10 (6.2)	14 (8.8)
Reticulocytosis	19 (11.8)	20 (12.5)	17 (10.6)
Gastrointestinal			
Nausea	58 (36.0)	65 (40.6)	53 (33.1)
Vomiting	48 (29.8)	58 (36.2)	44 (27.5)
Upper abdominal pain	41 (25.5)	36 (22.5)	38 (23.8)
Cardiovascular			
Palpitations	13 (8.1)	20 (12.5)	10 (6.2)
Prolonged QT interval on ECG	16 (9.9)	21 (13.1)	6 (3.8)
Respiratory: hemoptysis	19 (11.8)	15 (9.4)	17 (10.6)
Nervous system			
Headache	36 (22.4)	41 (25.6)	30 (18.8)
Paresthesias	17 (10.6)	20 (12.5)	12 (7.5)
Tremor	19 (11.8)	16 (10.0)	13 (8.1)
Insomnia	42 (26.1)	51 (31.9)	42 (26.2)
General			
Tinnitus	16 (9.9)	22 (13.8)	12 (7.5)
Asthenia	20 (12.4)	27 (16.9)	20 (12.5)
Malaise	12 (7.5)	16 (10.0)	12 (7.5)
Anorexia	23 (14.3)	34 (21.2)	24 (15.0)
Hyperhidrosis	9 (5.6)	17 (10.6)	8 (5.0)
Hyperuricemia	31 (19.3)	38 (23.8)	35 (21.9)
Hypokalemia	20 (12.4)	31 (19.4)	24 (15.0)

* With pairwise comparisons of the frequency of adverse events, only QT prolongation on electrocardiography (ECG) was significant (P=0.048 for the comparison of the 100-mg group with the placebo group and P=0.005 for the comparison of the 200-mg group with the placebo group). Furthermore, the Cochran–Armitage trend test used to evaluate for a dose–response trend in the incidence of adverse events across the three dose groups (0 mg, 100 mg, and 200 mg twice daily) yielded a P value of 0.004 for QT prolongation detected by means of ECG.

hepatotoxicity was not higher in the delamanid groups than in the placebo group. One patient died from tuberculosis during the trial. The Supplementary Appendix provides a summary of adverse events, including serious adverse events, discontinuation of the study drug due to adverse events, frequency of severe adverse events that developed during treatment, adverse events potentially related to the study drug, and details of all adverse events (>400) that occurred in one or more patients.

PHARMACOKINETICS

Delamanid steady-state exposure increased less than proportionally with the dose. An increase in the dose of delamanid from 100 mg twice daily to 200 mg twice daily yielded a 50% increase in exposure. Plasma concentrations of delamanid decreased rapidly (half-life, 38 hours) after drug discontinuation. Pharmacokinetic measures (maximum concentration after morning and evening doses, minimum concentration, and area under the plasma concentration–time curve from 0 to

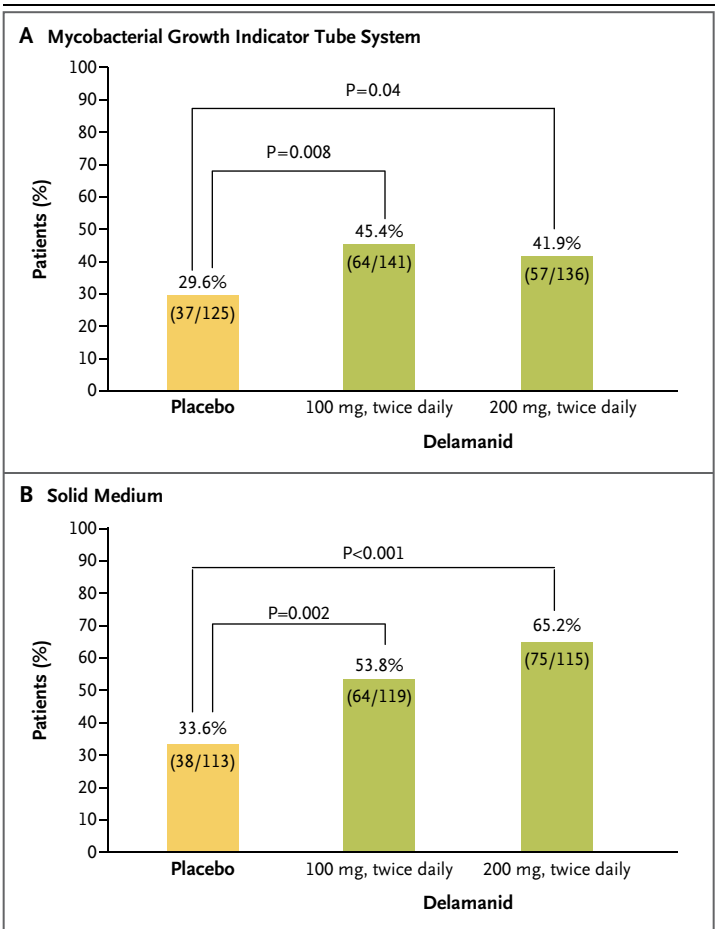

Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

24 hours) for delamanid on day 56 are shown in the Supplementary Appendix.

SPUTUM-CULTURE CONVERSION

Of 481 patients who underwent randomization, 402 (83.6%) had cultures that were positive for multidrug-resistant tuberculosis with the use of MGIT at baseline (the modified intention-to-treat population) and were included in the primary efficacy analysis. Of these 402 patients, the proportion who had sputum-culture conversion with MGIT by 2 months in the group of patients who received delamanid at a dose of 100 mg twice daily was 45.4%, as compared with 29.6% in the placebo group (Fig. 2A); this was a significant increase (53%; 95% CI, 11 to 112; P=0.008). The proportion who had sputum-culture conversion in the 200-mg group was similar (41.9%) and was significantly higher than that in the placebo group (P=0.04). Results from the secondary analysis of sputum-culture conversion, assessed with the use of solid medium (Fig. 2B), as well as sensitivity analyses of the primary analysis, were consistent with the results of the primary analysis. These analyses included examination of data sets of sputum-culture conversion with the use of last-observation-carried-forward, observed-cases, and per-protocol methods for both MGIT and solid medium, as well as evaluation of the data with the use of various less stringent definitions of sputum-culture conversion, including one routinely used in clinical practice (two consecutive negative cultures obtained 1 month apart) and a single negative culture at 2 months. In addition, a multiple-imputation strategy for dealing with missing sputum-culture results was used. In all cases, the proportion of patients with sputum-culture conversion was higher in the groups receiving delamanid plus the background drug regimen, and in nearly all analyses, the difference was significant.

An additional key secondary analysis assessed differences among the groups with respect to time to sputum-culture conversion. For this analysis, Kaplan–Meier curves representing the time to conversion according to culture medium type (Fig. 3) showed 10% separation between the delamanid groups and the placebo group by day 36 with MGIT. By the end of the 2-month treatment period, the difference in sputum-culture conversion between the delamanid groups and the placebo group was significant (P=0.001 for the comparisons of the 100-mg and 200-mg doses of delamanid with placebo); the same trend was observed with the use of solid medium (P=0.0004 and P<0.0001, respectively, by the log-rank test). In a Cox regression analysis of sputum-culture conversion, including study-drug assignment and the presence or absence of cavitation on chest radiography (a stratification variable), the hazard ratio for increased time to conversion to a negative sputum culture as assessed with the use of MGIT was 0.58 (95% confidence interval [CI], 0.39 to 0.89) in the 100-mg group and 0.63 (95% CI, 0.42 to 0.96) in the 200-mg group. The hazard ratio for increased time to conversion to a negative sputum culture as assessed with the use of solid medium was 0.54 (95% CI, 0.36 to 0.81) in the 100-mg group and 0.44 (95% CI, 0.29 to 0.64) in the 200-mg group.

DISCUSSION

In this study, which used a stringent definition of sputum-culture conversion (five successive weekly cultures that were negative for *M. tuberculosis*) and a more sensitive culture system (MGIT) than solid medium for detecting viable *M. tuberculosis*,[18] 45.4% of patients who received delamanid at a dose of 100 mg twice daily plus the background drug regimen had sputum-culture conversion after 2 months, as compared with 29.6% of those who received placebo plus the background drug regimen; this was a significant increase (53%; 95% CI, 11 to 112). This benefit, which was observed with both doses, was also observed with the use of solid-culture medium and was supported by sensitivity analyses and imputation strategies for missing sputum-culture results. Likewise, among patients who had sputum-culture conversion, those who received either delamanid dose plus the background drug regimen had sputum-culture conversion significantly earlier than those who received placebo plus a background drug regimen.

The safety analyses showed that delamanid at either dose did not have dose-limiting toxicity; however, patients who received delamanid plus the background drug regimen had more episodes of QT-interval prolongation on scheduled ECG, as compared with those who received placebo plus the background drug regimen. None of these episodes were associated with clinical manifestations such as syncope or arrhythmias.

An analysis by Wallis and colleagues of multiple controlled clinical trials of tuberculosis treatment involving 30 pairs of regimens and more than 5500 patients showed a strong association between increases in sputum-culture conversion at 2 months and lower tuberculosis relapse rates with the use of stepwise adjustments to treatment (e.g., adding a strong bactericidal agent to an existing regimen).[12] Similarly, cohort studies have shown more favorable long-term treatment outcomes among patients with multidrug-resistant tuberculosis who had sputum-culture conversion by 2 months as compared with those who did not.[13,14] This trial shows that delamanid administered with the background drug regimen for multidrug-resistant tuberculosis enhanced and accelerated sputum-culture conversion. Long-term, open-label surveillance of patients with multidrug-resistant tuberculosis treated with delamanid and the background drug regimen is under way to extend efficacy and safety observations from this trial and to further document the durability of response. Further analyses addressing pharmacology, long-term follow-up, and microbiologic data are also under way. A second large, randomized, controlled trial (ClinicalTrials.gov number, NCT01424670) of 6 months of treatment with delamanid as part of a full background drug regimen and including patients who have coinfection with HIV and multidrug-resistant tuberculosis and who are receiving antiretroviral drugs has been initiated and is designed to pro-

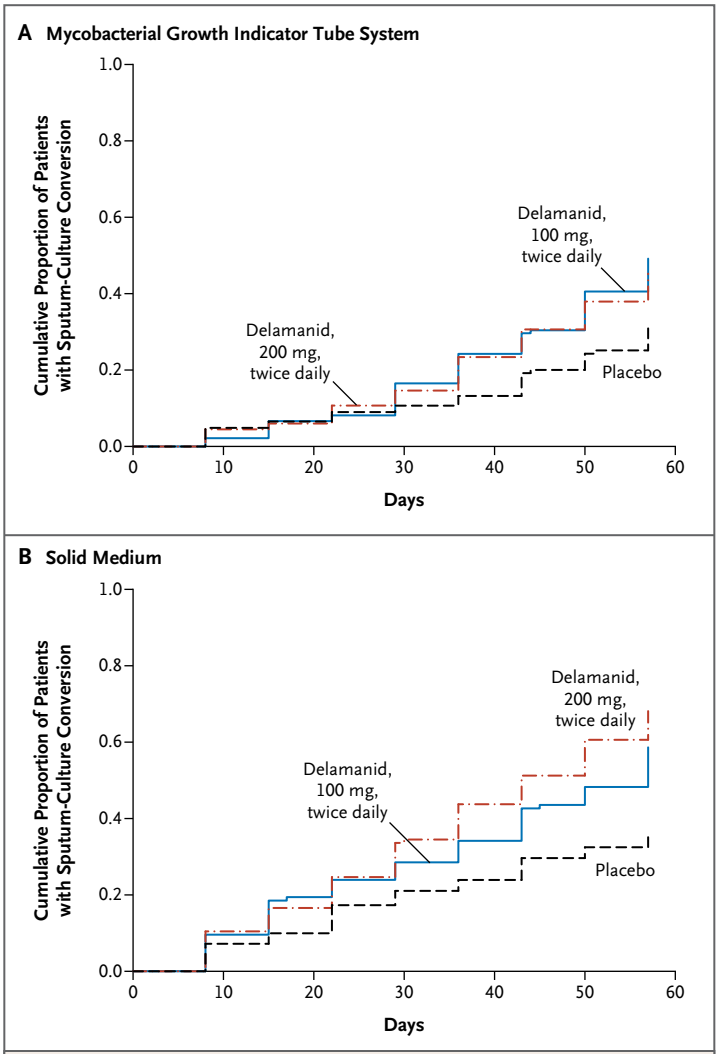

Figure 3. Survival Analysis of Days to Sputum-Culture Conversion, According to Culture Medium Type.

vide data on 30 months of follow-up of patients. It is important to learn more about the use of delamanid in combination with other new and existing antimycobacterial agents to develop better regimens for multidrug-resistant tuberculosis.

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

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