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## The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

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### ABSTRACT

#### BACKGROUND

The diarylquinoline TMC207 offers a new mechanism of antituberculosis action by inhibiting mycobacterial ATP synthase. TMC207 potently inhibits drug-sensitive and drug-resistant *Mycobacterium tuberculosis* in vitro and shows bactericidal activity in patients who have drug-susceptible pulmonary tuberculosis.

#### METHODS

In the first stage of a two-stage, phase 2, randomized, controlled trial, we randomly assigned 47 patients who had newly diagnosed multidrug-resistant pulmonary tuberculosis to receive either TMC207 (400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks) (23 patients) or placebo (24 patients) in combination with a standard five-drug, second-line antituberculosis regimen. The primary efficacy end point was the conversion of sputum cultures, in liquid broth, from positive to negative.

#### RESULTS

The addition of TMC207 to standard therapy for multidrug-resistant tuberculosis reduced the time to conversion to a negative sputum culture, as compared with placebo (hazard ratio, 11.8; 95% confidence interval, 2.3 to 61.3;  $P=0.003$  by Cox regression analysis) and increased the proportion of patients with conversion of sputum culture (48% vs. 9%). The mean  $\log_{10}$  count of colony-forming units in the sputum declined more rapidly in the TMC207 group than in the placebo group. No significant differences in average plasma TMC207 concentrations were noted between patients with and those without culture conversion. Most adverse events were mild to moderate, and only nausea occurred significantly more frequently among patients in the TMC207 group than among patients in the placebo group (26% vs. 4%,  $P=0.04$ ).

#### CONCLUSIONS

The clinical activity of TMC207 validates ATP synthase as a viable target for the treatment of tuberculosis. (ClinicalTrials.gov number, NCT00449644.)

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**T**UBERCULOSIS IS A LEADING CAUSE OF death from infectious disease, second only to human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS).<sup>1</sup> In 2006, there were 9.2 million new cases of tuberculosis and 1.7 million deaths, with the burden of the disease occurring predominantly in the developing world.<sup>2</sup> It is estimated that one third of the world's population is infected with latent *Mycobacterium tuberculosis*, providing an enormous reservoir for future disease.<sup>3</sup>

Treatment of tuberculosis is protracted and burdensome.<sup>4</sup> Tuberculosis control is further complicated by the synergy between tuberculosis and HIV/AIDS and by the emergence of multidrug-resistant strains of *M. tuberculosis*.<sup>3</sup> Multidrug-resistant tuberculosis — resistant to both isoniazid and rifampin — is prevalent in countries of the former Soviet Union, South Africa, and China<sup>5,6</sup> and is currently responsible for an estimated 490,000 incident cases of tuberculosis and 110,000 deaths worldwide each year.<sup>2</sup> Multidrug-resistant tuberculosis requires extended treatment with second-line drugs that are less effective and have more adverse effects than isoniazid-based and rifampin-based regimens.<sup>7</sup> Furthermore, extensively drug-resistant tuberculosis, defined as multidrug-resistant tuberculosis plus resistance to a fluoroquinolone and an injectable second-line drug, has recently emerged as a public health threat.<sup>8</sup>

TMC207 (formerly R207910) is an investigational diarylquinoline compound that offers a new mechanism of antituberculosis action by specifically inhibiting mycobacterial ATP synthase.<sup>9,10</sup> In vitro, TMC207 potently inhibits drug-sensitive and drug-resistant *M. tuberculosis* isolates<sup>9,11</sup> and is also bactericidal against dormant (nonreplicating) tubercle bacilli.<sup>12</sup> In the murine model of tuberculosis, TMC207 is as active as the combination of isoniazid, rifampin, and pyrazinamide,<sup>9</sup> whereas the addition of TMC207 to this triple-drug regimen results in accelerated clearance of bacilli<sup>9</sup> and synergistic interaction with pyrazinamide.<sup>13</sup> Similarly, TMC207 enhances the antibacterial activity of second-line drug combinations in the murine model of drug-sensitive tuberculosis.<sup>14</sup> Results from a phase 2a, proof-of-concept study indicate that TMC207 (400 mg) is associated with acceptable adverse-event rates and that short-term (7 days), once-daily admin-

istration has delayed bactericidal activity in patients with drug-susceptible pulmonary tuberculosis who have sputum smears that are positive for acid-fast bacilli and who have not previously received treatment.<sup>15</sup> A two-stage, phase 2, randomized, placebo-controlled trial, consisting of an exploratory stage (8 weeks) followed by a separate proof-of-efficacy stage (24 weeks), was initiated to assess the antibacterial activity of TMC207 in patients with newly diagnosed, smear-positive pulmonary infection caused by multidrug-resistant *M. tuberculosis*. We present here the results of the first stage of this study, which was undertaken to evaluate the safety, adverse-event profile, pharmacokinetics, and antibacterial activity of TMC207 during prolonged administration.

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## METHODS

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### PATIENTS

In this study, we included patients ranging in age from 18 to 65 years who had newly diagnosed pulmonary tuberculosis, as determined by sputum smears that were positive for acid-fast bacilli, and resistance to both isoniazid and rifampin, as demonstrated by susceptibility tests, rapid screening tests (FASTPlaque-Response assay [Biotec] and GenoType MTBDRplus assay [Hain Lifescience]), or both. Patients were excluded from participation if their isolates were not susceptible to aminoglycosides (other than streptomycin) and fluoroquinolones or if they had previously been treated for multidrug-resistant tuberculosis, if they had neurologic or severe extrapulmonary manifestations of tuberculosis, if they had tested positive for HIV with a CD4+ count of fewer than 300 cells per microliter or had received antiretroviral or antifungal medication or both in the previous 90 days, or if they had significant cardiac arrhythmia. Standard exclusion criteria concerning drug hypersensitivity, alcohol and drug abuse, concomitant illness, abnormal laboratory results, pregnancy, breast-feeding, and participation in other clinical studies were also applied.

### STUDY DESIGN

This was an 8-week phase 2, multicenter, placebo-controlled study, conducted among hospitalized patients in South Africa who had confirmed multidrug-resistant tuberculosis, to evaluate the safety, tolerability, pharmacokinetics, and antibacterial

activity of TMC207. After a 1-week screening period, during which first-line antituberculosis treatment was discontinued, patients were stratified according to study center and extent of lung cavitation ( $\geq 2$  cm bilaterally,  $\geq 2$  cm unilaterally, or  $< 2$  cm) and were randomly assigned in a 1:1 ratio to receive either TMC207 (400 mg once daily for weeks 1 and 2, followed by 200 mg three times a week for weeks 3 through 8) or placebo in a double-blind manner. This regimen was meant to maximize the initial exposure to TMC207 and was selected on the basis of a previous study that showed substantial bactericidal activity at a dose of 400 mg daily.<sup>15</sup> Subsequent intermittent dosing of 200 mg three times a week was selected to maintain plasma concentrations above a target average steady-state plasma concentration of 600 ng per milliliter.

The study drugs were provided as TMC207 100-mg tablets (Tibotec BVBA) and matching placebo tablets and were taken with water immediately after breakfast. The preferred background regimen, which was initiated at the start of the double-blind treatment phase, was specified before randomization and consisted of kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Modifications to this background regimen were allowed according to susceptibility-test results emerging during the study or because of unacceptable adverse events or supply interruption of the drugs. Intake of all study medication was supervised to ensure adherence by the patients. Use of known inducers and inhibitors of the cytochrome P-450 3A4 isoenzyme and of drugs with proarrhythmic potential was prohibited during the study. After completing 8 weeks of double-blind treatment, patients continued their background treatment regimen and were followed up for a total of 96 weeks.

The study was designed and conducted by the sponsor (Tibotec BVBA) and monitored by an independent data and safety monitoring committee. The data were collected and analyzed by the sponsor. The study protocol was approved by independent ethics committees and institutional review boards, and the study was performed in accordance with Good Clinical Practice guidelines and the guiding principles of the Declaration of Helsinki. All patients provided written

informed consent before entry into the study. All authors reviewed and edited the manuscript, had full access to all the data and analyses, and vouch for the accuracy and completeness of the data.

## STUDY PROCEDURES

### *Microbiologic Assessments*

Triplicate-spot sputum samples were collected before treatment initiation (day -1) and at weekly intervals during the double-blind treatment phase to assess the status of smears for acid-fast bacilli and the growth of *M. tuberculosis* in liquid broth medium (semi-automated mycobacteria growth indicator tube [MGIT] system). In addition, samples of sputum that had pooled overnight (16 hours) were collected from patients in two centers at baseline (day -1) and at weeks 1, 2, 4, 6, and 8 for quantitative serial sputum colony-counting (SSCC) analysis of *M. tuberculosis* with the use of quadruplicate 7H11 agar plates enriched with 5% bovine serum albumin to prevent carryover effects of TMC207.<sup>16</sup> All drug-susceptibility testing was performed with the proportion method<sup>17,18</sup> at baseline (day -1) and week 8 at a central laboratory (Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium) whose staff members were unaware of the treatment assignment. Results were not available within the first 8 weeks of treatment.

### *Pharmacokinetic Assessments*

Blood samples were collected before the drugs were taken at weekly intervals during the double-blind treatment phase for determination of plasma concentrations of TMC207. In addition, serial 24-hour blood sampling was conducted at week 2, and 48-hour blood sampling at week 8, for full pharmacokinetic profiling of TMC207. Plasma concentrations of TMC207 were determined with the use of a validated liquid chromatography-mass spectrometry method (lower limit of quantification, 2.0 ng per milliliter). Noncompartmental pharmacokinetic analysis of plasma TMC207 concentration-time data was performed with the use of WinNonlin Professional software (Pharsight). Peak plasma concentration and minimum plasma concentration were obtained directly from the data. The area under the plasma concentration-time curve from time 0 to  $\tau$  ( $AUC_{0-\tau}$ ), where  $\tau$  is the dosing interval, was calculated with the use of the linear trapezoidal method. The average

steady-state plasma concentration was calculated as  $AUC_{0-\tau} \div \tau$ . Pharmacokinetic analyses were performed by Kinesis Pharma, Breda, the Netherlands.

#### *Safety Assessments*

Physical examinations, assessment of vital signs, electrocardiography, and the monitoring of adverse events were performed at baseline and at regular weekly intervals during the study. The electrocardiographic QT interval was corrected with the use of Fridericia's formula: corrected QT interval =  $QT \times (1000 \div RR \text{ interval in milliseconds})^{0.33}$ . Clinical laboratory tests (blood chemical profile, hematologic analysis, and urinalysis), chest radiography, and audiometry tests were performed at regular intervals. Patients with adverse events or grade 3 or grade 4 laboratory abnormalities that were present at completion of the double-blind study period were followed until satisfactory clinical resolution or stabilization.

#### **STATISTICAL ANALYSIS**

Safety evaluations were performed on all patients who underwent randomization and who received at least one dose of study medication. Efficacy evaluations were restricted to patients who had positive liquid broth cultures (MGIT system) at baseline and who met none of the exclusion criteria (44 patients). Patients were considered to have "converted" if their sputum cultures at week 7 and week 8 were negative. The primary efficacy end point was the time to the conversion of sputum cultures from positive to negative in the MGIT culture system, which was defined for this analysis as the interval between the date of treatment initiation and the date of acquisition of the first of at least two consecutive negative weekly cultures. The data from patients who discontinued treatment prematurely were censored at their last microbiologic assessment. Secondary outcomes included the change from baseline in the  $\log_{10}$  count of colony-forming units (CFUs). Categorical and continuous variables were summarized with descriptive statistics with the use of SAS software. To compare the time to culture conversion between treatment groups, a Cox proportional-hazards model adjusting for stratification variables was used. Statistical analyses of demographic, efficacy, and safety and tolerability data were performed by SGS Life Science

Services, Mechelen, Belgium. All reported P values are two-sided and not adjusted for multiple testing.

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## RESULTS

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#### **STUDY POPULATION**

Recruitment started June 5, 2007, and the last treatment visit of the last patient was January 23, 2008. A total of 47 patients with newly diagnosed, smear-positive, multidrug-resistant pulmonary tuberculosis were randomly assigned to treatment with TMC207 (23 patients) or placebo (24 patients), of whom 41 patients (20 in the TMC207 group and 21 in the placebo group) completed the 8-week treatment period. Six patients (three in each treatment group) discontinued the study prematurely, including two who were withdrawn in the first week of treatment because they met a study exclusion criterion (they tested positive for extensively drug-resistant tuberculosis). Testing of the sputum cultures of one further patient, by means of the MGIT culture system, was negative throughout the study, and the patient was considered unable to be evaluated for the efficacy analysis (but able to be evaluated for the safety analysis). Consequently, the population for the primary efficacy analysis comprised 44 patients with multidrug-resistant tuberculosis (21 in the TMC207 group, and 23 in the placebo group), whereas a subgroup of 22 patients (9 receiving TMC207 and 13 receiving placebo) provided serial pooled-sputum collections with CFU counts that could be evaluated.

The study population was predominantly male (74%), black (55%), and HIV-negative (87%), with a median age of 33 years (range, 18 to 57). All patients were confirmed to have an organism resistant to both rifampin and isoniazid, as indicated by rapid screening tests, susceptibility tests, or both, and at least 85% of the patients showed mycobacterial susceptibility to each of the following drugs: capreomycin, kanamycin, ethionamide, and ofloxacin. There were no significant differences in demographic or baseline clinical characteristics between the two treatment groups (Table 1), and a backbone of similar second-line antituberculosis drugs was used in the two treatment groups during the study. Two patients in the placebo group had their background regimens modified empirically during the 8-week treatment period. Overall patient adherence with

**Table 1. Demographic and Baseline Clinical Characteristics and Drug Susceptibility of the Patients.**

Characteristic	TMC207 (N=23)	Placebo (N=24)	Total (N=47)
Age — yr			
Median	33	33	33
Range	18–57	19–57	18–57
Body-mass index*			
Median	18.3	18.5	18.3
Range	14.1–26.9	13.8–30.9	13.8–30.9
Male sex — no. (%)	18 (78)	17 (71)	35 (74)
Race — no. (%)†			
Black	13 (56)	13 (54)	26 (55)
White	0	1 (4)	1 (2)
Other	10 (44)	10 (42)	20 (43)
HIV-positive — no. (%)	3 (13)	3 (12)	6 (13)
CD4+ cell count — cells/mm <sup>3</sup>			
Median	675	591	
Range	310–1567	299–1273	
Lung cavitation — no. (%)			
Cavity ≥2 cm bilaterally	6 (26)	7 (29)	13 (28)
Cavity ≥2 cm unilaterally	14 (61)	13 (54)	27 (57)
No cavity ≥2 cm	3 (13)	4 (17)	7 (15)
Susceptibility-test results — no. (%)‡			
Pyrazinamide resistance	10 (59)	14 (70)	24 (65)
Ethambutol resistance	11 (65)	11 (55)	22 (59)
Kanamycin resistance	1 (6)	2 (10)	3 (8)
Ofloxacin resistance	1 (6)	2 (10)	3 (8)
Ethionamide resistance	2 (12)	1 (5)	3 (8)
Background regimen — no. (%)§			
Kanamycin or amikacin, ethionamide, and pyrazinamide	23 (100)	24 (100)	47 (100)
Ofloxacin	23 (100)	23 (96)	46 (98)
Ethambutol	14 (61)	15 (62)	29 (62)
Terizidone or cycloserine	12 (52)	16 (67)	28 (60)

\* Body-mass index is the weight in kilograms divided by the square of the height in meters.

† Race was determined by the investigator.

‡ Susceptibility-test results are for 37 patients: 17 in the TMC207 group and 20 in the placebo group.

§ Three patients in the placebo group received alternative drugs for multidrug-resistant tuberculosis: dapson, capreomycin, clarithromycin, and isoniazid.

the study medication was at least 97% in each treatment group.

#### SAFETY

Of the patients assigned to TMC207 and of those assigned to placebo, against a background regimen of multidrug-resistant tuberculosis therapy,

similar proportions completed the 8-week study (87% and 87%, respectively), and there were no premature discontinuations due to adverse events associated with treatment. Overall side-effect profiles were similar in the two treatment groups, with nausea, unilateral deafness, arthralgia, hemoptysis, hyperuricemia, pain in the extremities,

**Table 2. Incidence of Adverse Events.\***

Adverse Event	TMC207 (N=23)	Placebo (N=24)
	no. (%)	
Gastrointestinal		
Nausea	6 (26)	1 (4)
Diarrhea	3 (13)	1 (4)
Vomiting	1 (4)	2 (8)
Abdominal pain	0	2 (8)
Deafness		
Unilateral	3 (13)	5 (21)
Bilateral	2 (9)	3 (12)
Musculoskeletal and connective tissue		
Arthralgia	4 (17)	3 (12)
Extremity pain	2 (9)	4 (17)
Back pain	0	3 (12)
Respiratory		
Hemoptysis	3 (13)	4 (17)
Pleuritic pain	2 (9)	0
Chest pain	2 (9)	4 (17)
Pharyngolaryngeal pain	1 (4)	2 (8)
Cutaneous		
Rash	2 (9)	4 (17)
Pruritus	2 (9)	2 (8)
Central nervous system		
Dizziness	3 (13)	2 (8)
Headache	2 (9)	2 (8)
Hyperuricemia	4 (17)	3 (12)
Infections	3 (13)	5 (21)
Eye disorders	3 (13)	1 (4)
Reproductive system and breast disorders	1 (4)	3 (12)

\* The adverse events include those reported by at least two patients in either treatment group during the double-blind treatment period, regardless of severity or causality.  $P=0.04$  for nausea;  $P>0.05$  for all other adverse events.

rash, and chest pain being the most common adverse events associated with treatment (Table 2); of these, only nausea occurred in a significantly higher proportion of patients in the TMC207 group than in the placebo group (26% vs. 4%,  $P=0.04$ ).

Most adverse events were of mild or moderate intensity and of a type known to occur commonly in patients with tuberculosis or in patients undergoing the standard drug regimen for multidrug-resistant tuberculosis. One patient in each

treatment group had a serious adverse event (grade 4 diabetic ketoacidosis in the TMC207 group, and grade 4 pneumothorax in the placebo group); neither event was considered to be related to the study medication. There was no evidence of a difference between the two treatment groups, on the basis of changes from baseline, on laboratory safety assessments. No consistent or clinically relevant changes in heart rate or electrocardiographic QRS or PR interval were observed during the study. Increases in the mean corrected QT interval were observed in both treatment groups but were more pronounced in the TMC207 group, with intergroup differences ranging from 1.0 to 10.8 msec ( $P>0.05$ ). None of the absolute values for corrected QT interval were greater than 500 msec, and no adverse events were associated with electrocardiographic changes.

#### PHARMACOKINETICS

Mean plasma concentration–time profiles for TMC207 after treatment with 400 mg once daily (week 2) and 200 mg three times a week (week 8) are depicted in Figure 1. Mean ( $\pm$ SD) peak, minimum, and steady-state plasma concentrations of TMC207 at week 2 were  $3270\pm 1144$  ng per milliliter,  $956\pm 557$  ng per milliliter, and  $1770\pm 701$  ng per milliliter respectively, and at week 8 were  $1659\pm 722$  ng per milliliter,  $620\pm 466$  ng per milliliter, and  $902\pm 535$  ng per milliliter. The majority of patients achieved average steady-state plasma TMC207 concentrations above the target of 600 ng per milliliter throughout the dosing period. No significant differences in the average steady-state plasma concentrations of TMC207 were noted between patients with and those without sputum-culture conversion.

#### ANTIMYCOBACTERIAL ACTIVITY

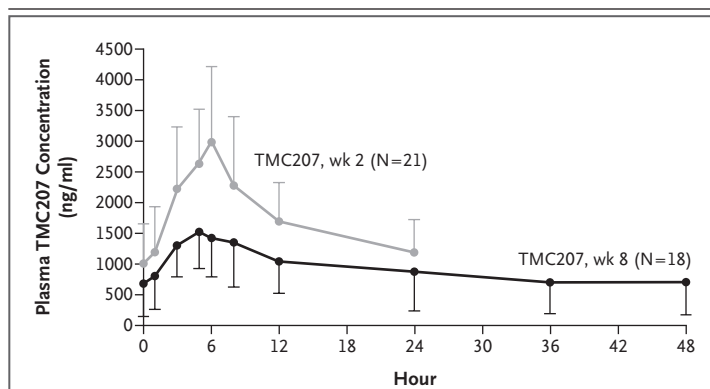
As compared with placebo, the addition of TMC207 to the standard drug regimen for multidrug-resistant tuberculosis resulted in quicker conversion to a negative sputum culture, according to the MGIT culture system (Fig. 2) (hazard ratio, 11.8; 95% confidence interval, 2.3 to 61.3;  $P=0.003$  by Cox regression analysis). The rates of conversion to a negative culture were 48% in the TMC207 group (10 of 21 patients) and 9% in the placebo group (2 of 23 patients). Treatment responses were similar for all trial centers and across all strata of lung cavitation. Over the course of the 8-week treatment period, the median  $\log_{10}$  CFU

count declined more rapidly in the TMC207 group than in the placebo group, and reductions (from baseline) in the  $\log_{10}$  CFU count in the TMC207 group exceeded those in the placebo group at all time points (Fig. 3). Rates of negative smears for acid-fast bacilli exceeded 50% in both groups from week 4 onward, despite positive cultures according to the MGIT system. Rates of negative smears for acid-fast bacilli at week 4 were 57% for the placebo group and 77% for the TMC207 group, and at week 8 were 68% for the placebo group and 84% for the TMC207 group.

## DISCUSSION

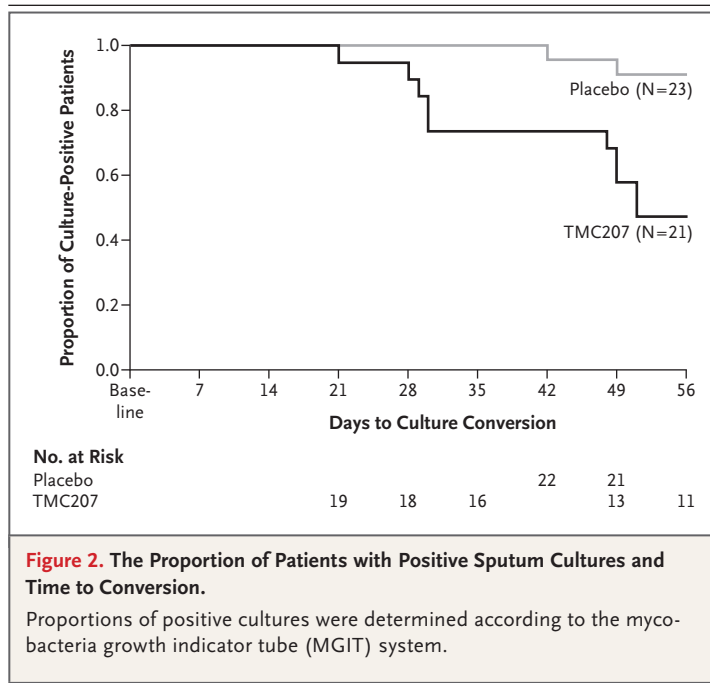
New drugs for the treatment of drug-resistant tuberculosis are direly needed. The poor therapeutic efficacy of multidrug-resistant tuberculosis regimens means that the treatment effects of investigational agents are more readily detectable in patients with multidrug-resistant tuberculosis than in those with drug-susceptible tuberculosis,<sup>19</sup> which allows for smaller-scale clinical trials. Demonstration of antituberculosis activity in patients with multidrug-resistant tuberculosis paves the way for larger-scale trials of first-line antituberculosis combination therapy for patients with drug-susceptible tuberculosis.<sup>20</sup> Our data present evidence that TMC207, in combination with a five-drug second-line regimen, had an acceptable side-effect profile; reduced the time to sputum-culture conversion in patients with newly diagnosed, smear-positive, multidrug-resistant tuberculosis; and significantly increased the proportion of patients with negative sputum cultures after 8 weeks.

It is well known that the evaluation of new antituberculosis agents and regimens is hampered by the lack of a reliable outcome measure for the early prediction of clinical cure and relapse.<sup>21</sup> Concern for resistance limits trials with single agents to a duration that might not be sufficient for the treatment effect to develop fully.<sup>22</sup> In fact, the efficacy of 400 mg of TMC207 in a study of 7 days of early bactericidal activity was only marginally significant from day 4 onward, and the overall reduction of 0.77  $\log_{10}$  CFU over the 7-day period failed to match the high expectations fostered by the promising preclinical results.<sup>15</sup> The subgroup assessed by quantitative SSCC in the present study confirms the relatively moderate effect of TMC207 up to day 7, as re-



**Figure 1.** Mean ( $\pm$ SD) Plasma Concentration–Time Profiles for TMC207 at Week 2 and Week 8.

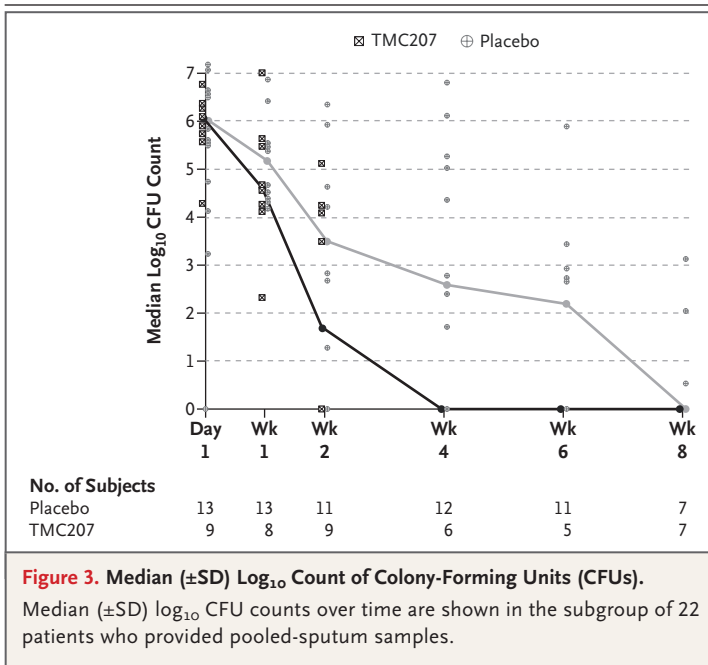
Dosing was selected to maintain plasma TMC207 concentrations above a target average steady-state plasma concentration of 600 ng per milliliter. T bars indicate standard deviations.



**Figure 2.** The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

flected in a reduction of 0.57  $\log_{10}$  CFU as compared with the placebo group. Beyond 1 week, however, TMC207 appreciably accelerated the bactericidal activity of the background regimen for up to 4 weeks. This underscores the time-dependent bactericidal activity of TMC207 and its unique mode of action, involving disruption of energy homeostasis, and suggests that studies of monotherapy with new antituberculosis compounds may need to be extended to 14 days in some



**Figure 3. Median ( $\pm$ SD)  $\text{Log}_{10}$  Count of Colony-Forming Units (CFUs).**

Median ( $\pm$ SD)  $\text{log}_{10}$  CFU counts over time are shown in the subgroup of 22 patients who provided pooled-sputum samples.

cases. Furthermore, the delayed onset of activity confirms the absence of a carryover effect, since the highest exposure to TMC207 is achieved toward the end of the 14-day, once-daily dosing period, when cultures in the MGIT system and on agar plates were still positive.

Since multidrug-resistant tuberculosis clinical isolates are known to grow poorly on solid media,<sup>23</sup> liquid broth (the MGIT system) was used for cultures from all patients, and SSCC on 7H11 agar plates for cultures from a subgroup of patients. Our results also confirm that liquid broth

cultures, which were still positive at 8 weeks for the majority of participants, are more sensitive than solid agar for detecting *M. tuberculosis* in sputum samples.<sup>24,25</sup> All patients included in stage 1, as well as those in stage 2, are closely monitored at regular intervals for 2 years to ensure treatment adherence, confirm culture conversion, and detect treatment failure or relapse.

In conclusion, the safety and efficacy findings from this study clinically validate ATP synthase as a new target for antituberculosis therapy. The findings also confirm the earlier results obtained with TMC207 in the murine model of tuberculosis<sup>14</sup> and show the potential of TMC207 in the treatment of patients with multidrug-resistant tuberculosis.

Drs. De Marez, van Heeswijk, Lounis, Meyvisch, Verbeeck, de Beule, Parys, Andries, and McNeeley report being employees of Tibotec or Tibotec BVBA, Johnson & Johnson companies, who are responsible for the development of TMC207; Drs. De Marez, van Heeswijk, Lounis, Verbeeck, de Beule, Parys, Andries, and McNeeley report holding equity shares in Johnson & Johnson; Dr. Pym reports receiving consulting fees for the evaluation of new diagnostics for tuberculosis infection for UBS Optima, a non-profit organization that is not involved in drug development and has no activities or financial arrangements with Johnson & Johnson; and Dr. Andries reports being inventor or coinventor on three patents on the use of quinoline derivatives for the treatment of mycobacterial diseases (all rights to these patents have been transferred to Johnson & Johnson). No other potential conflict of interest relevant to this article was reported.

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