Janssen Research & Development

Clinical Study Report Synopsis
[TMC207-C208; Phase 2]

TMC207 (bedaquiline)

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- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS

Trial Identification and Protocol Summary

Company: Janssen Research & Development **Trade Name**: - **Indication**: pulmonary disease due to MDR-TB	**Drug Substance**: TMC207 **Trial no**.: TMC207-C208 **Clinical Phase**: II
Title: A Phase II, placebo-controlled, double-blind, randomized trial to evaluate the antibacterial activity, safety, and tolerability of TMC207 in subjects with sputum smear-positive pulmonary infection with multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB).	
Investigator: [redacted] M.D., [redacted] South Africa.	**Country**: multicountry
Trial Period: Start: 23-Apr-2008 Last subject last contact up to cut off date for final analysis: 31-Jan-2012	**No. of Investigators**: 15 **No. of Subjects (randomized)**: 161 **No. of Subjects (randomized and treated)**: 160

Objectives: The primary objective of Stage 2 is to demonstrate superiority in the antibacterial activity of TMC207 compared to placebo when added to a background regimen (BR) for 24 weeks in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.
The primary outcome parameter is the time to sputum culture conversion during treatment with TMC207 or placebo, which was analyzed using Week 24 data. The endpoint time to sputum culture conversion was not derived in the final analysis and the key efficacy parameter of interest in the final analysis is therefore considered to be sputum culture conversion (responder/nonresponder with subcategories for nonresponder, including relapse).
The secondary objectives are to investigate the pharmacokinetics of TMC207 and its *N*-monodesmethyl metabolite (M2) in plasma and sputum of subjects receiving multiple doses of TMC207 in combination with a BR, during treatment and after discontinuation; to explore pharmacokinetic/pharmacodynamic relationships for antibacterial activity and tolerability/safety; and to evaluate and compare the safety and tolerability of 24-week treatment with TMC207 or placebo in addition to the BR.
Rollover arm:
The primary objective of the rollover arm is to offer open-label treatment with TMC207 to subjects from Stage 2 who received placebo and were not adequately responding to their BR regimen (including subjects diagnosed with extensively drug resistant [XDR]-TB during double-blinded treatment in Stage 2) and to offer open-label treatment with TMC207 to subjects for whom there is evidence that they were infected with XDR-TB prior to randomization into the trial.
The secondary objective of the rollover arm is to evaluate safety, pharmacokinetics, and antibacterial activity of TMC207 in these groups of subjects.

Design: This was a stratified, randomized, double-blind, placebo-controlled Phase II trial to evaluate the antibacterial activity, safety, and tolerability of TMC207 when added to a BR of MDR-TB therapy, compared to placebo plus BR, in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.
MDR-TB is defined as being resistant to at least the 2 first line anti-TB drugs isoniazid (INH) and rifampin (RMP). XDR isolates are resistant to RMP and INH, and to fluoroquinolone (FQ) antibiotics, and also to any of the 3 injectable TB drugs (i.e., amikacin [AMK], kanamycin [KAN] and capreomycin [CAP]). MDR-TB strains that have become resistant to any drug in only one of both classes (i.e., to either any second-line injectable drug or any FQ) are called pre-extensively drug resistant TB (pre-XDR). Although the clinical definition of MDR-TB encompasses pre-XDR- and XDR-TB, in this report the term $MDR_{H\&R}$ will be used to refer to MDR excluding pre-XDR and XDR. Subjects infected with pre-XDR strains were allowed to participate in the trial. However, subjects infected with XDR strains were to be withdrawn from the trial upon availability of drug susceptibility testing (DST) results confirming XDR status.
The trial was conducted in 2 consecutive stages: an exploratory stage (Stage 1) and a proof-of-efficacy stage (Stage 2). Subjects participating in Stage 1 were not allowed to enter Stage 2. The two stages are analyzed separately. This report presents results of Stage 2 consisting of the 24-week investigational treatment period and the 96-week follow-up period. In Stage 2, 160 subjects were randomized and treated with either TMC207 or placebo for 24 weeks in addition to a BR. TMC207 was administered as 400 mg once daily (q.d.) for the first 2 weeks, and as 200 mg 3 times/week (t.i.w.) for the following 22 weeks.

After the double-blind treatment phase, subjects continued to receive their MDR-TB treatment. They were followed for safety, tolerability, pharmacokinetics, and microbiological efficacy for 96 weeks after receiving their last dose of TMC207 or placebo. The Data and Safety Monitoring Board (DSMB) reviewed this data on a regular basis throughout the entire trial.
After implementation of Protocol Amendment IV (dated 10 April 2009), subjects from the placebo treatment arm (including subjects diagnosed with XDR-TB during the double-blinded treatment period of Stage 2) were given the option to rollover to a TMC207-containing treatment regimen for 24 weeks provided the rollover criteria as mentioned in the Section "Subject Selection" below were met.
In the rollover arm, subjects received TMC207 for 24 weeks in addition to their BR. This BR was optimized based on information gained from the Week 24 DST. Additionally, subjects with pre-existing XDR-TB for whom second-line drug susceptibility results only became available after randomization had the option to immediately receive open-label treatment with TMC207 in the rollover phase for a total duration of 24 weeks. After 24 weeks of treatment with TMC207, all rollover subjects continued to receive their MDR-TB treatment and were followed for safety, tolerability and microbiological efficacy for 96 weeks after receiving their last dose of TMC207.

Statistical Analyses

Results of the Stage 1 analyses were described in separate Clinical Study Reports (TMC207-C208-CRR-Stage1 and TMC207-C208-CRR-Final-Stage-1-Update).
The primary analysis of Stage 2 was conducted when all subjects completed Week 24 of the trial or had discontinued earlier. An interim analysis was conducted on data up to the cut-off date of 10 May 2011 for efficacy data and of 10 June 2011 for safety data, when all subjects had completed at least the Week 72 visit of the trial or had discontinued earlier (cut-off dates defined in view of the new drug application [NDA]/marketing authorization application [MAA] 2012 submission to account for the time it takes for isolates to grow [long turnaround on the availability of microbiology data] and to allow a maximum of safety data to be collected).
This report contains the results of the final analysis of Stage 2, which was performed when all subjects had completed the trial (except for the rollover arm) or had discontinued earlier, including the completed 24-week investigational treatment period and completed 96-week follow-up period. As follow-up in the rollover arm is still ongoing, a data cut-off date of 31 January 2012 has been applied for the single subject enrolled in the rollover arm and long term follow-up for collection of survival data in subjects who prematurely discontinued the trial.

Subject Selection

Inclusion Criteria

1. Male or female subjects. Females could participate if they were of non-childbearing potential, if they were using effective non-hormone based birth control methods and were willing to continue practicing birth control methods throughout MDR-TB treatment, or if they were non-heterosexually active or willing to practice sexual abstinence throughout MDR-TB treatment.
2. Aged between 18 and 65 years, extremes included.
3. Subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection as defined hereafter, with confirmed resistance to at least both RMP and INH by previous screening from a TB treatment facility, who are willing to start TB-therapy per protocol.
   Resistance to RMP and INH could be shown by the use of the proportion method and/or the rapid screen tests, i.e., fast plaque and Genotype MTBDR plus line probe (if resistance to RMP or INH was based on rapid screen tests, these tests needed to be repeated at the screening visit and both tests had to be positive).
   Subjects with newly diagnosed MDR-TB were defined as a) subjects with MDR-TB who had never been treated for TB before, or b) subjects with MDR-TB who had previously been treated with only first-line TB drugs (INH, RMP, ethambutol [EMB], pyrazinamide [PZA], or streptomycin [SM]).
4. Positive for acid fast bacilli (AFB) on direct smear examination of expectorated sputum specimen (≥1+ smear positive).
5. Subjects with a sputum production of a magnitude that made ability to produce 10 mL per night likely.
6. Subjects had to consent to human immunodeficiency virus (HIV)-testing unless a HIV-test was performed within 1 month prior to trial start and documentation could be provided (enzyme-linked immunosorbent assay [ELISA] and/or Western Blot).
7. Subjects had to be willing to discontinue all TB drugs to allow 7 days washout before baseline assessments and starting treatment with TMC207 or placebo.
8. Subjects having a Quetelet Index (Body Mass Index [BMI]) between 15.0 and 28.0 kg/m^2, extremes included.
9. Subjects had signed informed consent form (ICF) voluntarily before first trial-related activity.
10. Subjects agreed to hospitalization if needed per local standard of care.

Exclusion Criteria

1. Previously been treated for MDR-TB.
   Subjects previously treated for MDR-TB were defined as those having received any second-line TB drug, including any of the following anti-bacterials: any aminoglycoside except SM, any FQ, the thioamides protionamide or ethionamide (ETH), and cycloserine (CS).
2. Subjects having a known or suspected hypersensitivity or serious adverse reaction to the study medication.
3. Subjects having a current or past history of alcohol and/or drug use that, in the investigator's opinion, could compromise the subject's safety or compliance with the study protocol procedures.
4. Subjects having a clinically significant active medical condition, which in the opinion of the investigator could prevent appropriate participation in the trial.
5. Subjects having a significant cardiac arrhythmia that required medication.
6. HIV infected subjects, a) having a CD4+ count < 300 cells/μL or b) having received antiretroviral therapy (ART) and/or oral or intravenous antifungal medication within the last 90 days were not eligible for the trial. Also subjects, who, in the opinion of the investigator, might need to start ART during the 8-week treatment period of Stage 1 or the 24-week treatment period of Stage 2, were not eligible for the trial.
7. Subjects with complicated or severe extrapulmonary manifestations of TB or neurological manifestations of TB.
8. Subjects having any concomitant severe illness or rapidly deteriorating health condition, including immune deficiency that would make implementation of the protocol or interpretation of the study results difficult, or gastrointestinal disease that might, in the judgment of the investigator, interfere with the absorption of TMC207.
9. Subjects who, upon the evaluation of their pulmonary disease, required surgical procedure for management of their TB within the 8-week treatment period of Stage 1 or the 24-week treatment period of Stage 2.
10. Subjects with the following QT/QTc interval characteristics at screening:
    a. A marked prolongation of QT/QTc interval, e.g., repeated demonstration of QTcF (Fridericia correction) interval > 450 ms;
    b. A history of additional risk factors for Torsade de Pointes, e.g., heart failure, hypokalemia, family history of Long QT Syndrome;
    c. The use of concomitant medications that prolong the QT/QTc interval listed as disallowed medication in the trial protocol.
11. Subjects with the following toxicities at screening as defined by the enhanced Division of Microbiology and Infectious Diseases (DMID) adult toxicity table:
    - Creatinine grade 2 or greater (>1.5 times the upper limit of normal [ULN]);
    - Pancreatic lipase grade 2 or greater (>1.5 times ULN);
    - Pancreatic amylase grade 3 or greater (>2.00 times ULN);
    - Hemoglobin grade 4 (<6.5 gm/dL);
    - Platelet count grade 3 or greater (≤ 49999/mm^3);
    - Absolute neutrophil count grade 3 or greater (≤ 749/mm^3);
    - Aspartate aminotransferase (AST) grade 2 or greater (>2.5 times ULN);
    - Alanine aminotransferase (ALT) grade 2 or greater (>2.5 times ULN);
    - Alkaline phosphatase (ALP) grade 2 or greater (>2.5 times ULN);
    - Total bilirubin grade 2 or greater (>1.6 times ULN);
    - Any grade 3 musculoskeletal toxicity [severe muscle tenderness with marked impairment of activity]; any grade 4 musculoskeletal toxicity [frank myonecrosis]).
12. Subjects having evidence of chorioretinitis, optic neuritis, or uveitis at screening;
13. Subjects having previously participated in an investigational drug trial with TMC207.
14. Subjects having participated in other clinical trials with investigational agents, within 8 weeks prior to trial start.
15. Subjects having had a drug susceptibility test performed prior to screening and their MTB isolate being not susceptible to at least 3 of the 5 classes of TB drugs used to treat MDR-TB.
16. Subjects having any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the trial.
17. Subjects unlikely to comply with the protocol, e.g., uncooperative attitude or unlikelihood of completing the trial.
18. Women who were pregnant and/or breastfeeding.

Rollover criteria

1. Subjects from the placebo treatment arm (including subjects diagnosed with XDR-TB during the double-blinded treatment period of Stage 2, see rollover criterion 2 below) are given the option to rollover to a TMC207-containing treatment regimen for 24 weeks provided the following 3 conditions are met:
   - they completed 24 weeks of double-blind treatment in Stage 2 of the trial;
   - they had at least 2 positive sputum culture specimens taken at Week 24 and at Week 28 (if necessary sputum culture specimen could be taken during an unscheduled visit). The rollover visit was anticipated to be at Week 36 when the confirmatory culture results were available, as well as the Week 24 susceptibility results to guide selection of an appropriate BR during the rollover;
   - they rolled over by Week 48 at the latest.

   NOTE: An earlier rollover, given completion of the 24 weeks treatment, for subjects diagnosed with XDR-TB during the double-blind treatment period, could be discussed with the Medical Leader.
2. Subjects with pre-existing XDR-TB for whom second-line susceptibility results only become available after randomization had the option to immediately receive open label treatment with TMC207 in the rollover phase.

Treatment	TMC207	Placebo
Concentration Dosage Form (F No.) Usage	100 mg tablet (F001) oral	- tablet (F002) oral
Batch Number	07F18/F001, 07F25/F001, 08B26/F001, 08K17/F001, 07B19/F001, 09D22/F001, 09E05/F001	07B15/F002, J074017
Dose Regimen	Investigational treatment period: Weeks 1 and 2: 400 mg TMC207 or placebo q.d. administered as 4 tablets, and BR* Week 3 to 24: 200 mg TMC207 or placebo t.i.w. administered as 2 tablets, and BR Overall treatment period: MDR-TB treatment for 18-24 months*, at least 12 months after the first documented negative culture *The BR was specified prior to randomization and was preferably composed of the following drugs: KAN, ofloxacin (OFL), ETH, PZA and CS/terizidone (TRD). Substitutions were permissible in case of shortage of drug supply or because of the subject's intolerance to a selected BR drug component.	
Duration of Treatment	Duration of TMC207/placebo intake: 24 weeks investigational treatment period for subjects not eligible for rollover or 48 weeks for placebo subjects meeting the rollover criteria Duration of BR intake: 72 to 96 weeks background treatment (i.e., including intake during the investigational treatment period)	
Duration of Trial	Screening: 1 week Investigational treatment: 24 weeks for TMC207 and placebo subjects not eligible for rollover or 48 weeks for placebo subjects meeting the rollover criteria. Follow-up (BR only treatment + treatment-free follow-up): 96 weeks	

Disallowed Medication	Concomitant nonantibiotic treatments were to be kept to a minimum during the trial. However, if concomitant nonantibiotic treatments were considered to be necessary for the subject's welfare and were unlikely to interfere with the study medication, they could be given at the discretion of the investigator. The following medications were disallowed: ▪ the systemic use of cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole) for more than 3 consecutive days during treatment with TMC207 or placebo, as well as during the first 4 months after the last dose of study medication; ▪ the systemic use of CYP3A4 inducers (e.g., phenytoin, rifamycins) during treatment with TMC207 or placebo; ▪ the use of antiretroviral (ARV) medication during treatment with TMC207 or placebo, as well as during the first 4 months after the last dose of study medication. ▪ medications of the statin class of compounds; ▪ tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine, clomipramine; ▪ the nonsedating antihistamines astemizole and terfenadine; ▪ the neuroleptics-phenothiazines thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole, and pimozide; ▪ the prokinetic cisapride; ▪ quinoline antimalarials (e.g., chloroquine and quinacrine). **Prior to implementation of Protocol Amendment III** (dated 29 April 2008), no oral or parenteral concomitant antibiotic treatments were permitted for the duration of the trial unless discussed with the Medical Leader. **After implementation of Amendment III**, concomitant antibiotic treatments of any kind were discouraged during the period of study drug administration. During the course of the trial, short course (< 2 weeks) antimicrobial therapy could be administered for concurrent illnesses. However, the following agents used to treat *Mycobacterium tuberculosis* (*M. tuberculosis*) infections were not to be used during the trial except after discussion with the sponsor's Medical Leader: ▪ thiacetazone; ▪ isoniazid; ▪ any rifamycin antibiotic; ▪ para-aminosalicylic acid (except when used to replace one of the BR drugs to which the subject was demonstrated to have resistance); ▪ dapsone; ▪ any macrolide antibiotic; ▪ amoxicillin-clavulanic acid/clavulanate; ▪ viomycin; ▪ clofazimine; ▪ capreomycin; ▪ linezolid. Short courses of antibiotic therapy (< 2 weeks) with drugs not indicated for the treatment of TB should be limited and the illness for which they were prescribed had to be recorded as an adverse event (AE). The administration of any concomitant antibiotic therapy for > 2 weeks had to be discussed with the sponsor's Medical Leader in advance.

Disallowed Medication, Cont'd	**After implementation of Amendment IV** (dated 10 April 2009), the following additional antibiotic medications were disallowed during administration of TMC207 and up to 1 month after completion of the 6-month intensive phase of MDR-TB treatment: moxifloxacin and gatifloxacin. Rifamycin antibiotics (including rifabutin) and macrolide antibiotics were allowed after 1 month after completion of the 6-month intensive phase of MDR-TB treatment. In addition, the following medications were disallowed during administration of TMC207 and up to 1 month after the last dose of TMC207 in the **Stage 2 *rollover arm*:** ▪ the systemic use of CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin; and macrolide antibiotics other than azithromycin) for more than 3 consecutive days; ▪ the systemic use of CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort, and rifamycins); ▪ (boosted) HIV protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). ▪ moxifloxacin and gatifloxacin The following medications are disallowed during administration of TMC207 in the rollover arm: ▪ medications of the statin class of compounds; ▪ tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine, clomipramine; ▪ the nonsedating antihistamines astemizole and terfenadine; ▪ the neuroleptics-phenothiazines thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole, and pimozide; ▪ the prokinetic cisapride; ▪ quinoline antimalarials (e.g., chloroquine and quinacrine). Use of disallowed medication by a subject had to be immediately discussed with the sponsor in order to determine what course of action had to be taken regarding subject's continuation in the trial.
Assessments	
Pharmacokinetics	
Substudy	In a subset of Stage 2 subjects, full pharmacokinetic profiling was performed during double-blind treatment at Weeks 2 and 24. Pharmacokinetic sampling occurred predose and 1, 3, 5, 6, 8, 12, and 24 h after dosing. At Week 24, 48-hour pharmacokinetic profiling (i.e., additional samples at 36 h and 48 h after dosing) was done. Sputum concentrations of TMC207 and M2 were determined in a subset of subjects, in an aliquot of the overnight sputum samples collected on Day 7 and at Weeks 2, 8, 16, and 24.
Main Study	Predose[a] sampling for determination of plasma concentrations of TMC207 and M2 occurred in all subjects during double-blind treatment on Day 7 and at Weeks 2, 4, 8, 10, 12, 16, and 24, as well as during follow-up at Weeks 28, 32, 36, 48, 60, 72, 84, 96, and 120. Prior to implementation of Protocol Amendment III, for all Stage 2 subjects, an additional sample at 5 h after dosing was collected at Weeks 2, 8, 16 and 24. After implementation of Protocol Amendment III, an additional sample at 5 h after dosing was collected at Weeks 2 and 24 only. At Weeks 8 and 16, an additional sample was collected at anytime postdose. In the rollover arm of Stage 2, predose sampling for the determination of plasma concentration of TMC207 and M2 occurred at Week 2R, 12R and 24R. [a.] Within 10 minutes before scheduled intake of study medication prior to Protocol Amendment III, or before breakfast within 1 hour before scheduled intake of study medication after implementation of Amendment III.

Efficacy	Triplicate spot sputum samples to assess the presence or absence of *M. tuberculosis* by qualitative culturing (Mycobacteria Growth Indicator Tube [MGIT]) and AFB smear were collected at every visit, except Day 1, and in case of withdrawal and at follow-up after withdrawal. Samples were to be taken before study medication intake. Overnight (16 h) sputum samples (starting at 4 p.m. of the indicated visit day and continuing until 8 a.m. the following morning) were collected from a subset of subjects to quantitatively analyze *M. tuberculosis* using solid culture media (colony forming units [CFU] count): ▪ on Days −1 and 7; ▪ at Weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24 The MGIT based on triplicate spot sputum samples was used for the assessment of the primary efficacy parameter, time to culture conversion and to collect time to positive signal in the MGIT using liquid media. *M. tuberculosis* identification was done on Day –1.
Chest X-ray	A postero-anterior chest X-ray, including assessment of the cardiac silhouette, was taken at screening, at Weeks 8, 16, 24, and 48, in case of withdrawal, and at follow-up after withdrawal. After implementation of Protocol Amendment III, X-rays could be taken more frequently as needed for any evidence of worsening pulmonary health, as determined by the investigator.
Drug Susceptibility Testing	Drug susceptibility testing for TMC207 and first- and second-line anti-TB drugs was done on Day –1, at Weeks 8 and 24, and one year after the last dose of TMC207 or placebo (i.e., at Week 72). Additional drug susceptibility assessments were to be made in case of failure to respond to treatment, relapse, or new infection/re-infection.
Safety Adverse Events	AEs were monitored throughout the trial, from signing of ICF onwards until the last trial-related activity.
Clinical Laboratory	Blood samples[a] for hematology and biochemistry measurements and a urine sample[b] were taken: ▪ at screening and Day –1; ▪ at Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24; ▪ at all visits during the follow-up period; ▪ in case of withdrawal and at follow-up after withdrawal. a. Subject had to have fasted for at least 10 h (overnight) prior to sampling. b. Urine samples had to be taken before study medication intake. A CD4+ cell count was performed at screening for all subjects and at Weeks 8, 16, 24, 36, 48, 60, 72, 84, 96, 108, and 120 and in case of withdrawal for HIV-positive subjects.
Cardiovascular Safety	Vital signs (i.e., pulse rate, blood pressure, and respiratory rate) were recorded at every visit including screening and in case of withdrawal and at follow-up after withdrawal. Assessments had to occur before study medication intake. Electrocardiograms (ECGs) were taken (before blood sampling): ▪ at screening[a], at Day −1[a,b], Day 1[a,b], Day 7, and Weeks 2[a,b], 3, 4, 5, 6, 7, 8[a,b], 10, 12, 14, 16, 18, 20, 22, and 24[a,b]; ▪ at Weeks 28, 32, 36[a], 48[a], 60, 72, 84, 108, and 120; ▪ in case of withdrawal and at follow-up after withdrawal. Unscheduled ECG evaluations were to be made for subjects having grade 3 or 4 elevation in troponin or creatine phosphokinase muscle-brain isoenzyme (CPK-MB). a. Triplicate ECGs were taken at these visits. After implementation of Amendment III, triplicate ECGs were taken at each pharmacokinetic timepoint in the subpopulation undergoing full pharmacokinetic profiling at Week 2 and Week 24. b. At 0 and 5 h (and at 36 and 48 h at Week 24) relative to dosing or 8 a.m. if no dosing (if possible, after breakfast).

Physical Examination	A physical examination was performed at all visits and included weight, temperature, and a complete ophthalmologic exam including fundoscopy with an ophthalmoscope. After implementation of Amendment III, the ophthalmologic exam including a fundoscopy with an ophthalmoscope was only performed at screening and at the end of treatment period. At the other visits, the ophthalmologic exam included a check of the red reflex of the fundus with an external light source. For females, the physical examination included a history of menstrual cycle. Assessments were to be made before study medication intake.
Audiometry	Audiometry was performed at Day –1, and at Weeks 4, 8, 12, 16, 20, and 24. If needed, additional tests could be performed.
Statistical Methods Performed	Intent-to-treat analysis, modified intent-to-treat analysis, descriptive statistics, frequency tabulations, population pharmacokinetic modeling, Kaplan-Meier, Cox proportional hazards model, logistic regression model, ANCOVA

Main Features of the Subject Sample and Summary of the Results

Baseline Characteristics - Subject Disposition	ITT			mITT		
	TMC207/ BR N = 79	**Placebo/ BR N = 81**	**All Subjects N = 160**	**TMC207/ BR N = 66**	**Placebo/ BR N = 66**	**All Subjects N = 132**
Number of Subjects Entered (M/F)	52/27	49/32	101/59	45/21	40/26	85/47
Age: median (range), years	31.0 (18, 63)	35.0 (18, 61)	34.0 (18, 63)	32.0 (18, 63)	34.0 (18, 57)	33.5 (18, 63)
Race, n (%)	**79**	**81**	**160**	**66**	**66**	**132**
Black	29 (36.7)	27 (33.3)	56 (35.0)	24 (36.4)	25 (37.9)	49 (37.1)
Caucasian/white	8 (10.1)	12 (14.8)	20 (12.5)	6 (9.1)	8 (12.1)	14 (10.6)
Hispanic	13 (16.5)	15 (18.5)	28 (17.5)	12 (18.2)	10 (15.2)	22 (16.7)
Oriental/asian	9 (11.4)	6 (7.4)	15 (9.4)	9 (13.6)	6 (9.1)	15 (11.4)
Other	20 (25.3)	21 (25.9)	41 (25.6)	15 (22.7)	17 (25.8)	32 (24.2)
Pooled center[a]	**79**	**81**	**160**	**66**	**66**	**132**
Asia	8 (10.1)	4 (4.9)	12 (7.5)	8 (12.1)	4 (6.1)	12 (9.1)
Eastern Europe	8 (10.1)	11 (13.6)	19 (11.9)	6 (9.1)	7 (10.6)	13 (9.8)
South Africa - All	43 (54.4)	45 (55.6)	88 (55.0)	37 (56.1)	42 (63.6)	79 (59.8)
South Africa - 1	*17 (21.5)*	*18 (22.2)*	*35 (21.9)*	*14 (21.2)*	*17 (25.8)*	*31 (23.5)*
South Africa - 2	*14 (17.7)*	*14 (17.3)*	*28 (17.5)*	*13 (19.7)*	*13 (19.7)*	*26 (19.7)*
South Africa - Other	*12 (15.2)*	*13 (16.0)*	*25 (15.6)*	*10 (15.2)*	*12 (18.2)*	*22 (16.7)*
South America	20 (25.3)	21 (25.9)	41 (25.6)	15 (22.7)	13 (19.7)	28 (21.2)
Extent of resistance of *M. tuberculosis*	**79**	**77**	**156**	**66**	**66**	**132**
DS-TB	4 (5.1)	4 (5.2)	8 (5.1)	0	0	0
MDR-TB[b]	75 (94.9)	73 (94.8)	148 (94.9)	66 (100)	66 (100)	132 (100)
$MDR_{H\&R}$-TB	*40 (50.6)*	*47 (61.0)*	*87 (55.8)*	*39 (59.1)*	*46 (69.7)*	*85 (64.4)*
pre-XDR-TB	*16 (20.3)*	*12 (15.6)*	*28 (17.9)*	*15 (22.7)*	*12 (18.2)*	*27 (20.5)*
XDR-TB	*3 (3.8)*	*4 (5.2)*	*7 (4.5)*	*0*	*0*	*0*
Cavitations (as stratified)	**79**	**81**	**160**	**66**	**66**	**132**
Cavitations >= 2 cm in Both Lungs	13 (16.5)	16 (19.8)	29 (18.1)	12 (18.2)	15 (22.7)	27 (20.5)
Cavitations >= 2 cm in One Lung Only	50 (63.3)	49 (60.5)	99 (61.9)	42 (63.6)	41 (62.1)	83 (62.9)
No Cavitations or Cavitations < 2 cm	16 (20.3)	16 (19.8)	32 (20.0)	12 (18.2)	10 (15.2)	22 (16.7)
HIV status, n (%)	**79**	**81**	**160**	**66**	**66**	**132**
Negative	71 (89.9)	65 (80.2)	136 (85.0)	61 (92.4)	52 (78.8)	113 (85.6)
Positive	8 (10.1)	16 (19.8)	24 (15.0)	5 (7.6)	14 (21.2)	19 (14.4)
PZA susceptibility	**65**	**68**	**133**	**56**	**59**	**115**
Resistant	43 (66.2)	37 (54.4)	80 (60.2)	38 (67.9)	33 (55.9)	71 (61.7)
Susceptible	22 (33.8)	31 (45.6)	53 (39.8)	18 (32.1)	26 (44.1)	44 (38.3)
Completed	**50 (63.3)**	**49 (60.5)**	**99 (61.9)**	**43 (65.2)**	**41 (62.1)**	**84 (63.6)**
Discontinued	**29 (36.7)**	**31 (38.3)**	**60 (37.5)**	**23 (34.8)**	**24 (36.4)**	**47 (35.6)**
Adverse event	9 (11.4)	6 (7.4)	15 (9.4)	8 (12.1)	5 (7.6)	13 (9.8)
Subject ineligible to continue the trial	2 (2.5)	6 (7.4)	8 (5.0)	0	0	0
Subject is pregnant	3 (3.8)	2 (2.5)	5 (3.1)	3 (4.5)	2 (3.0)	5 (3.8)
Subject lost to follow-up	5 (6.3)	3 (3.7)	8 (5.0)	5 (7.6)	3 (4.5)	8 (6.1)
Subject non-compliant	3 (3.8)	7 (8.6)	10 (6.3)	2 (3.0)	7 (10.6)	9 (6.8)
Subject withdrew consent	6 (7.6)	7 (8.6)	13 (8.1)	5 (7.6)	7 (10.6)	12 (9.1)
Other	1 (1.3)	0	1 (0.6)	0	0	0
Rollover	**0**	**1 (1.2)**	**1 (0.6)**	**0**	**1 (1.5)**	**1 (0.8)**

ITT: intent-to-treat population; mITT: modified ITT population; DS: drug susceptible, $MDR_{H\&R}$: multi-drug resistant, excluding pre-XDR and XDR; XDR: extensively drug-resistant

Footnotes: see next page

[a] Individual centers with low numbers of randomized subjects were pooled together based on geographic region to account for possible differences in resistance patterns. The pooling of centers was determined prior to database lock of the primary efficacy analysis and prior to unblinding of the randomization codes. Centers of the Republic of South Africa were pooled in 'South Africa-other' unless the investigator was [redacted] ('South Africa-1') or [redacted] ('South Africa-2').

[b] For 26 subjects (16.3%; i.e., 16 in the TMC207 group and 10 in the placebo group) in the ITT population and 20 subjects (15.2%; i.e., 12 in the TMC207 group and 8 in the placebo group) in the mITT population, no confirmation from the central laboratory of INH and RMP resistance was available. These subjects were considered MDR based on the subject's medical history (based on previous DST).

Inclusion/Exclusion **Reason for exclusion from mITT population** **n (%)**	**TMC207/BR** **N = 79**	**Placebo/BR** **N = 81**	**All subjects** **N = 160**
Excluded from mITT	**13 (16.5)**	**15 (18.5)**	**28 (17.5)**
MGIT results did not allow for primary efficacy evaluation[a]	6 (7.6)	3 (3.7)	9 (5.6)
Subject not MDR-TB / pre-XDR-TB[b]	6 (7.6)	11 (13.6)	17 (10.6)[c]
Subjects infected with DS or XDR-TB or subjects for whom the MDR-TB status could not be confirmed[b] and MGIT results did not allow for primary efficacy evaluation[a]	1 (1.3)	1 (1.2)	2 (1.3)[c]
Included in mITT[d]	**66 (83.5)**	**66 (81.5)**	**132 (82.5)**

N = number of subjects; n = number of subjects with observation
[a] no evidence of culture positivity prior to first intake or no results during the first 8 weeks after first intake
[b] not confirmed based on subject's medical history (based on previous DST) or central DST results
[c] Of the 19 subjects who were excluded from the mITT population because they were infected with DS-TB or XDR-TB (or for whom the MDR-TB status could not be confirmed), 7 subjects were infected with an XDR *M. tuberculosis* strain, 8 with a DS *M. tuberculosis* strain, and 4 had an unknown extent of resistance of *M. tuberculosis* strain.
[d] Four subjects in the TMC207 group and 5 subjects in the placebo group for whom no MGIT results were available at baseline were included in the mITT population based on positive MGIT results during the first week of intake

Pharmacokinetics

This report contains the washout data of TMC207 and M2 of follow-up pharmacokinetic assessments collected at Weeks 28, 32, 36, 48, 60, 72, 84, 96, and 120.

Pharmacokinetics of TMC207 (mean ± SD, t_{last}: median [range])	**400 mg TMC207 q.d.** **(Week 1 and 2) + 200 mg TMC207 t.i.w. (Week 3-24)**
Follow-up beyond Week 24	
n	51[b]
C_{last}, ng/mL	72.02 ± 88.97
t_{last}, months	22.40 (13.93-23.40)
CL/F, L/h[a]	8.058 ± 3.510
V_d/F, L	55702 ± 42281
λ_z, 1/h	0.0001788 ± 0.00009616
$t_{1/2term}$, h	5340 ± 3329
$t_{1/2term}$, days	214.9 ± 131.2
$t_{1/2term}$, months	7.163 ± 4.374

[a] Determined during previous analysis based on data up to Week 24, 48 hours post dose
[b] n=45 for C_{last} and t_{last}, n=17 for CL/F and n=15 for V_d/F

Pharmacokinetics of M2 (mean ± SD, $_{tlast}$: median [range])	**400 mg TMC207 q.d. (Week 1 and 2) + 200 mg TMC207 t.i.w. (Week 3-24)**
Follow-up beyond Week 24	
n	52[a]
C_{last}, ng/mL	19.04 ± 23.11
t_{last}, months	22.37 (8.43-23.40)
λ_z, 1/h	0.0001915 ± 0.0001037
$t_{1/2term}$, h	4984 ± 3174
$t_{1/2term}$, days	207.7 ± 132.2
$t_{1/2term}$, months	6.923 ± 4.407

[a] n=46 for C_{last} and t_{last}

Efficacy

MGIT Response Rates - mITT	**TMC207/BR N = 66**		**Placebo/BR N = 66**		**TMC207/BR vs Placebo/BR**		
	N	**n (%)**	**N**	**n (%)**	**Difference (SE)**	**95% CI**	**p-Value[a]**
Week 24							
Responder (missing = failure)[b]	66	52 (78.8)	66	38 (57.6)	21.2 (7.90)	5.59, 36.83	0.008
Responder (no overruling)[c]	66	53 (80.3)	66	43 (65.2)	15.2 (7.64)	0.04, 30.26	0.049
Endpoint							
Responder (missing = failure)[b]	66	41 (62.1)	66	29 (43.9)	18.2 (8.54)	1.28, 35.08	0.035
Responder (no overruling)[c]	66	52 (78.8)	66	41 (62.1)	16.7 (7.81)	1.22, 32.11	0.035

[a] Logistic regression model
[b] Sputum culture conversion (defined as 2 consecutive negative cultures from sputa collected at least 25 days apart; all intermediate cultures have to be negative as well) had occurred, was not followed by a confirmed positive MGIT result, and the subject did not discontinue during the time frame of interest.
[c] Sputum culture conversion had occurred and was not followed by a confirmed positive MGIT result.
N = number of subjects; n = number of subjects with observation

Response Rates at Endpoint vs Response Rates at Week 24 - Missing = Failure - mITT n (%)	**TMC207/BR**		**Placebo/BR**	
	Week 24		**Week 24**	
	Non-Responder N = 14	**Responder N = 52**	**Non-Responder N = 28**	**Responder N = 38**
Endpoint				
Non-Responder	**14 (100.0)**	**11 (21.2)**	**24 (85.7)**	**13 (34.2)**
Death - death after being converted	2 (14.3)	2 (3.8)	0	0
Death - failure to convert	0	0	1 (3.6)	0
Death - relapse	1 (7.1)	1 (1.9)	0	0
Discontinued after being converted	2 (14.3)	5 (9.6)	7 (25.0)	5 (13.2)
Failure to convert	8 (57.1)	0	14 (50.0)	0
Relapse	1 (7.1)	3 (5.8)	2 (7.1)	8 (21.1)
Responder	**0**	**41 (78.8)**	**4 (14.3)**	**25 (65.8)**

N = number of subjects; n = number of subjects with observation

Response Rates at Endpoint vs Response Rates at Week 24 - Sensitivity Analysis - No Overruling - mITT n (%)	**TMC207/BR**		**Placebo/BR**	
	Week 24		**Week 24**	
	Non-Responder N = 13	**Responder N = 53**	**Non-Responder N = 23**	**Responder N = 43**
Endpoint				
Non-Responder	10 (76.9)	4 (7.5)	17 (73.9)	8 (18.6)
Responder	3 (23.1)	49 (92.5)	6 (26.1)	35 (81.4)

N = number of subjects; n = number of subjects with observation

MGIT Response Rates by Subgroups - Missing = Failure - mITT	TMC207/BR		Placebo/BR	
	N	n (%)	N	n (%)
Cavitation (as Stratified)				
No cavitations or cavitations < 2 cm	12	8 (66.7)	10	6 (60.0)
Cavitations >= 2 cm in one lung only	42	26 (61.9)	41	19 (46.3)
Cavitations >= 2 cm in both lungs	12	7 (58.3)	15	4 (26.7)
Cavitation (X-Ray)				
No cavitations or cavitations < 2 cm	14	9 (64.3)	16	9 (56.3)
Cavitations >= 2 cm in one lung only	41	26 (63.4)	36	17 (47.2)
Cavitations >= 2 cm in both lungs	11	6 (54.5)	14	3 (21.4)
Pooled Center				
Asia	8	6 (75.0)	4	3 (75.0)
Eastern europe	6	3 (50.0)	7	4 (57.1)
South-Africa-All	37	20 (54.1)	42	15 (35.7)
South-Africa - 1	*14*	*7 (50.0)*	*17*	*6 (35.3)*
South-Africa - 2	*13*	*8 (61.5)*	*13*	*7 (53.8)*
South-Africa - other	*10*	*5 (50.0)*	*12*	*2 (16.7)*
South-America	15	12 (80.0)	13	7 (53.8)
HIV Status at Baseline				
Negative	61	38 (62.3)	52	23 (44.2)
Positive	5	3 (60.0)	14	6 (42.9)
Extent of Resistance to *M. tuberculosis*				
$MDR_{H\&R}$-TB	39	27 (69.2)	46	20 (43.5)
pre-XDR-TB	15	9 (60.0)	12	5 (41.7)
Baseline PZA Susceptibility (MGIT960)				
Resistant	38	23 (60.5)	33	11 (33.3)
Susceptible	18	13 (72.2)	26	14 (53.8)
Baseline Injectables Susceptibility				
Resistant	9	6 (66.7)	8	4 (50.0)
Susceptible	45	30 (66.7)	50	21 (42.0)
Baseline Fluoroquinolone Susceptibility				
Resistant	6	3 (50.0)	4	1 (25.0)
Susceptible	48	33 (68.8)	54	24 (44.4)
Previous use of First Line Drugs				
No	6	5 (83.3)	8	5 (62.5)
Yes	60	36 (60.0)	58	24 (41.4)
Number of Potentially Active Drugs in BR at Baseline (AGAR)				
< 3 active drugs	13	6 (46.2)	11	5 (45.5)
>= 3 active drugs	40	30 (75.0)	44	19 (43.2)
Number of Potentially Active Drugs in BR at Baseline (AGAR, C208 interim)				
< 3 active drugs	13	6 (46.2)	11	5 (45.5)
>= 3 active drugs	41	30 (73.2)	46	20 (43.5)
Baseline BMI				
< 18	24	13 (54.2)	29	11 (37.9)
>=18-<20	10	7 (70.0)	13	5 (38.5)
>=20-<25	28	19 (67.9)	18	9 (50.0)
>=25	4	2 (50.0)	6	4 (66.7)
Baseline Albumin Grade				
Grade 0	38	26 (68.4)	24	13 (54.2)
Grade 1	11	7 (63.6)	14	7 (50.0)
Grade 2	14	7 (50.0)	27	9 (33.3)
Grade 3	3	1 (33.3)	1	0

N = number of subjects; n = number of subjects with observation

Clinical Correlates of Microbiological Outcome

Overall, there was a poor correlation between chest X-ray results and microbiologic outcome. The difference in microbiologic outcome between the TMC207 and placebo groups was not reflected in the analysis of chest X-ray results. Baseline chest X-ray composite scores were somewhat higher in non-responders (8.82 and 9.36 in the TMC207 and placebo group, respectively) compared to responders (7.63 and 7.67, respectively). The improvement in mean composite chest X-ray score observed at Week 24 in both responders and non-responders was maintained at endpoint, except that there was less mean improvement in non-responders in the TMC207 group at endpoint compared to Week 24. Note that the number of non-responders in the TMC207 group was smaller at Week 24 compared to endpoint (6 versus 14 subjects, respectively). At endpoint, mean decrease from baseline was 3.20 for responders (N = 52) and 1.39 for non-responders (N = 14) in the TMC207 group and 3.10 for responders (N = 41) and 1.95 for non-responders (N = 24) in the placebo group.

Overall, the proportion of subjects with stable weight, a weight increase or a weight decrease of >5% was similar between treatment groups. When % weight change was categorized by final microbiological status (no overruling, mITT population), a weight increase of > 5% was observed more frequently in responders than non-responders while a weight decrease of > 5% was observed more frequently in non-responders than responders in both treatment groups.

Drug Susceptibility

TMC207 MICs were determined using 2 methods: on solid medium (7H11 agar) and in liquid medium (7H9 broth) using the REMA method. For simplicity, only DST results for TMC207 MICs determined on solid medium (7H11 agar) are discussed in this report as the major conclusions were similar. At baseline, the isolates from 99 of 115 subjects were inhibited at a concentration of 0.06 µg/mL. The MIC_{50} and MIC_{90} were 0.06 µg/mL and 0.12 µg/mL, respectively. No clear trend towards a correlation between baseline TMC207 MIC values and response rate was noted. In the TMC207 group, isolates from 2 of 11 subjects with paired data had at least a 4-fold increase (both had a 4-fold increase) in TMC207 MIC at endpoint compared to baseline.

Resistance to at least 1 of the tested anti-TB drugs had emerged during the trial in isolates from 2 of 12 subjects with paired specimens in the TMC207 group and in isolates from 16 of 31 subjects with paired specimens in the placebo group (regardless of use in BR). Isolates from subjects in the TMC207 group acquired resistance to EMB and CAP in 1 subject and to SM in 1 other subject. In the placebo group, resistance was most frequently acquired to OFL and EMB and had emerged in isolates from 7 of 27 subjects and 6 of 15 subjects whose isolates were susceptible at baseline, respectively. Resistance to high concentration INH had emerged in isolates of 1 subject (CRF ID [redacted]). This subject did not use INH in the BR and had central DST results available at baseline (so isolate was resistant to [low concentration] INH at baseline). Of the 2 subjects in the TMC207 group and 16 subjects in the placebo group whose isolates developed resistance to at least 1 anti-TB drug during the trial, 1 and 9 subjects, respectively, were non-responders (no overruling, all available data selection). Of these non-responders whose isolates developed resistance to at least 1 anti-TB drug, isolates from 6 subjects in the placebo group acquired a pre-XDR or XDR resistance profile while none of the subjects in the TMC207 group had a change in resistance profile (i.e., 5 subjects in the placebo group with $MDR_{H\&R}$-TB at baseline acquired a pre-XDR-TB phenotype and 1 subject in the placebo group with pre-XDR-TB at baseline acquired an XDR-TB phenotype).

Evaluation of possible cross-resistance between TMC207 and other anti-TB drugs in both groups revealed no clear correlation between baseline resistance to anti-TB drugs and baseline TMC207 MIC values.

Safety

Safety (ITT Population)	TMC207/BR N = 79	Placebo/BR N = 81
Most frequent AEs (reported in > 10% of subjects in TMC207 group during Overall Treatment phase), n (%)		
Nausea	32 (40.5)	30 (37.0)
Arthralgia	29 (36.7)	22 (27.2)
Vomiting	23 (29.1)	22 (27.2)
Headache	23 (29.1)	18 (22.2)
Hyperuricemia	20 (25.3)	27 (33.3)
Hemoptysis	16 (20.3)	14 (17.3)
Insomnia	13 (16.5)	10 (12.3)
Pruritus	11 (13.9)	15 (18.5)
Dizziness	11 (13.9)	11 (13.6)
Nasopharyngitis	11 (13.9)	4 (4.9)
Abdominal pain upper	10 (12.7)	8 (9.9)
Chest pain	10 (12.7)	8 (9.9)
Deafness unilateral	10 (12.7)	7 (8.6)
Gastritis	9 (11.4)	16 (19.8)
Injection site pain	9 (11.4)	10 (12.3)
Back pain	9 (11.4)	8 (9.9)
Anorexia	9 (11.4)	6 (7.4)
Pyrexia	8 (10.1)	7 (8.6)
n (%) with at least 1 AE	78 (98.7)	79 (97.5)
n (%) with at least 1 TB-related AE	36 (45.6)	44 (54.3)
n (%) with at least 1 grade 3-4 AE	34 (43.0)	29 (35.8)
n (%) with at least 1 SAE	18 (22.8)	15 (18.5)
n (%) with at least 1 AE leading to permanent stop of TMC207/placebo	4 (5.1)	5 (6.2)
n (%) with at least 1 AE leading to permanent stop of BR	10 (12.7)	10 (12.3)

N = number of subjects; n = number of subjects with observation

Overall, 10 of 79 subjects in the TMC207 group and 2 of 81 subjects in the placebo group died during the trial or during long-term follow-up for survival, of subjects who prematurely discontinued from the trial.
In total, 7 subjects, i.e., 6 subjects (7.6%) in the TMC207 group and 1 subject (1.2%) in the placebo group died during the trial. Four of these 7 subjects (3 in the TMC207 group and 1 in the placebo group) died due to an SAE starting during the Overall Treatment phase. SAEs leading to death that started during the Overall Treatment Phase were tuberculosis (2 subjects) and alcohol poisoning (1 subject) in the TMC207 group; hemoptysis was the cause of death in the subject in the placebo group. Of note, the subject who died of alcohol poisoning is the only subject who died during TMC207 intake. The investigator considered the SAEs leading to death not related to TMC207 intake in the 3 subjects in the TMC207 group and doubtfully related to TMC207/placebo in the subject of the placebo group. Three subjects (TMC207 group) died due to SAEs that started during follow-up; causes of death were cerebrovascular accident (in 1 subject), peritonitis and septic shock (in 1 subject), and hepatitis and hepatic cirrhosis (in 1 subject). These events were considered not related to TMC207 by the investigator.
For all 40 subjects who were eligible for long-term follow-up for survival after premature discontinuation (i.e., 17 subjects in the TMC207 group and 23 subjects in the placebo group), long-term survival data were collected. Four subjects in the TMC207 group and 1 subject in the placebo group died after they discontinued the trial. Of these subjects, 2 subjects in the TMC207 group and the subject in the placebo group discontinued the trial due to non-compliance, were non-responders at study endpoint and died due to TB-related illnesses. One subject in the TMC207 group discontinued because [redacted] was infected with an XDR-TB strain at baseline, was a non-responder at endpoint and died due to a TB-related illness. The remaining subject in the TMC207 group discontinued due to an AE (increased transaminases), was a non-responder at endpoint and died due to a motor vehicle accident. No QTcF abnormalities of ≥ 500 ms were observed at any timepoint during the trial in any of the subjects who died. In general, the causes of death reported for the majority of the subjects are similar to the causes of death reported from a study from 1963 that utilized autopsies from 295 patients treated for pulmonary TB to ascertain probable causes of death in TB in the pre-and post antibiotic era in the US.

Safety, Cont'd

Serious adverse events reported for more than 1 subject in either group during the Overall Treatment phase were tuberculosis, hemoptysis, pulmonary tuberculosis, pneumonia, and surgery. Seven subjects (10.8%) in the TMC207 group and 1 subject (2.3%) in the placebo group experienced one or more SAEs during treatment-free follow-up. Each of these events were reported in at most 1 subject per treatment group.

One or more AEs led to discontinuation of TMC207/placebo in 4 subjects (5.1%) and to discontinuation of placebo in 5 subjects (6.2%). The final analysis showed 1 additional subject (TMC207 group) with an AE leading to permanent discontinuation of BR after the cut-off date of the interim analysis. Hence, AEs leading to permanent discontinuation of any BR drug were recorded in 10 subjects (12.7%) in the TMC207 group and 10 subjects (12.3%) in the placebo group.

During the Overall Treatment phase, 98.7% of subjects in the TMC207 group and 97.5% of subjects in the placebo group experienced at least one AE. The most frequently reported AEs in the TMC207 group with a higher incidence (> 5 % difference) in the TMC207 group compared to the placebo group were arthralgia (at most grade 3), headache (at most grade 3), and nasopharyngitis (at most grade 2). During treatment free-follow-up, 1 or more grade 3 or 4 AEs were reported in 9.2% of subjects in the TMC207 group and 2.3% of subjects in the placebo group.

Adverse events of interest were identified using standardized MedDRA Queries (SMQs). Adverse events identified by the selected sub-SMQs from drug-related hepatic disorders occurred in 15.2% of subjects in the TMC207 group and 6.2% of subjects in the placebo group during the Overall Treatment phase. None of these events were reported as an SAE and 3 events of transaminases increased in the TMC207 group led to permanent discontinuation of TMC207. For 2 of these subjects, the AE hepatitis B was concurrently reported. Adverse events identified by the SMQs for acute pancreatitis, severe cutaneous AEs and Torsades de Pointes/QT prolongation were reported for at most 5.1% of subjects in the TMC207 group and 4.9% of subjects in the placebo group. Of note, no AEs with a preferred term of Torsade de Pointes were reported. No subjects experienced a rhabdomyolysis/myopathy SMQ event during the trial. None of these events were reported as SAE or led to permanent discontinuation of the investigational medication, except for 3 events of pancreatitis in 1 subject that were reported as grade 3 SAEs and an event of blood amylase increased and lipase increased which were both reported as grade 3 AE that led to permanent discontinuation of placebo.

Clinical Laboratory Tests	The observations made with regard to laboratory abnormalities during the Overall Treatment phase in the final analysis were similar to the observations made in the interim analysis. Mean values for creatine kinase, creatine kinase-MB, creatinine, uric acid, albumin, hemoglobin, lymphocytes (%), and total bilirubin slightly increased and mean values for gastrin, platelet count, WBC count, neutrophils (%) and total neutrophil count decreased over time for both treatment groups during the 24-week investigational treatment period. For pepsinogen I and II, no treatment-related differences were noted. Mean troponin I and trypsin-like factor did not change over time. Mean and median AST values increased over time during the 24-week investigational treatment period and remained elevated after Week 24 in both treatment groups. Treatment-emergent graded laboratory toxicities of grade 3 or 4 observed in more than 5.0% of subjects during the Overall Treatment phase and more frequently (> 5% difference) observed in the TMC207 group compared to the placebo group were WBC increased, AST increased, GGT increased, and ALT increased. Of the 9 subjects in the TMC207 group and 4 subjects in the placebo group with grade 3 or 4 AST increased during the Overall Treatment phase, the grade 3 or 4 abnormalities in AST levels were associated with grade 3 or 4 increased ALT levels in 5 subjects in the TMC207 group and in 2 subjects in the placebo group, grade 3 or 4 increased GGT levels in 6 subjects in the TMC207 group and in 1 subject in the placebo group, and grade 2 increased total bilirubin in 2 subjects in the TMC207 group. One subject (TMC207 group) met the laboratory criteria for Hy's Law. Medical assessment suggests the hepatic toxicity in this subject was more likely caused by the background TB regimen and alcohol abuse than by TMC207.

Clinical Laboratory Tests, Cont'd	The most frequently observed treatment-emergent graded laboratory abnormalities during the Overall Treatment phase with a higher incidence (> 5% difference) in the TMC207 group compared to the placebo group were AST increased, ALT increased, pancreatic amylase increased, ALP increased, GGT increased, and hypernatremia. The most frequently observed treatment-emergent nongraded laboratory abnormalities during the Overall Treatment phase with a higher incidence (> 5% difference) in the TMC207 group compared to the placebo group were LDH above normal, basophils (%) above normal and monocytes (%) below normal. Of note, the most frequent nongraded lab abnormality during the Overall Treatment phase in the interim analysis (i.e., creatine kinase above normal observed in 71.8% and 64.2% of subjects in the TMC207 and placebo group, respectively) was also analyzed as a graded abnormality according to the DMID Toxicity Grading List (with incidence of 14.1% and 17.3%, respectively [any grade]). The worst toxicity grade in creatine kinase was grade 4 and was observed in 1 subject in each treatment group during the Overall Treatment phase.
Cardiovascular Safety	Mean absolute values in QTcF increased during the 24-week investigational treatment period in the TMC207 group with mean increases from reference noted at Week 1 and of more than 10 ms from Week 5 onwards up to Week 24. After this time point, mean absolute values in QTcF generally decreased. In the placebo group, mean changes from reference were generally minor, except for the Week 24, 5 hours postdose assessment (15.6 ms). In both treatment groups, mean changes from reference for QTcF at the 5-hour assessment time points were comparable to those at predose time points, except for Week 24, 5 hours postdose assessment in the placebo group. This suggests there is no direct relationship between C_{max} and QTcF prolongation but does not exclude a delayed effect. There were no additional subjects with abnormalities in ECG during the Overall Treatment phase in the final analysis compared to the interim analysis. Only 1 subject in the TMC207 group had an absolute QTcF value of more than 500 ms, and 10 subjects (13.0%) in the TMC207 group and in 2 subjects (2.5%) in the placebo group had an increase from reference in QTcF of more than 60 ms during the Overall Treatment phase. For 4 of the subjects in the TMC207 group and both subjects in the placebo group, this increase in QTcF of more than 60 ms corresponded to an abnormal value (i.e., above 450 ms). Mean supine pulse rate slightly decreased during the first 24 weeks, while supine SBP increased over time with the largest increases observed at the end of the Overall Treatment phase in both treatment groups. In the final analysis, grade 3 increased supine DBP was observed in 4 subjects (5.1%) in the TMC207 group during the Overall Treatment phase. Grade 3 increased supine SBP was observed in 2 subjects (2.5%) in the placebo group during the Overall Treatment phase. Compared to the interim analysis, one additional subject (TMC207 group) was reported with grade 3 increased supine DBP during the Overall Treatment phase in the final analysis.
Physical Examination	The number of subjects with post-baseline abnormal physical examination findings was comparable to that at baseline or decreased over time for all body system categories. A marked decrease was observed for the incidence of abnormalities related to the respiratory system.
Lung Resection	A lung resection was performed in 4 subjects (5.1%) in the TMC207 group and 7 subjects (8.6%) in the placebo group. The date of surgery was after the 24-week treatment period for all subjects, except for one subject in the TMC207 group (CRF [redacted] relapser) who underwent a pneumonectomy of the right lung on Day 126 (no culture was performed on the tissue and the surgery did not affect the TB treatment regimen).

Conclusions

The efficacy observed in the interim analysis was confirmed in the final analysis. No new safety signals were identified between the cut-off date of the interim analysis and the final analysis, apart from the imbalance in mortality.

The higher responder rates (missing = failure) observed after treatment with TMC207 in combination with a preferred BR compared to placebo in combination with a preferred BR at Week 24 (78.8% vs. 57.6%, respectively; P = 0.008) are also seen at study endpoint (62.1% vs. 43.9%, respectively; p = 0.035). Emergence of 4-fold increase in TMC207 MIC was infrequent and of unclear clinical significance. Overall, there was a poor correlation between all clinical correlates and microbiologic outcome. Fewer resistance results were available in subjects in the TMC207 group compared to the placebo group because TMC207-treated subjects achieved culture conversion more frequently and therefore submitted a larger proportion of sputum samples that did not grow in a culture for resistance testing. Emergence of resistance to other TB drugs was more frequent in the placebo group and several subjects in this group developed a pre-XDR-TB or XDR-TB resistance profile. Despite the low number of observations, it is noteworthy that TMC207 may protect against the acquisition of additional resistance to second line anti-TB drugs leading to XDR-TB in subjects with MDR-TB.

Overall safety of TMC207 in combination with a preferred MDR-TB treatment regimen was consistent with observations from the interim analysis. The selected TMC207 dosing regimen for 24 weeks was well tolerated as part of a multidrug MDR-TB therapy, although an imbalance in the number of deaths was identified between the TMC207 group and the placebo group (10/79 subjects [12.7%] versus 2/81 subjects [2.5%], respectively) despite better microbiologic outcomes in the TMC207 group. The reason for the increased overall mortality in the TMC207 group compared to the placebo group in this trial is as yet unclear. In a study from 1963 that analyzed autopsy findings over an 11-year period from 295 patients treated in the pre- and post-antibiotic era for pulmonary TB, causes of death included progressive TB and, increasingly, conditions related to TB but not necessarily to active disease. In general, the causes of death reported for the majority of the subjects are similar to the causes of death reported from the pre-antibiotic era. The causes of death in this study were varied (only death due to TB was reported more than once), and there was a wide range in time of death after last dose of TMC207/placebo (range: 2-911 days) with only 1 occurring during treatment with TMC207. In addition, all deaths in the TMC207 arm were considered not related to study drug by the investigator and none had treatment-emergent QTcF values of more than 500 ms. Mean absolute values in QTcF increased during the 24-week investigational treatment period in the TMC207 group with mean increases from reference noted at Week 1 and of more than 10 ms from Week 5 up to Week 24. After this time point, mean absolute values in QTcF generally decreased.

Based on the plasma concentrations obtained at the Week 28 to Week 120 study visits mean $t_{1/2term}$ values of 214.9 days (7.2 months) and 207.7 days (6.9 months) were obtained for TM207 and M2 respectively. Individual $t_{1/2term}$ values ranged between 2.3 and 22.5 months and between 2.0 and 20.8 months respectively. TMC207 plasma concentrations at the last visit (Week 120 visit; 96 weeks after the last dose) were still quantifiable in all but 2 of the 46 subjects for whom a plasma sample was available.