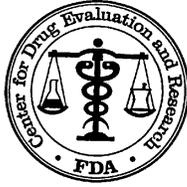


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204384Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 204384 (SN0013/SND14,10/26/2012; SN0021/SDN21, 12/7/2012)  
**Supplement #:**  
**Drug Name:** Bedaquiline (TMC 207); 400 mg daily for 2 weeks, followed by 200 mg three times a week for (b)(4). Tablet: 100 mg  
**Indication(s):** Multi-Drug Resistant Pulmonary Tuberculosis  
**Applicant:** Janssen Research & Development  
**Date(s):** 6/29/2012. PDUFA due date: 12/29/2012  
**Review Priority:** Priority

**Biometrics Division:** DBIV  
**Statistical Reviewer:** Xianbin Li  
**Concurring Reviewers:** Karen Higgins

**Medical Division:** Division of Anti-Infective Products (DAIP)  
**Clinical Team:** Ariel Porcalla  
**Project Manager:** Fariba Izadi

This amendment includes 1) FDA’s additional analysis results used in the label or communicated with the sponsor from Study C208 Stage 2, the pivotal study to seek an accelerated approval for this NDA, and Study C209; 2) errata in the statistical review.

## 1. Mortality in Study C208 Stage 2

The submission SN0013/SDN0014 contains the Four Month Safety Update (4MSU) to NDA 204-384 and an “Overview of Deaths in the TMC207 Phase II Trials”. According to the 4MSU, there were 10 deaths and 2 deaths in the TMC207 group and placebo group. According to SN0021, after the cut-off dates for the 4MSU, 2 additional deaths (IDs: 4154 and 4453) were reported, both from the placebo group. There have been no additional reports of deaths in the TMC207 group.

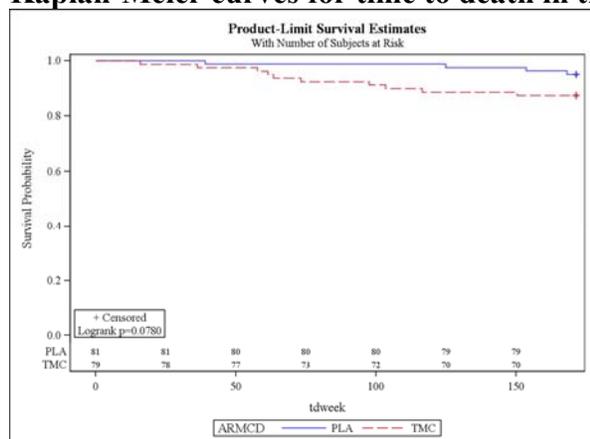
The following table lists the disposition type, time of conversion, relapse, discontinuation, and death in days, and reported cause of death for the 14 deaths in Study C208 Stage 2:

### Disposition type, time of conversion, relapse, discontinuation, and death in days, and reported cause of death for 14 deaths in Study C208 Stage 2

ID	Group	Disposition Type	Conversion	Relapse	Discontinuation	Death	Cause of death
4041	TMC	Discontinued	56		98	(b) (6)	Alcoholic poisoning
4120	PLA	Discontinued			252		Hemoptysis
4127	TMC	Discontinued			61		TB related
4145	TMC	Discontinued	84	224	308		TB related
4153	TMC	Discontinued	154	261	504		TB
4154	PLA	Ongoing					MDR-TB
4155	PLA	Discontinued			434		TB related
4224	TMC	Discontinued	196	252	420		TB
4378	TMC	Discontinued	54	98	155		MVA
4399	TMC	Ongoing	196				CVA/hypertension
4453	PLA	Discontinued			128		Pneumothorax/empyema
4464	TMC	Discontinued			99		TB related
5067	TMC	Ongoing	98				Septic shock/peritonitis
5069	TMC	Discontinued	42		228		Hepatitis/hepatic cirrhosis

Note that three deaths occurred well after 120 weeks (840 days) post randomization. Individual patient involvement in Study C208 was to end at this time point. The following Kaplan-Meier curves censors all subjects at 1200 days or approximately 171 weeks (at a time point past the last death) to best show the survival proportions in the ITT population. Note however, not all subjects were followed out to 1200 days, though the figure assumes that all deaths out to day 1200 were captured.

## Kaplan-Meier curves for time to death in the ITT population in Study C208 Stage 2



Based on the study report and data for Study c208 Stage 2, the mean time for the final Week 120 visit for the 43 subjects who completed the study was 843 days (standard deviation 6.8 days) with a range of 834 to 875 days. There were 2 deaths in the placebo group and 1 death in the TMC207 that occurred after well after the latest time of the week 120 visit day of 875. An analysis excluding these 3 deaths yields a mortality rate for bedaquiline of 9/79 (11.4%) and for placebo of 2/81 (2.5%) for a difference of 8.9% (exact 95% CI [1.1%, 18.2%]), Fisher's exact p-value 0.031). Alternatively, the relative risk is 4.61 with an exact 95% CI [1.13, 54.2]. This analysis also shows that there was an increased risk in mortality in the TMC207 group. We believe this analysis is the most appropriate analysis to report in the label.

## 2. Culture Conversion Proportions at Weeks 24 and 74 in Study C208 Stage 2

In the statistical review we only reported FDA's additional analysis at Week 24. There was no further analysis for reasons of failure. We did not conduct a similar analysis for Week 72. Since these results were included in the label, we report here.

Subject 4135 was excluded in the sponsor's analysis due to lack of post-baseline sputum culture results. In this analysis, the subject was included in the TMC207 group and considered as a treatment failure. The following table shows the culture conversion proportions and differences at Weeks 24 and 72. There was a statistically significant difference in culture conversion proportions at Week 24, but the difference was no longer statistically significant at Week 72.

### Culture conversion Status at Week 24 and Week 72 in the mITT population in Study C208 Stage 2

Microbiologic Status	TMC207 N=67	Placebo N=66	Difference [95% CI] p-value
Treatment success	52 (77.6%)	38 (57.6%)	20.0% [4.5%, 35.6%] 0.014
Treatment failure	15 (22.4%)	28 (42.4%)	
Lack of conversion	5 (7.5%)	16 (24.2%)	
Discontinuation	10 (14.9%)*	12 (18.2%)	

<b>Microbiologic Status</b>	<b>TMC207 N=67</b>	<b>Placebo N=66</b>	<b>Difference [95% CI] p-value</b>
<b>Week 72</b>			
Treatment success	47 (70.1%)	37 (56.1%)	14.1% [-2.1%, 30.3%] 0.092
Treatment failure	20 (29.9%)	29 (43.9%)	
Lack of conversion	3 (4.5%)	7 (10.6%)	
Discontinuation	17 (25.4%)*	22 (33.3%)	

Patients who discontinued considered as non-responders

\*Including one subject discontinued without post-baseline culture results

### **3. Culture Conversion Proportion in the TMC207 Group by Baseline Minimal Inhibitory Concentration (MIC) in Study C208 Stage 2 and Study C209**

The following table shows the culture conversion proportions at week 24 defined based on the primary endpoint by baseline MIC for the ITT population in Study C208 Stage 2 and all subjects in Study C209 combined. On December 19, 2012, the table was communicated with the sponsor. The results were slightly different from sponsor's analyses because in sponsor's analyses, week 24 conversion was based on Sensitivity 2 (no overruling) and the analysis populations were mITT populations.

#### **Culture conversion at Week 24 by baseline MIC (Agar proportion method) for TMC207 group in Study C208 Stage 2 in the ITT population and all subjects in Study C209**

<b>µg/ml</b>	<b>n/N (%)</b>
0.0075	2/2 (100)
0.015	14/24 (58)
0.03	51/64 (80)
0.06	90/127 (71)
0.12	36/48 (75)
0.24	0/1 (0)
0.48	5/6 (83)
>0.48	0/1 (0)
Total	198/273

#### **Culture conversion at Week 24 by baseline MIC (REMA method) for TMC207 group in Study C208 Stage 2 in the ITT population and all subjects in Study C209**

<b>µg/ml</b>	<b>n/N (%)</b>
0.0039	4/6 (67)
0.0078	19/25 (76)
0.0156	38/46 (83)
0.0313	82/108 (76)
0.0625	50/73 (68)
0.125	3/5 (60)
0.25	4/5 (80)
0.5	0/1 (0)
Total	200/269

#### **4. Errata in the Statistical Review for this NDA**

In Table 10: Culture conversion rates in the mITT population, Study C208 Stage 1, the difference at Week 24 should be 15.7% rather than 14.8% and the Fisher's exact p-value should be 0.32, not 0.29.

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/s/  
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XIANBIN LI  
12/21/2012

KAREN M HIGGINS  
12/21/2012



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 204384, 0000 (6/29/2012), 0005 (8/14/2012), 0010 (9/27/2012), 0013 (SND 14; 10/26/2012)

**Supplement #:**

**Drug Name:** Bedaquiline (TMC 207); 400 mg daily for 2 weeks, followed by 200 mg three times a week for (b)(4). Tablet: 100 mg

**Indication(s):** Multi-Drug Resistant Pulmonary Tuberculosis

**Applicant:** Janssen Research & Development

**Date(s):** 6/29/2012. PDUFA due date: 12/29/2012

**Review Priority:** Priority

**Biometrics Division:** DBIV

**Statistical Reviewer:** Xianbin Li

**Concurring Reviewers:** Karen Higgins

**Medical Division:** Division of Anti-Infective Products (DAIP)

**Clinical Team:** Ariel Porcalla

**Project Manager:** Fariba Izadi

**Keywords:** Clinical studies, Double-blind, Cox regression, Kaplan-Meier product limit

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## 1 EXECUTIVE SUMMARY

This NDA was submitted to seek an accelerated approval for TMC207 for the treatment of newly diagnosed sputum smear-positive pulmonary multi-drug resistant tuberculosis (MDR-TB) infection with resistance to at least both rifampin and isoniazid in adult patients. TMC207 is given for 24 weeks on top of an optimized background regimen given for 72 to 96 weeks. A traditional approval will be based on results from a Phase III confirmatory study to be completed. In this NDA, clinical efficacy data from two phase II trials were submitted and reviewed. Study C208 is a Phase II, multicenter, stratified, double-blind, randomized, placebo-controlled trial with two consecutive but completely separate stages. The first stage is exploratory and the second stage is a proof-of-efficacy stage (pivotal study) to demonstrate the superiority of TMC207 over placebo in time to culture conversion. C209 is a single-arm, open-label study to provide additional efficacy and safety data.

In C208 Stage 2, the primary analysis was conducted when all subjects completed week 24 or had discontinued earlier. The primary endpoint was time to culture conversion during the 24-week TMC207/placebo treatment. Discontinued subjects, including deaths, were censored at the last culture visit. One hundred sixty subjects were randomized and treated, 67 and 66 subjects were included in the TMC207 and placebo groups in the mITT population in FDA's analysis. A Cox proportional hazards regression model demonstrated that there was a statistically significant treatment effect measured by relative risk between the two treatment groups (relative risk 2.15, with a 95% confidence interval (CI): [1.39, 3.31], and p-value: 0.0005). A secondary endpoint, culture conversion at Week 24 also demonstrated a statistically significant treatment effect (78% (52/67) versus 58% (38/66), with a difference of 20% (95% CI: [4.5%, 35.6%]) and p-value: 0.014). In this analysis all discontinuations including deaths were considered as having not converted. Sensitivity analyses using different methods for handling missing culture results for evaluation of the primary endpoints produced similar results. Additional analyses using data when all subjects completed at least 72 weeks or discontinued earlier showed a statistically significant but apparently diminishing treatment effect (relative risk 1.65, 95% CI: [1.05, 2.59] and p-value: 0.029).

Based on a 4-month safety update report submitted in October, 2012, in the ITT population there were 10 and 2 deaths during the trial or after discontinuation from the trial in the TMC207 and placebo groups, respectively. The difference of 10.2% (an exact 95% confidence interval [2.1%, 19.7%]) in mortality between the two groups (10/79 versus 2/81) was statistically significant with a p-value of 0.0167.

The final analysis of Stage 2 will be conducted when all subjects complete 120 weeks of study. Though the study is now complete, this information has not yet been submitted to the NDA.

The efficacy results from C208 Stage 1 and C209 were supportive. In C208 Stage 1, the treatment effect from the primary analysis in the mITT population with 21 and 23 subjects in the TMC207 and placebo groups was statistically significant (relative risk 11.77 [95% CI: 2.26 – 61.23], p-value: 0.0034). At week 8, 24, and at the final analysis, the differences in culture

conversion were 38.9% (95% CI: [12.3%, 63.1%] and p-value: 0.004), 14.8% (95% CI: [-11.9%, 41.9%] and p-value: 0.29), and 4.6% (95% CI: [-25.5%, 34.1%], p-value: 0.76], respectively. There were 2 deaths in each group.

In C209 in the mITT population, 80% (163/205) of subjects achieved culture conversion at the end of Week 24 (95% CI: [73%, 85%]). There were 16 deaths (6.9%, 16/233) based on incomplete follow-up data from this ongoing trial.

The efficacy of TMC207 was supported by these efficacy studies for an accelerated approval. However, the statistically significant difference in mortality in the pivotal study was concerning. A regulatory decision should be made based on overall risk-benefit analysis from a clinical perspective and the elevated morality risk in the TMC207 group should be appropriately conveyed in the labeling.

## 2 INTRODUCTION

The applicant submitted a New Drug Application (NDA) to support the use of TMC207 in the treatment of multidrug-resistant tuberculosis (MDR-TB) in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB. MDR-TB is resistant to both isoniazid and rifampin, two first-line anti-TB drugs.

The supporting data are from two Phase II trials: C208 is double-blind, randomized, placebo-controlled superiority trial, conducted in 2 consecutive but completely separate stages: an exploratory stage (Stage 1) and a proof-of-efficacy stage (Stage 2); C209 is an open-label, single-arm ongoing trial.

This NDA seeks an accelerated approval based on an early efficacy endpoint: time to sputum culture conversion up to week 24. Traditional approval will be based on the results of a Phase 3 randomized placebo-controlled clinical trial.

### 2.1 Overview

TMC207, a diarylquinoline, has a novel mechanism of action for TB drugs (specific inhibition of mycobacterial adenosine triphosphate [ATP] synthase) and introduces a new class of anti-TB drugs. The intended indication is multidrug-resistant TB (MDR-TB), which is defined as being resistant to at least the 2 first-line anti-TB drugs isoniazid (INH) and rifampin (RMP).

The studies selected for full statistics review and evaluation are Studies C208 and C209. The first study has two consecutive but completed separate stages. The first stage is exploratory and completed. The stage 2 was still ongoing at the time of NDA submission. The primary objective of this study is to demonstrate superiority in antibacterial activity of TMC207 compared to placebo when added to a background regimen (BR) for 24 weeks with the time to sputum culture conversion during treatment as the primary endpoint. The second trial is an ongoing open-label, single-arm study to evaluate the efficacy and safety of TMC207. FDA reviewed the protocols for the two studies and agreed with the design and planned analyses of the studies stated in the IND submissions.

**Table 1: List of all studies included in analysis**

	<b>Phase and Design</b>	<b>Treatment Period</b>	<b>Follow-up Period</b>	<b># of Subjects per Arm</b>	<b>Study Population</b>
C208 Stage 1	Phase 2, double-blind randomized, placebo controlled. Six investigators in South Africa.	8 weeks	96 weeks	TMC207: 23 Placebo: 24	Newly diagnosed MDR-TB

	<b>Phase and Design</b>	<b>Treatment Period</b>	<b>Follow-up Period</b>	<b># of Subjects per Arm</b>	<b>Study Population</b>
C208 Stage 2	Phase 2, multicenter, double-blind, randomized, placebo controlled.	24 weeks	96 weeks	TMC207: 79 Placebo: 81	Newly diagnosed MDR-TB
C209	Phase 2, multicenter, single-arm open-label	24 weeks	96 weeks	TMC207: 233	MDR- & extensively drug-resistant (XDR)-TB

The submission contains primary analysis and final analysis results for Stage 1 and primary analysis and updated additional analysis (called “interim analysis” by the sponsor) results for Week 24 and 72 for Stage 2, because there is a final analysis to be completed. Study C209 is an ongoing study with interim analyses of Week 24 data submitted.

## 2.2 Data Sources

Data sources, including all material reviewed, e.g. applicant study reports, data sets analyzed, and literature referenced, are located at <\\CDSESUB1\EVSPROD\NDA204384>. SDTM data formats were used and there is no software code submitted.

The quality and integrity of the data will be discussed in Section 3.1.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

In general the submitted data sets were of high quality. However, the primary endpoint, time to culture conversion during TMC207 or placebo treatment period, for Stage 2 was not submitted in the initial submission and the final culture conversion variable for Study C208 Stage 1 was not submitted. Information on temperature in one data set used different units (Celsius centigrade and Fahrenheit). Therefore, caution was needed when using these submitted data sets.

The randomization was stratified by study site and lung cavitation. The study sites were pooled into regions. An examination of randomization by region (not by study site) and cavitation versus calendar time in Study C208 Stage 2 indicated that the randomization scheme worked.

The Final Statistical Analysis Plan for Study C208 was submitted with the NDA submission. Important relevant decisions such as pooling of study site and analysis populations were made prior to unblinding. Blinding and unblinding procedure were clearly documented in the protocol.

Data quality control/assurance was discussed in the Study Report Section 3.11. The sponsor ensured that quality control procedures were included in the different clinical processes.

## **3.2 Evaluation of Efficacy**

### **3.2.1 Study Design and Endpoints**

#### **3.2.1.1 Study C208**

Study C208 is a stratified, multicenter, randomized, double-blind, placebo-controlled Phase II trial in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection, with two consecutive but completely separate stages.

Stage 1 of Study C208, an exploratory stage, is to evaluate the efficacy and safety of 8-week TMC207 on top of a background regimen (72 – 96 weeks, or approximately 18 – 24 months).

Stage 2 of Study C208, a proof-of-efficacy stage, is to evaluate efficacy, safety, and tolerability of 24-week treatment of TMC207 on top of a background regimen (72 – 96 weeks, or approximately 18 – 24 months) to demonstrate the superiority of TMC207 over placebo in time to culture conversion.

The two stages have similar designs, with the major difference being the length of the investigational treatment phase (8 weeks versus 24 weeks).

### **Main Inclusion/Exclusion Criteria**

The main inclusion criteria were male or female subjects, aged 18 to 65 years, with newly diagnosed sputum smear-positive pulmonary MDR-TB infection with confirmed resistance to at least both RMP and INH by previous screening from a TB treatment facility. 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, EMB, PZA, or SM).

The main exclusion criteria included:

1. Previously having been treated for MDR-TB. These subjects were defined as those having received any second-line TB drug.
2. HIV-infected subjects, a) having a CD4+ count < 300 cells/μL or b) having received antiretroviral therapy and/or oral or intravenous antifungal medication within the last 90 days, or c) possibly needing to start ART during the investigational treatment period.
3. Subjects with complicated or severe extra-pulmonary manifestations of TB or neurological manifestations of TB.

### **Randomization**

Eligible patients with newly diagnosed sputum smear-positive pulmonary MDR-TB infection were randomized in a 1:1 ratio to receive TMC207 or placebo in addition to a BR of MDR-TB

therapy. Randomization was stratified by trial site and the extent of lung cavitation (i.e. no cavity [or cavitations of <2 cm], cavitation in one lung, or cavitation in both lungs, with cavitation defined as the presence of at least one cavity  $\geq 2$ cm), as determined by chest X-ray at screening. Randomization was performed using a central randomization system (the interactive voice response system). A minimization technique was used to ensure balance across the treatment groups in each stratum.

## **Blinding**

During treatment with TMC207 or placebo, neither the investigator, nor the sponsor or subject knew the subject's randomized treatment group. The code was only to be broken in case of an emergency where the further treatment of a subject was dependent on the received treatment (TMC207 or placebo). If the code was broken by the investigator or by a member of his/her staff, the subject had to be withdrawn from the trial and had to be followed as appropriate. If the sponsor broke the code for safety reporting purposes, the subject could remain in the trial.

For the primary efficacy analysis, once all subjects had completed treatment with TMC207 or placebo (or had discontinued earlier), the treatment code was broken by the sponsor, however, the individual subject treatment information was not revealed to the investigators and subjects, to allow objective collection of safety information during the follow-up period.

## **Doses**

TMC207 was dosed as 400 mg once daily for the first 2 weeks, followed by 200 mg, 3 times/week given at least one day apart, for the following 6 weeks for Stage 1 and 22 weeks for Stage 2. Treatment throughout Stage 2 and throughout the follow-up period was administered by directly observed treatment (DOT).

## **Addition of a Rollover Arm in Stage 2**

Based on the efficacy observed in the TMC207 arm in the interim analysis results of Stage 1 and a safety profile after 8 weeks of study drug administration, a rollover arm was added to Stage 2 in Protocol Amendment IV. The objective was to give subjects who were not adequately responding to their MDR-TB treatment (including subjects diagnosed with XDR-TB during double-blinded treatment in Stage 2 of the trial) or subjects for whom there was evidence they were infected with XDR-TB prior to randomization into the trial the option to receive TMC207 for 24 weeks in addition to their MDR-TB treatment.

## **Study Visits**

Study visits included screening visit, Day-1, Day 1, Day 2, Day 7, weekly visits from Week 2 to Week 8, biweekly visits from Week 10 to Week 24; Weeks 26, 28, 32, 36, 48, 60, 72, 96, 104 (Stage 1 only), 108 (Stage 2 only), 120 (Stage 2 only).

The follow-up period in this trial was 96 weeks after the last intake of TMC207 or placebo, corresponding to approximately 5 times the estimated half life of TMC207 after treatment discontinuation. There were 9 and 10 planned follow-up visits after Week 24 in Stages 1 and 2.

### **Efficacy Analyses**

The primary efficacy analysis in Stage 1 and Stage 2 was performed when all subjects completed 8 weeks and 24 weeks of treatment with TMC207 or placebo (or had discontinued earlier), respectively.

An additional statistical analysis of Stage 2 was performed to support submission to Health Authorities, as planned per protocol, using cut-off dates of 10 May 2011 for efficacy data and of 10 June 2011 for safety data. At the time of these cut-off dates, all subjects had completed at least the Week 72 visit or had discontinued earlier. In October of 2012, a 4-month safety update report for Stage 2 was submitted.

Final analysis in Stage 1 was performed when all subjects completed 104 weeks (i.e. 8 weeks of TMC207 + 96 weeks of MDR-TB treatment and follow-up) or discontinued earlier. In Stage 2 final analysis will be performed when all subjects have completed 120 weeks (i.e. 24 weeks of TMC or placebo + 96 weeks of MDR-TB treatment and follow-up) or discontinued earlier.

### **Primary Endpoints**

According to the Study Report, the primary endpoint was time to sputum culture conversion during treatment with TMC207 or placebo, which was based on the qualitative assessment of culture growth in MGIT using spot sputum samples. The following definitions were used to determine time to sputum culture conversion:

- Sputum culture conversion was defined as 2 consecutive negative cultures from sputa collected at least 25 days apart. All intermediate cultures have to be negative as well. A cut-off of 25 days was chosen as most visits are scheduled to be 28 days apart. Sputum culture conversion was overruled when followed by a confirmed positive MGIT culture result (defined as 2 consecutive visits with positive sputum results, not taking into account intermittent missing or contaminated results, or a single positive sputum result after which the subject discontinued or completed).
- Time to sputum culture conversion was calculated as the interval in days between the date of treatment initiation for MDR-TB and the date of the first of the 2 consecutive negative sputum cultures from sputa collected at least 25 days apart.

In Stage 1, because of the shorter investigational phase, there was no requirement of 25 days apart for two consecutive culture results in the week 8 primary efficacy analysis; however in the week 24 and final analyses, there was such a requirement.

In Stage 2, for subjects who discontinued before the end of the analyzed time period, the following methods for the primary and sensitivity analyses were applied to calculate the time to culture conversion:

- They were considered treatment failures (i.e., no culture conversion event) and their time to culture conversion was censored at their last assessment with sputum culture (missing = censored; primary analysis).

*Comment: The sponsor referred to this analysis as missing=failure. However, failure and missing value were censored in this definition, which means in the time-to-event analysis subjects were excluded from the analysis from the censoring time on and not considered as failure.*

- They were considered treatment failures (i.e., no culture conversion event) and were carried forward as not converting through the considered time period (missing = failure, end-censored). The subjects' time to culture conversion was censored on the last day of the analyzed time period.
- The discontinuation information was not taken into account (no overruling for discontinuation). For subjects whose microbiological status had converted before discontinuation, the actual time of conversion was used. For subjects with no sputum culture conversion before discontinuation, their time to culture conversion was censored at their last assessment with sputum culture.

For detail of how the endpoints were defined please see Appendix 6.1.

The definition of time to sputum culture in the protocol version 7 (October 29, 2011, submitted on 11/8/2011, SN286/SDN301, page 56) was similar to the one used in the Study Report, except for the following:

- There is no mention of overruling sputum culture conversion when followed by a confirmed positive MGIT culture result. As a result there was also no definition of confirmed positive culture result following a sputum culture conversion.
- The dates of the first of the 2 consecutive negative sputum cultures from sputa collected were to be at least 28 days apart.

*Comment: Note that it appears for the NDA submission that the sponsor considered a subject as having a culture conversion by a certain data cutoff if at least the first of the two required negative sputa occurred by the data cutoff date. For example, Subject 4100 was considered as converted with one negative on Day 166 and one negative on Day 197, the first follow-up visit.*

## **Major Secondary Endpoint**

### ***Culture Conversion Rate***

The division considered the culture conversion rate is an important endpoint in accessing the effect of TMC207. The sponsor listed this endpoint under the Primary Efficacy Endpoint section.

The proportion of subjects with MGIT sputum culture conversion was determined according to the following definitions:

- **Responder (missing = failure):** sputum culture conversion had occurred, was not followed by a confirmed positive MGIT result, and the subject did not discontinue during the considered time frame.
- **Non-responder (missing=failure):** the last available microbiological status was 'not converted', or status was 'converted' but followed by a confirmed positive result, or the subject discontinued during the considered time frame regardless of the status at the last assessment.

Culture Conversion (Missing=Failure) were further subdivided in the following categories for non-response:

- Failure to culture convert (at any time point during the trial)
- Relapse: having a confirmed positive sputum culture (or a single positive sputum culture after which the subject discontinues) during or after treatment after having been defined converted with isolation of a *M. tuberculosis* strain with the same genotype compared to baseline or with unknown genotype as compared to baseline.
- Re-infection: having a confirmed positive sputum culture after having been defined converted with isolation of a *M. tuberculosis* strain with a different genotype compared to baseline.
- Discontinued with microbiological status 'converted'.
- Discontinued with microbiological status 'not converted'.

*Comment: There were no genotype data available in the submission.*

## **Additional Secondary Endpoints**

The following are the additional secondary endpoints discussed in this review.

### ***1. CFU Counts***

Observed values and changes from baseline in  $\log_{10}$  mean CFU counts were summarized with descriptive statistics by treatment group and analysis time point for CFU evaluable subjects only. Subjects were not evaluable for CFU when:

- CFU counts are 0, missing or contaminated at baseline
- CFU counts are positive ( $>0$ ) at baseline but negative (0) at every other visit.

*Comment: Item 1 was considered as "false negative" in the Stage 1 Study Report. It is not clear why the second item was considered in the sponsor's analysis.*

### ***2. Chest X-Ray Composite Score***

The Chest X-ray composite score is determined based on the disease and the cavitation levels of six different zones of the lung, with a lower score indicating a better condition.

The study report also includes time to AFB smear conversion and time to positive signal in MGIT. Time to AFB smear conversion and the proportion of subjects with AFB smear conversion were determined according to the same definitions described for time to sputum culture conversion and culture conversion rates. Time to positive signal in MGIT were the changes on the time required to signal in MGIT (i.e., time to positive signal) over time were descriptively summarized. We will not discuss further in this review.

### **3.2.1.2 Study C209**

Study C209 is an ongoing Phase II, single-arm, open-label trial to evaluate efficacy, safety, and tolerability of TMC207 on top of background regimen in the treatment of MDR-TB.

Subjects with confirmed pulmonary MDR-TB infection were included. Subjects infected with XDR-TB were also allowed to enter the trial if they had at least 3 anti-TB drugs in their background regimen to which their *M. tuberculosis* isolate was likely to be susceptible. HIV infected subjects having a CD4+ count < 250 cells/μL were excluded, compared 300 cells/μL in Study C208 Stage 2. Unlike in Study C208, HIV-infected subjects receiving antiretroviral treatment were allowed to enter the trial if they met some specified conditions.

The TMC207 dose, treatment duration, and follow-up duration were the same as in Study C208 Stage 2. However, the schedule of follow-up visits was different in the two studies. In Study C209 subjects were to be seen on day 1, weeks 2, 4, 8, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, much less often in the first 36 weeks as in Stage 2. The primary efficacy endpoint and main secondary efficacy endpoints were defined the same as in Study C208 Stage 2. A clinical study report includes results from planned interim analysis performed when all subjects had completed 24 weeks of treatment with TMC207 or had discontinued earlier (cut-off date 29 March 2011).

## **3.2.2 Statistical Methodologies**

### **3.2.2.1 Study C208**

As stated above, Stage 2 of study C208 is the proof-of-efficacy stage of this study. For that reason, this section focuses on Study C208 Stage 2. Unless stated otherwise, the descriptions also apply to Stages 1.

### **Analysis Populations**

**ITT Population:** All subjects who were randomized and received at least one dose of TMC207 or placebo. This population was used for safety analysis set.

*Comment: Strictly speaking, this is a modified ITT population, because of the exclusion of subjects who do not receive at least one dose of randomized treatment. However, given that it is a blinded study, this exclusion is acceptable and we will refer to it as an ITT population.*

**mITT Population:** According to the Study Report, the ITT population excluding subjects

- Who had drug-sensitive TB (DS-TB), XDR-TB, or MDR-TB for whom the MDR-TB status could not be confirmed based on susceptibility results taken prior to randomization;
- or whose MGIT results did not allow for primary efficacy evaluation (i.e., no evidence of culture positivity prior to first intake or no results during the first 8 weeks after first intake).

Unless specified otherwise, the mITT population was used for all efficacy analyses.

*Comment: Note that we do not agree with the exclusion of subjects for not having results during the first 8 weeks of treatment since the exclusion of these subjects could be due to the subject's randomized therapy. In the protocol reviewed by the Agency, this exclusion was not included. In the protocol version 6, dated May 20, 2011, mITT population excluded "all subjects from the ITT population who turned out to be XRD-TB or non-MDR TB based on the susceptibility results from samples taken prior to randomization". The definition of exclusions from the mITT population was essentially limited to the first bullet in the above definition. The second exclusion (second bullet above), "whose MGIT results did not allow for primary efficacy evaluation (i.e., no evidence of culture positivity prior to first intake or no results during the first 8 weeks after first intake)" was not included in the protocol.*

*In the SAP, issued on September 14, 2011, mITT was defined as follows:*

*Modified Intent-to-treat population (mITT): is the subset of the ITT population excluding*

- *Subjects whose MGIT results did not allow for primary efficacy evaluation.*
- *Drug Susceptible (DS-TB), XDR TB subjects or subjects for whom the MDR-TB status could not be confirmed based on susceptibility results taken prior to randomization.*

*The definitions in the Study Report and Statistical Analysis Plan dated 9/14/2011 were consistent. One subject (4135) in Stage 2 in the TMC207 group had positive culture results at baseline. We will conduct alternative analyses with this excluded subject in the mITT population.*

**Per Protocol population (PP):** the subset of the mITT population defined above that has no major protocol violations.

## **Analysis Methods for the Primary Endpoint in Stage 2**

For the comparison of the treatment groups, a Cox proportional model was used with degree of lung cavitation and trial center as covariates. In the protocol, baseline log-CFU counts were to be included as a covariate, but this variable was not in the analysis. Treatment by center and treatment by cavitation interactions were explored with this model. A two-sided 5% significance level was used.

*Comment: In Stage 1 and 2 Log-CFU was not included in the sponsor's primary analysis using a Cox proportional hazards model. The reason was not found in the Study Report. However one possible reason might be that only 34 and 39 subjects from a few centers had CFU data in Stages 1 and 2, which would reduce the sample size for the primary efficacy analysis.*

According to the SAP, the pooling of centers was determined prior to database lock of the primary analysis (of Week 24 Stage 2 data) and prior to unblinding of the randomization codes. The pooling was determined as follows:

- Eastern Europe : Centers from Russia and Latvia
- Asia : Centers from India, Thailand and Philippines
- South-America : Centers from Peru and Brazil
- Centers of the Republic of South Africa were pooled ('South Africa-other') unless the two largest study sites 'South Africa-1' and 'South Africa-2', each site with only one investigator.

In Stage 1, there were only 3 pooled regions from South Africa.

### **Analysis Methods for Additional Interim Analyses in Stage 2**

After the primary efficacy analysis was completed after all subjects reached week 24 or discontinued sooner, three interim analyses were conducted with different data selection dates: "Week 24 data selection", "Week 72 data selection", "All available data selection".

Time to culture conversion was the primary efficacy endpoint for interim analyses at each data selection. Two sensitivity analyses for handling subjects who discontinued described in the primary endpoint section were also conducted. In addition, a binary outcome (treatment success/failure) was created to calculate culture conversion rates at these time points. The same statistical methods for the Stage 2 primary endpoint were used for time-to-culture-conversion endpoint analyses.

In Stage 1, the primary endpoint was initially defined as time to sputum culture conversion during the 8-week investigational treatment phase with 2 consecutive negative cultures 28 days apart (then changed to 25 days in Stage 2). The primary endpoint was modified in order to account for the short duration of investigational treatment phase in Stage 1. Based on a blinded evaluation of the data, the sponsor decided that the definition of culture conversion should not require 25 days apart for the 2 consecutive culture negative assessments due to the short duration of investigational treatment phase in this stage, as mentioned previously.

#### **3.2.2.2 Study C209**

The similar statistical methodologies were used in Study C209 as in Study C208. However, the study population included XDR-TB subjects and this was an uncontrolled study, and no comparison analysis with a control group could be conducted.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

#### 3.2.3.1 Study C208

##### Stage 1

A total of 25 subjects per group were planned. During Stage 1, 47 subjects were randomized to receive either TMC207 (n = 23) or placebo (n = 24). Six investigators in South Africa participated in this stage. When these subjects were enrolled, data collected from these subjects were considered sufficient by the sponsor to meet the objective of Stage 1. The rate of study discontinuation was high at 44% for TMC207 and 54% for placebo; however, 83% and 92% had data available for the primary efficacy analysis at week 8. The common reasons for discontinuations were non-compliance and consent withdrawal. Notice in the placebo two subjects developed XDR-TB during the trial. One subject (ID: 3079) in the TMC207 group discontinued due to fatal myocardial infarction. The mITT population included 44 subjects. Two subjects with XDR-TB at baseline and one subject with culture negative results at all time points were excluded from the mITT population.

**Table 2: Numbers of subjects randomized, and inclusion/exclusion in the mITT population, Study C208 Stage 1**

	<b>TMC207</b> N=23	<b>Placebo</b> N=24
Completed	13	11
Discontinued	10	13
<i>Non-compliance</i>	4	4
<i>Consent withdrawal</i>	3	4
<i>Loss to follow-up</i>	1	1
<i>XDR-TB at baseline</i>	1	1
<i>XDR-TB developed during trial</i>	0	2
<i>Transfer to other place</i>	0	1
<i>Adverse event (fatal myocardial infarction)</i>	1	0
mITT	21	23
<i>Excluded due to XDR-TB at baseline</i>	1	1
<i>Culture negative MGIT at all time points</i>	1	0

##### Stage 2

A total of 282 subjects were enrolled and 161 were randomized. There were 121 screening failures (103 not fulfilling all inclusion/exclusion criteria, 7 withdrawing consent, 2 having adverse event (AE), and 9 for other reasons).

Of those randomized, 1 subject (ID: 6004) was not treated due to AE(s) (vomiting and dizziness).

*Comment: Because the study was double-blind, it is acceptable not to include this subject in the analysis population.*

The two groups were numerically comparable with respect to the numbers of screened, randomized, and treated. More patients in the placebo group were excluded from the mITT population due to infection with DS or XDR-TB or unconfirmed MDR-TB status.

**Table 3: Numbers of subjects screened and randomized, and inclusion/exclusion in the mITT population, Study C208 Stage 2**

	<b>TMC207</b>	<b>Placebo</b>
Screened	80	81
Randomized but not treated	1	0
Randomized and treated (ITT)	79	81
mITT	66	66
Excluded from mITT	13	15
<i>MGIT results did not allow for primary efficacy evaluation</i>	6	3
<i>Infected with DS or XDR-TB or MDR-TB status could not be confirmed</i>	7	12

The following table contains a listing of subjects who were excluded from the sponsor’s mITT population for not meeting the second exclusion bullet, “whose MGIT results did not allow for primary efficacy evaluation (i.e., no evidence of culture positivity prior to first intake or no results during the first 8 weeks after first intake).” One subject, subject 4135, was excluded solely for not having any post-randomization results. The other excluded subjects in the table below had either missing or negative baseline cultures. An additional analysis will be presented using an FDA’s mITT analysis population that includes subject 4135.

**Table 4: Subjects who did not have MGIT results that would allow for the primary analysis, Study C208 Stage 2**

Subject	ARM	TB Type	Baseline Culture	Results on the first 8 weeks								Comments
				N	N	N	N	P	P	N	N	
4102	PLA		NN	N	N	N	N	P	P	N	N	
4232	PLA	MDR	NN	N	N	N	C	N	N	N	N	First positive on Follow-up visit 9 on Day 840
4482	PLA		M		C							M: Unscheduled visit on Day -7; C at dropout visit 1 on Day 14.
4000	TMC	Pre-XDR	M	M	M		M	M	M	M	M	First two Positives at Weeks 14 and 16 (Days 100 and 115)
4015	TMC		NN	N	N	N	N	N	N	P		Then negative at 11 visits from Week 10 to Follow-up 7 (Day 591)
4135	TMC	MDR	PP									No results afterwards
4370	TMC		NN	N	N	N	N	N	C	N	N	Only one positive at Week 24. All negative at all other treatment and follow-up visits up to Week 120 (Day 847)

Subject	ARM	TB Type	Baseline Culture	Results on the first 8 weeks								Comments
				N	N	N	N	C	N	N	P*	
4381	TMC		NN	N	N	N	N	C	N	N	P*	*Drop out at Day 56 with a positive result and negative at Day 63 (Dropout visit 2)
6000	TMC		NN	N	N	N	N	N	P	N	N	Negative up to Follow-up 7 (Day 588)

C: Contaminated; M: Missing; N: Negative; P: Positive.

Trial discontinuation reasons and numbers are tabulated in the following table. The numbers of subjects ongoing, completed, and discontinued were evenly distributed between the two groups. The reasons for discontinuations were similar between the two groups too.

**Table 5: Trial discontinuation reasons and numbers (percentages) for the ITT and mITT populations, Study C208 Stage 2**

Type	ITT		mITT	
	TMC207 N=79	Placebo N=81	TMC207 N=66	Placebo N=66
Completed	18 (22.8)	20 (24.7)	15 (22.7)	14 (21.2)
Ongoing	34 (43.0)	30 (37.0)	30 (45.5)	28 (42.4)
Discontinued	27 (34.2)	30 (37.0)	21 (31.8)	23 (34.8)
Reasons for discontinuation				
<i>Adverse event</i>	7	6	6	5
<i>Ineligibility to continue the trial</i>	2	6	0	0
<i>Pregnancy</i>	3	2	3	3
<i>Lost to follow-up</i>	5	3	5	5
<i>Non-compliance</i>	3	6	2	2
<i>Consent withdrawal</i>	6	7	5	5
<i>Other (became XDR)</i>	1	0	0	0
Rollover	0 (0)	1 (1.2)	0	1 (1.5)

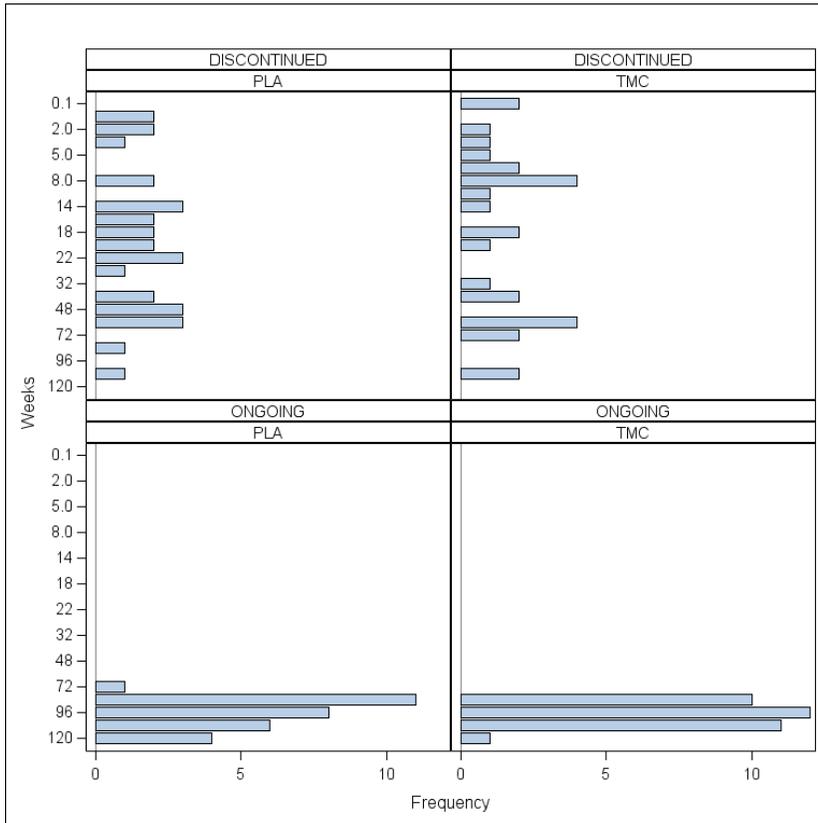
The numbers of subjects at each pre-planned study visit by disposition type are included in the following table. The disposition type was defined based on whether or not a subject completed Week 120 visit (including availability of microbiological culture results). All completed subjects completed Week 120 visit. For discontinued subjects, as the visit time increased, the numbers of subjects reduced. Almost all ongoing subjects completed Week 84 visits; one and four subjects in the TMC207 and placebo groups, respectively, completed Week 120 visit, but were considered as ongoing because the last microbiological assessment results were not available yet at Week 120 visit in the data set. One subject (ID: 4013) in the placebo was rolled over after Week 36 due to treatment failure and then was followed-up for 10 visits in 48 weeks after rollover.

**Table 6: Numbers of subjects at each study visit by disposition type in the ITT population, Study C208 Stage 2**

Visit	Completed		Discontinued		Ongoing		Rollover	Total
	TMC207	Placebo	TMC207	Placebo	TMC207	Placebo	Placebo	
Day-1	18	20	27	30	34	30	1	160
Day1	18	20	27	30	34	30	1	160
Day7	18	20	25	29	34	30	1	157
Week2	18	20	25	26	33	30	1	153
Week3	18	20	24	25	34	30	1	152
Week4	18	20	23	24	34	30	1	150
Week5	18	20	23	25	34	30	1	151
Week6	18	20	21	24	34	30	1	148
Week7	18	20	21	25	34	30	1	149
Week8	17	20	20	25	34	30	1	147
Week10	18	20	16	23	34	30	1	142
Week12	18	20	16	23	33	30	1	141
Week14	18	20	15	23	34	30	1	141
Week16	18	20	14	19	33	30	1	135
Week18	17	20	13	17	33	30	1	131
Week20	18	20	12	16	34	30	1	131
Week22	18	18	11	13	34	30	1	125
Week24	17	20	11	11	34	30	1	124
Week28	18	20	10	11	34	29	1	123
Week32	18	20	11	10	33	30	1	123
Week36	18	20	10	10	34	29	1	122
Week48	18	20	8	8	34	30		118
Week60	18	20	8	5	33	30		114
Week72	18	20	4	2	34	30		108
Week84	18	20	1	2	34	29		104
Week96	18	20	2	1	24	18		83
Week108	18	20	2	1	12	10		63
Week120	18	20			1	4		43

The last visit distribution (excluding unscheduled visits) by disposition type is shown in the following figure. The last visits for the two treatment groups appear well balanced for both discontinued subjects and for ongoing subjects.

**Figure 1: Last visit distribution by disposition type in the ITT population, Study C208 State 2**



The time on study in weeks by disposition type and treatment group is shown in the following table. The length of time was well balanced between the two treatment groups among completed, discontinued, or ongoing subjects.

**Table 7: The time on study in weeks by disposition type and treatment group in the ITT population, Study C208 Stage 2**

	<b>TMC207 N=79</b>	<b>Placebo N=81</b>
<b>Completed</b>		
N	18	20
Mean(SD) [Range]	120.3 (0.8) [119.1, 122.1]	120.5 (1.3) [119.6, 125.0]
<b>Discontinued</b>		
N	27	30
Mean(SD) [Range]	31.2 (32.3) [0.1, 108.3]	28.6 (35.8) [0.9, 107.0]
<b>Ongoing</b>		
N	34	30
Mean(SD) [Range]	97.3 (10.5) [83.1, 119.6]	97.1 (13.8) [72.0, 121.4]
<b>Rollover</b>		
N		1
Mean		48.3

According to the protocol, Dropout Visit 1 was to be performed at time of withdrawal from the trial or the following morning. Dropout Visit 2 was to be scheduled between 5 and 7 days after withdrawal from the trial (other than withdrawal of consent). Subjects who prematurely discontinued the trial (except for withdrawal of consent) were to be followed for survival until the last follow-up visit for the last subject in the trial. Investigators were asked to provide minimal information about the survival/clinical outcome of subjects, approximately every 6 months.

Demographic and baseline characteristics are summarized in the following two tables. Baseline variables were generally balanced, except for HIV status. A higher proportion of HIV positive patients were included in the placebo group, both in the ITT and mITT populations. The difference was not statistically significant in the ITT population (Chi-square test p-value 0.088), but statistically significant in the mITT population (Fisher's exact p-value 0.045). It is not surprising to find some significant differences with so many baseline variables in the table to compare. We explored if this imbalance might overly affect the results and we do not believe that it did affect the efficacy results. The efficacy results by HIV status will be included later in the review.

**Table 8: Demographic characteristics, Study C208 Stage 2**

	ITT		mITT	
	TMC207 N=79	Placebo N=81	TMC207 N=66	Placebo N=66
<b>Sex, n (%)</b>				
Male	52 (65.8)	49 (60.5)	45 (68.2)	40 (60.6)
Female	27 (34.2)	32 (39.5)	21 (31.8)	26 (39.4)
<b>Age (years)</b>				
Mean (SD)	36.0 (13.14)	35.8 (11.02)	35.8 (13.28)	34.7 (10.29)
Median (range)	31.0 (18, 63)	35.0 (18, 61)	31.0 (18, 63)	34.0 (18, 57)
<b>Body mass index (kg/m<sup>2</sup>)</b>				
Mean (SD)	20.0 (3.4)	19.9 (3.7)	19.9 (3.4)	19.7 (3.7)
Median (range)	19.6 (14.8, 32.4)	18.6 (15.2, 29.8)	19.7 (14.8, 32.4)	18.5 (15.2, 29.8)
<b>Race, n (%)</b>				
Black	29 (36.7)	27 (33.3)	24 (36.4)	25 (37.9)
Caucasian/White	8 (10.1)	12 (14.8)	6 (9.1)	8 (12.1)
Hispanic	13 (16.5)	15 (18.5)	12 (18.2)	10 (15.2)
Oriental/Asian	9 (11.4)	6 (7.4)	9 (13.6)	6 (9.1)
Other	20 (25.3)	21 (25.9)	15 (22.7)	17 (25.8)
<b>Region, n (%)</b>				
Asian (India, Philippine, Thailand)	8 (10.1)	4 (4.9)	8 (12.1)	4 (6.1)
Eastern Europe (Latvia & Russia)	8 (10.1)	11 (13.6)	6 (9.1)	7 (10.6)
South Africa	43 (54.4)	45 (55.6)	37 (56.1)	42 (63.6)
South-America (Brazil & Peru)	20 (25.3)	21 (25.9)	15 (22.7)	13 (19.7)
Separate them				

**Table 9: Baseline characteristics, Study C208 Stage 2**

	ITT		mITT	
	TMC207 N=79	Placebo N=81	TMC207 N=66	Placebo N=66
<b>TB resistance type, n (%)</b>				
DS-TB	4 (2.5)	4 (2.5)	0	0
MDR-TB	40 (50.6)	46 (56.8)	39 (59.1)	45 (68.2)

	ITT		mITT	
	TMC207 N=79	Placebo N=81	TMC207 N=66	Placebo N=66
Pre-XDR-TB	16 (20.3)	12 (14.8)	15 (22.7)	12 (18.2)
XDR-TB	3 (3.8)	4 (4.9)	0	0
Unknown*	16 (20.3)	15 (18.5)	12 (18.2)	9 (13.6)
<b>Cavitations, n (%)</b>				
>=2 cm in both lung	13 (16.5)	16 (19.8)	12 (18.2)	15 (22.7)
>=2 in one lung	50 (63.3)	49 (60.5)	42 (63.6)	41 (62.1)
None or < 2 cm	16 (20.3)	16 (19.8)	12 (18.2)	10 (15.2)
<b>HIV status, n (%)</b>				
Negative	71 (89.9)	65 (80.3)	61 (92.4)	52 (78.8)
Positive	8 (10.1)	16 (19.8)	5 (7.6)	14 (21.2)
<b>CD4 cell count, n (%)</b>				
N	76	81	63	66
Mean (SD)	689.4 (312.6)	681.6 (290.1)	691.6 (317.16)	656.3 (248.90)
Median (Range)	642.0 (127, 1711)	621.0 (291, 1655)	635.0 (127, 1711)	596.0 (310, 1369)
<b>CD4 Cell count HIV negative</b>				
N	68	65	58	52
Mean (SD)	712.3 (320.1)	737.4(292.38)	712.0 (321.85)	712.2 (246.06)
Median (Range)	661.5 (127, 1711)	682.0 (291, 1655)	661.5 (127, 1711)	678.5 (344, 1369)
<b>CD4 Cell count HIV positive</b>				
N	8	16	5	14
Mean (SD)	494.6 (132.66)	455.1 (125.9)	455.2 (84.7)	448.9 (115.8)
Median (Range)	487.0 (340, 692)	432.5 (310, 670)	463.0 (352, 559)	432.5 (310, 667)
<b>Previous use of first-line TB drugs, n (%)</b>				
No	7 (8.9)	11 (13.6)	6 (9.1)	8 (12.1)
Yes	72 (91.1)	70 (86.4)	60 (90.9)	58 (87.9)

\*Subject with missing values in TB type had no TB results from the central laboratory. They were considered as MDR-TB based on medical history.

### 3.2.3.2 Study C209

In Study 209, a total of 294 subjects in Asia, Eastern Europe, South Africa, and South America were screened and 233 were treated (ITT population). The mITT population included 205 subjects. A total of 28 subjects were excluded (3 with DS-TB at baseline and 25 with no positive MGIT at baseline or screening). A total of 203 subjects completed 24-week investigation period and were ongoing. Twenty subjects discontinued before Week 24 and 10 discontinued after Week 24. In the ITT population, 37 (15.9%) subjects were infected with XDR-TB, and 11 (4.9%) were HIV-positive.

## 3.2.4 Results and Conclusions

### 3.2.4.1 Sponsor's Primary Efficacy Analysis

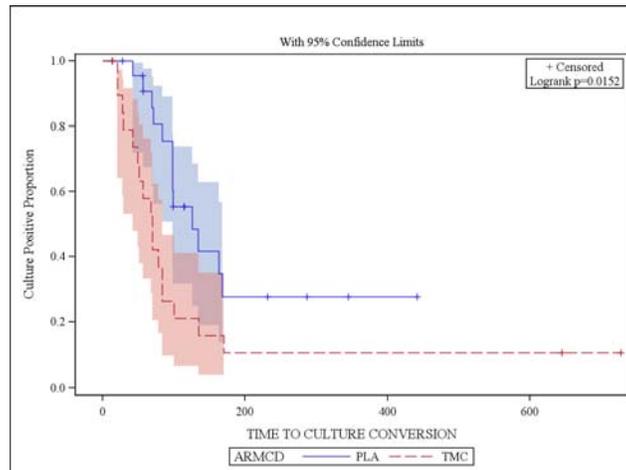
#### 3.2.4.1.1 Study C208

##### 3.2.4.1.1.1 Study C208 Stage 1

###### *Stage 1 primary results*

The Stage 1 primary efficacy results show that the time to sputum culture conversion by Week 8 was faster in the TMC207 group compared to the placebo group (Log-rank test p-value=0.0019). This significance remained in an analysis of the 24 week data as well as the full study data when all subjects had reached week 96 of follow-up or discontinued earlier (Log-rank test p-value=0.0152). The Cox proportional hazards model with covariates lung cavitation and pooled center showed a significant treatment effect (relative risk of 11.77, and a 95% CI [2.26, 61.23], with a p-value of 0.0034). Other covariates and interaction terms between other covariates and treatment were not significant. The Kaplan-Meier curves for time to culture conversion for the final analysis are shown in the following figure (log-rank p-value 0.0152).

**Figure 2: Kaplan-Meier survival curves for final analysis in the mITT population, Study C208 Stag 1**



Stage 1 analysis of culture conversion rates at Week 8 showed a statistically significantly higher rate for TMC207 than for placebo with a difference of 38.9% at Week 8. The results of analyses of culture conversion rates at the later time points were no longer significant and the treatment effects were diminishing. Compared with the above Kaplan-Meier survival figure, subjects with culture conversion were no longer considered as successes once they discontinued the trial. Therefore, the culture conversion rates in the table were much lower than in the survival curves.

**Table 10: Culture conversion rates in the mITT population, Study C208 Stage 1**

Microbiologic Status	TMC207 N=21	Placebo N=23	Difference [exact 95% CI] p-value
Week 8 Treatment success	10/21 (47.6%)	2/23 (8.7%)	38.9% [12.3%, 63.1%] 0.004
Week 24 Treatment success	17/21 (81.0%)	15/23 (65.2%)	14.8% [-11.9%, 41.9%] 0.29
Final Treatment success	11/21 (52.4%)	11/23 (47.8%)	4.6% [-25.5%, 34.1%] 0.76

According to the sponsor’s Advisory Committee Meeting briefing document, there were 2 deaths in each group. One death in the TMC207 group occurred during the trial and the other 3 were during the follow-up after discontinuation.

### 3.2.4.1.1.2 Study C208 Stage 2

In the Study Report, Stage 2 primary analysis, interim primary analysis and sensitivity analyses for Week 24 Data Selection, Week 72 Data Selection, and Last Available Data Selection are included. The Last Available Data Section used all available data from each subject; therefore the analyses contain more data than Week 24 and Week 72, because some subjects had data available after Week 72.

*Comment: Since the Last Available Data Selection used different follow-up time for each subject, it is difficult to interpret the culture conversion rate with this selection. In this review, we will not cover the analysis results based on this selection. Note that Study C208 Stage 2 has since completed and should be submitted to the NDA for complete review.*

## Stage 2: Primary Endpoint: Time to Culture Conversion up to Week 24

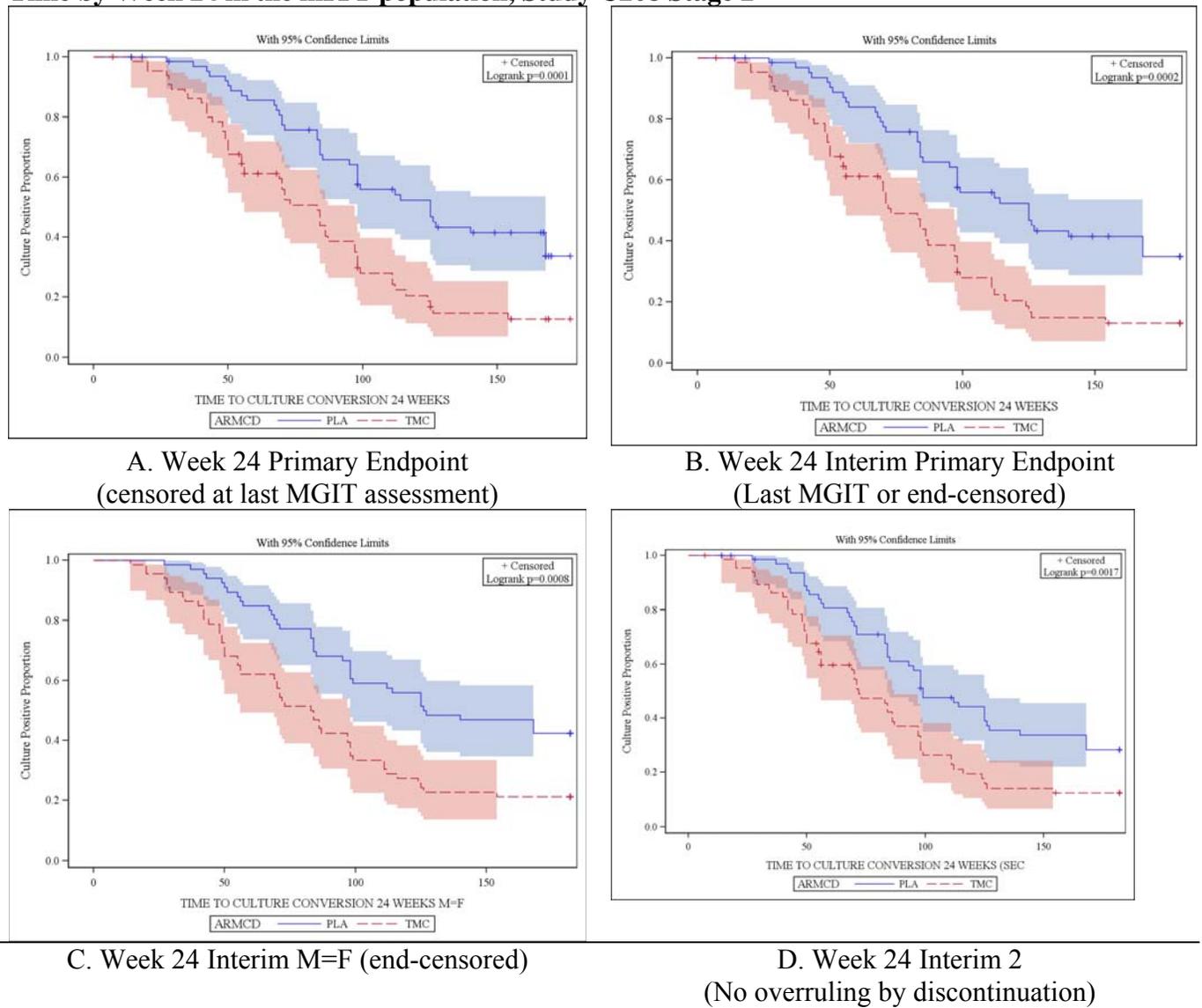
The primary efficacy analysis was performed when all Stage 2 subjects had completed their 24-week treatment with TMC207 or placebo (or had discontinued earlier).

Sputum culture conversion was defined as 2 consecutive negative cultures from sputa collected at least 25 days apart. All intermediate cultures had to be negative as well (if applicable). This condition was overruled when followed by a confirmed positive result. Time to sputum culture conversion was calculated as the interval in days between the date of treatment initiation for multi-drug resistant TB and the date of the first of the 2 consecutive negative sputum cultures from sputa collected at least 25 days apart. If the first day of such a conversion occurred before the end of double-blind treatment, this event was taken into account. Subjects who discontinued during the first 24 weeks of the trial were considered as not converted and the time to culture conversion was censored at the last MGIT culture result.

Time to culture conversion (in MGIT) based on the primary efficacy analysis is plotted in Figure 3A. In this analysis, the sponsor concluded that culture conversion was considerably faster and was seen more frequently in the TMC207 group compared to the placebo group (with a median time to culture conversion of 83 days [95% CI: 56, 97] in the TMC207 group versus 125 days [95% CI: 98, 168] in the placebo group and log-rank test p-value 0.0001).

A Cox proportional hazards model with covariates treatment, lung cavitation, and pooled center (region), the primary endpoint analysis, showed a statistically significant treatment effect (hazard ratio [95% CI] for TMC207: 2.44 [1.57, 3.80]).

**Figure 3: Kaplan-Meier survival curves: proportions of culture positive subjects over Time by Week 24 in the mITT population, Study C208 Stage 2**



**Table 11: Estimates from Cox proportional hazards model for the primary endpoint in the mITT population, Study C208 Stage 2**

Parameter	Level	Estimate	SD	p-value	HR	HR 95% CI
<b>Arm</b>	TMC207	0.89	0.23	<0.0001	2.44	1.57, 3.80
<b>Pooled Center</b> (South America as reference)	Asia	0.53	0.40	0.1813	1.70	0.78, 3.70
	Europe	-0.61	0.49	0.2104	0.54	0.21, 1.42
	South Africa 1	-0.27	0.35	0.4469	0.77	0.39, 1.52
	South Africa 2	-0.09	0.34	0.7984	0.92	0.47, 1.79
	South Africa Other	-0.37	0.37	0.3070	0.69	0.34, 1.41
<b>Cavitation</b> (no as reference)	≥ 2cm in both lungs	-0.88	0.37	0.0159	0.42	0.20, 0.85
	≥ 2cm in one lung only	-1.17	0.30	0.0001	0.31	0.17, 0.56

The estimates from a Cox proportional hazards model on the primary endpoint are shown in Table 11. Compared with subjects with no cavitation present, subjects with cavitation  $\geq$  2cm in both lungs or in one lung only were statistically significantly less likely to have culture conversion.

## Stage 2: Additional Primary Endpoint Analysis Results

### *Time to culture conversion at Week 24*

As discussed above, the sponsor conducted additional analyses of the time to culture conversion at Week 24. One is updated primary endpoint analysis, and two are sensitivity analyses. These three analyses are discussed here. For details of the differences of these endpoints please see Appendix 6.2.

#### *1. The Interim Week 24 primary endpoint Time to culture conversion*

The definition of time to culture conversion in this interim primary analysis was the same as in the stage 2 primary endpoint time to culture conversion, except that censoring time for culture conversion was changed from last MGIT visit time to Day 182 in this analysis for some ongoing and discontinued subjects. In addition, two responders' time to culture conversion was changed due to different evaluation of a culture result (see Appendix 6.2).

Time to culture conversion (in MGIT) based on this interim primary efficacy analysis is plotted in Figure 3B. It is noted that several censored time points around Day 170 in the placebo group were changed to Day 182, and one subject censored at Day 125 in the TMC207 group was changed to Day 182. Besides these differences, there was no discernable difference in Kaplan-Meier curves between the Stage 2 primary endpoint and interim Week 24 primary endpoint.

The results from the Cox proportional hazards model show a similar significant treatment effect on this interim primary endpoint as on the Stage 2 primary endpoint (Table 12).

#### *2. The Interim Week 24 Time to culture conversion: Non-responder End-censored*

In this analysis, all non-responders (including those who discontinued prior to week 24) were end-censored (censored at Day 182), as shown in the Kaplan-Meier survival curve in Figure 3C. Compared with the Stage 2 primary endpoint, the conversion rates were about 7~8% lower in

each treatment group (87% versus 79% in the TMC207 group; 66% versus 58% in the placebo group) because non-responders remained in the risk sets (i.e., a larger denominator for culture conversion rate calculation). However, a 21% difference between the TMC207 and placebo groups existed in both endpoints.

The results from the Cox proportional hazards model also demonstrated the significant treatment effect (Table 12).

### ***3. The Interim Week 24 Time to culture conversion: No Overruling by Discontinuation***

In this analysis, for discontinued subjects, the censoring status was based on MGIT results, not on their discontinuation status. Compared with the Stage 2 primary endpoint, the difference in conversion rates between the two treatment groups were smaller (15% versus 21%) (Figure 3D). However, the results from the Cox proportional hazards model also demonstrated the significant treatment effect, although the magnitude of effect was slightly reduced (Table 12).

Based on the interim analyses, TMC207 showed a significant treatment effect compared with placebo on the time to culture conversion in three endpoints considered. The interim analyses were consistent with the Week 24 primary endpoint, although the estimated treatment effects were slightly lower.

**Table 12: Treatment effect (relative risk to culture conversion): estimated from Cox proportional hazards models on Week 24 time to culture conversion in the mITT population, Study C208 Stage 2**

<b>Endpoint</b>	<b>Relative Risk</b>	<b>95% CI</b>	<b>p-value</b>
Stage 2 Primary Endpoint	2.44	1.57, 3.80	<0.0001
Interim Primary Endpoint	2.41	1.55, 3.75	<0.0001
Interim End-censored	2.22	1.43, 3.43	0.0003
Interim Sensitivity 2	1.98	1.30, 3.02	0.0015

### ***Time to culture conversion at Week 72***

The data submitted to this NDA contains at least 72-week data for all subjects unless they discontinued earlier. This section contains the three analysis results for Week 72: primary, end-censored, and no overruling by discontinuation.

#### ***1. The Interim Week 72 primary endpoint Time to culture conversion***

The Kaplan-Meier survival curve for this interim analysis is shown in the following figure (Plot A). Notice the biggest difference between the two groups occurred approximately at Day 150. Then the difference became smaller as time increased.

#### ***2. The Interim Week 72 Time to culture conversion: Non-responder End-censored***

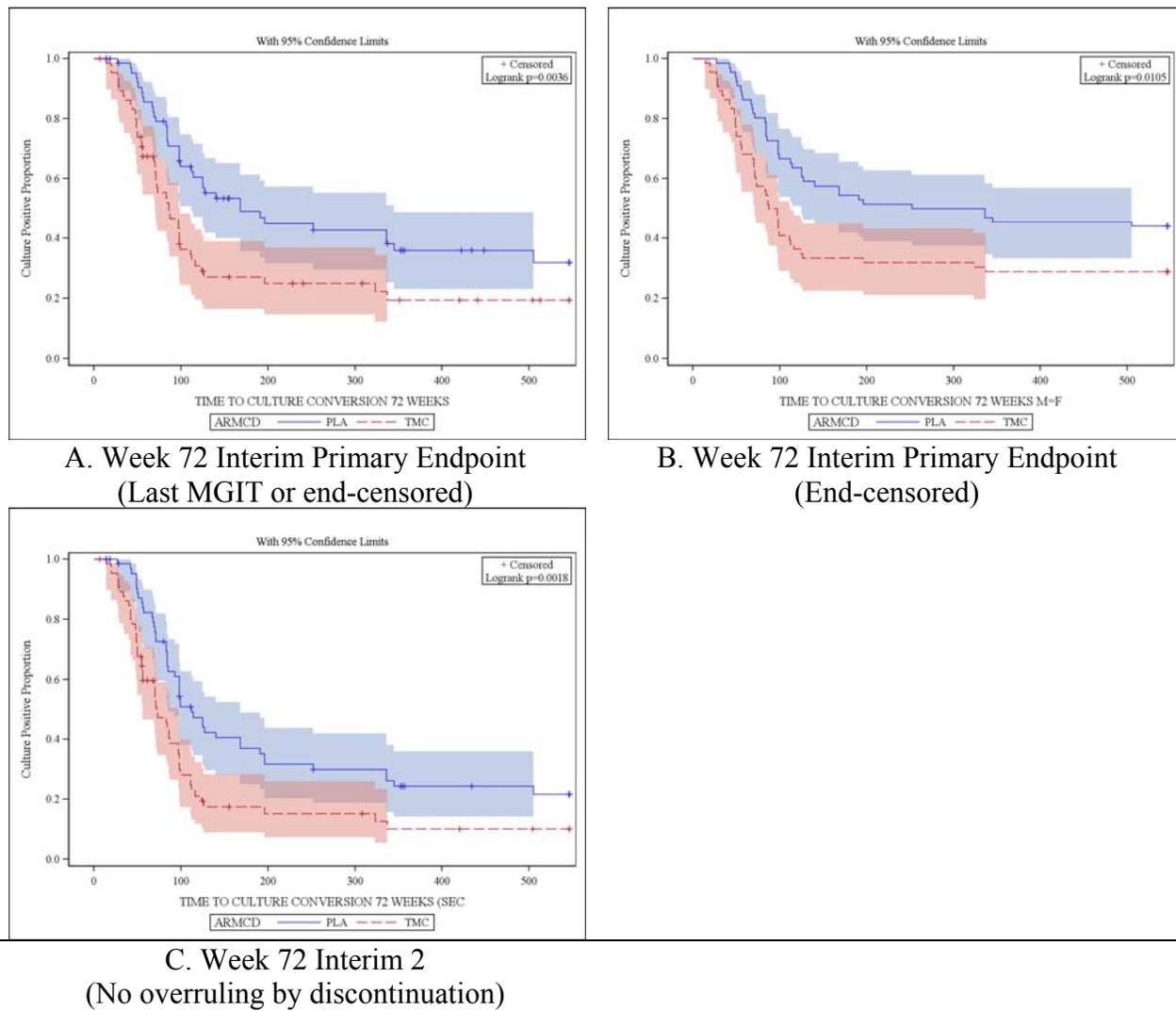
The Kaplan-Meier survival curve for this analysis is shown in Plot B in the following figure. The difference between the two groups showed the similar trend over time as in Plot A. However, the

proportions of culture conversion were lower (i.e. the survival (no conversion) proportions were higher) because subjects censored at the end of Week 72 remained in the risk sets in the survival proportion calculation, as explained in the Week 24 analysis using the same method to handle missing values.

### 3. The Interim Week 72 Time to culture conversion: No Overruling by Discontinuation

The Kaplan-Meier survival curves are shown in Plot C of the following figure. Since the actual MGIT time was used and not overruled by discontinuation for discontinued subjects, the culture conversion proportions were higher, compared with the Week 72 primary endpoint. Nevertheless, the difference between the two groups showed similar trend as in the Plots A and B.

**Figure 4: Kaplan-Meier survival curves: proportions of culture positive subjects over Time by Week 72 in the mITT population, Study C208 Stage 2**



The following table shows the treatment effect of TMC207 from the Cox proportional hazards models on Week 72 data. There was a statistically significant treatment effect from each of the endpoints. However, compared with the results from Week 24 data analyses, the treatment effect was slightly reduced.

**Table 13: Treatment effect (relative risk to culture conversion): estimated from Cox proportional hazards models on Week 72 time to culture conversion in the mITT population, Study C208 Stage 2**

Endpoint	Relative Risk	95% CI	p-value
Interim Primary	1.65	1.05, 2.59	0.0290
Interim End-censored	1.56	1.00, 2.43	0.0487
Interim Sensitivity 2	1.86	1.22, 2.82	0.0036

*Comment: For rollover subject 4013 if original data (censored on day 354) was used we got the same results as the sponsor. The subject was rolled-over, so the rollover time at follow-up Week 36 should be used in the analyses. However the results were very similar to the reported results. Therefore, we did not change this subject's time to conversion for Week 72 analyses. This time did not affect the Week 24 primary endpoint analysis.*

## Stage 2: Major Secondary Endpoint

### *Culture conversion rates at Week 24 and Week 72*

Based on the time-to-culture-conversion variable, a binary culture conversion was generated in order to calculate culture conversion rates.

Culture conversion rates based on the primary efficacy analysis at Week 24 are provided in the following table. There was a statistically significant difference in culture conversion rates between the two treatment groups. The reasons for failures were included in the table.

**Table 14: Culture conversion rates at Week 24 in the mITT population, Study C208 Stage 2**

Microbiologic Status at Week 24	TMC207	Placebo	Diff [95% CI] p-value
Treatment success	52 (79%)	38 (58%)	21% [5.7%, 36.7%] 0.008
Treatment failure	14 (21%)	28 (42%)	
Failure due to lack of conversion	5 (7.6%)	16 (24.2%)	
Failure due to discontinuation	9 (13.6%)	12 (18.1%)	

Adapted from Table 30, Study Report (page 144). The reported 95% CI was calculated by the reviewer.

*Comment: The p-value from the Chi-square test was 0.009. The p-value from the sponsor's analysis using a logistic regression was 0.008. Note: the success (or culture conversion) and failure rates were slightly different from these derived in Figure 3A., where censored observations were censored at the last MGIT time and not included in the risk set after censoring, therefore, in the graph, the success rates were higher (87% versus 65%). The conversion rates were matched with the Figure 3C, where failed subjects were censored at the last day of the analysis period.*

The following table shows the culture conversion rates at Week 72 in the mITT population. The difference in culture conversion rate at Week 72 between the treatment groups was no longer statistically significant, as shown in the following table.

**Table 15: Culture conversion rates at Week 72 in the mITT population, Study C208 Stage 2**

Microbiologic Status at Week 72	TMC207	Placebo	Diff [95% CI] p-value
Treatment success	47 (71%)	37 (56%)	15% [-1.1%, 31.4%] 0.070
Treatment failure	19 (29%)	29 (44%)	
Failure due to lack of conversion	5 (7.6%)	7 (10.6%)	
Failure due to discontinuation	17 (25.8%)	22 (33.3%)	

The following table shows the cross-tabulation of culture conversion rates at Week 24 and Week 72. For most subjects the results from the two time points were consistent; however, there were some subjects who did not culture convert at Week 24 but converted at Week 72 and some subjects vice versa.

**Table 16: Cross-tabulation of culture conversion rates at Week 24 and Week 72 in the mITT population, Study C208 Stage 2**

W24	Week 72					
	TMC207 N=66			Placebo N=66		
	Conversion	Failure	Success	Total	Failure	Success
Failure (n %)	11 78.57	3 21.43	14	22 78.57	6 21.43	28
Success (n %)	8 15.38	44 84.62	52	7 18.42	31 81.58	38
<b>Total</b>	19	47	66	29	37	66

The following table shows the sputum culture conversion at Week 24 by disposition type and treatment group. In the mITT population, for each disposition type (except for rollover), the TMC207 group had a higher conversion rate than the placebo group. Because all completed and ongoing subjects had completed Week 72 visit, completed subjects and ongoing subjects had a similar culture conversion rate at Week 24, as expected. In each treatment group, completed and ongoing subjects had the highest conversion rate at Week 24. In the ITT populations similar results were obtained.

**Table 17: Culture conversion at Week 24 by disposition type and treatment group in the mITT and ITT populations, Study C208 Stage 2**

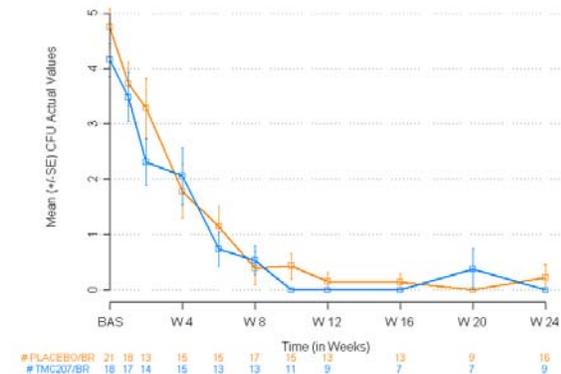
Disposition type	MITT		ITT	
	TMC207	Placebo	TMC207	Placebo
Completed	15/15 (100%)	11/14 (78.6%)	18/18 (100%)	17/20 (85.0%)
Discontinued	8/21 (38.1%)	5/23 (21.7%)	8/27 (29.6%)	6/30 (20.0%)
Ongoing	29/30 (96.7%)	22/28 (78.6%)	33/34 (97.1%)	23/30 (76.7%)
Rollover		0/1 (0)		0/1 (0)
Total	52/66 (78.8%)	38/66 (57.6%)	59/79 (74.7%)	46/81 (56.8%)

The following table shows the sputum culture conversion at Week 72 by disposition type and treatment group. In the mITT population, for each disposition type (except for rolled-over subjects), the TMC207 group had a higher conversion rate than the placebo group. In the ITT populations similar trends were observed.

**Table 18: Culture conversion at Week 72 by disposition type and treatment group, Study C208 Stage 2**

Disposition type	MITT		ITT	
	TMC207	Placebo	TMC207	Placebo
Completed	15/15 (100%)	11/14 (78.6%)	18/18 (100%)	17/20 (85.0%)
Discontinued	3/21 (14.3%)	3/23 (13.0%)	3/27 (11.1%)	3/30 (10.0%)
Ongoing	29/30 (96.7%)	23/28 (82.1%)	33/34 (97.1%)	25/30 (83.3%)
Rollover		0/1 (0)		0/1 (0)
Total	47/66 (71.2%)	37/66 (56.1%)	54/79 (68.4%)	45/81 (55.6%)

**Figure 5: Mean and SD of log CFU over time in the mITT population, Study C208 Stage 2**



Source: Study Report Figure 20, p176

## Stage 2: Additional Secondary Endpoints

### Log<sub>10</sub>CFU

Log<sub>10</sub>CFU over time was plotted in Figure 5. Specimens to determine sputum CFU were only collected at selected sites. Therefore only 39 subjects (18 in the TMC207 group and 21 in the placebo group) were used for this analysis.

At baseline, mean (SE) log<sub>10</sub> CFU count was 4.15 (0.301) in the TMC207 group and 4.74 (0.339) in the placebo group, which was not statistically significantly different. No difference was observed in the decrease in mean log<sub>10</sub> CFU count between the TMC207 group and the placebo group. During the 24-week investigational treatment phase, the maximum mean (SE) decreases in log<sub>10</sub> CFU count from baseline was 4.25 (0.557) in the TMC207 group (observed at Week 12) and 4.41 (0.398) in the placebo group (observed at Week 16).

For additional analysis of log<sub>10</sub>CFU please see reviewer's analysis below.

### Chest X-Ray

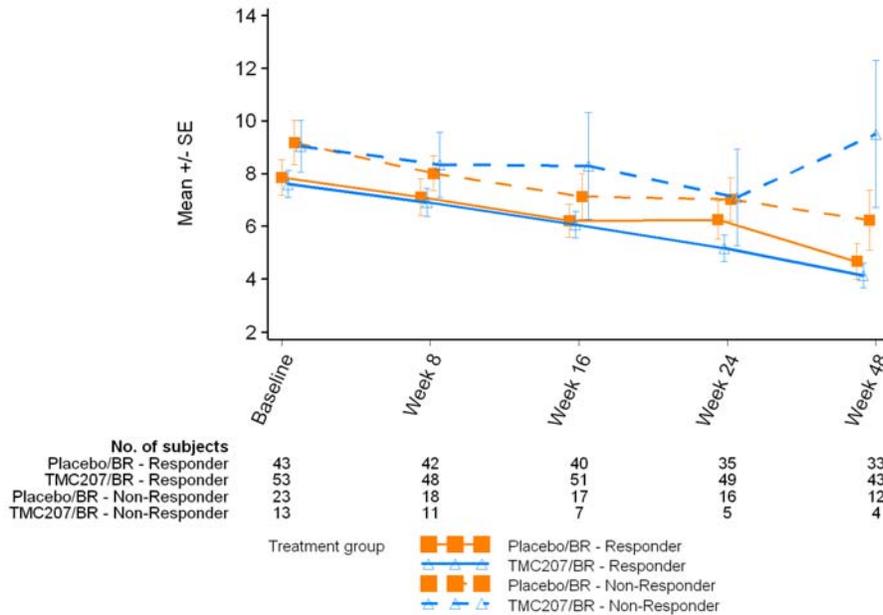
Chest X-ray was taken at baseline, Weeks 8, 16, 24, and 48 for all subjects. The maximum possible composite score is 24, with a lower score indicating a better condition of the lung.

Overall, mean baseline composite score was 7.88 in the TMC207 group and 8.31 in the placebo group. At Week 24, mean decrease from baseline was 2.43 in the TMC207 group and 1.82 in the placebo group.

The following figure shows the chest X-ray composite score by final microbiological status (mITT population). At Week 24, mean decrease from baseline was 2.33 for responders and 3.45 for non-responders in the TMC207 group and 1.86 for responders and 1.75 for non-responders in the placebo group. Overall, the TMC207 group started with lower scores and the changes over time were parallel. There was a concerning increase at Week 48 for the 4 subjects in the TMC207 group. However, there were no Week 48 data in the data set submitted to the NDA, and no more details about the 4 non-responders at Week 48 in the TMC207 group.

*Comment: Once the full study report and data are submitted, we will provide detailed analyses of this endpoint.*

**Figure 6: Chest X-ray composite scores over time in the mITT population, Study C208 Stage 2**



Source: Study Report Figure 21, p177

The cross-tabulation of cavitation status at baseline and post-baseline at Weeks 8, 16, 24, 48 were included in the study report. There were 11 and 15 subjects with missing cavitation data at Week 24 in the TMC207 and placebo groups, respectively. The results for baseline and Week 24 are as follows:

**Table 19: Lung cavitation status at baseline and Week 24 in the mITT population, Study C208 Stage 2**

Cavitation	Week 24					
	TMC207			Placebo		
Baseline	No or <2 cm	≥ 2 cm in one lung only	≥ 2 cm in both lungs	No or <2 cm	≥ 2 cm in one lung only	≥ 2 cm in both lungs
No or <2 cm	13 (92.9%)	1 (7.1%)		8 (80.0%)	1 (10.0%)	1 (10.0%)
≥ 2 cm in one lung only	18 (54.5%)	13 (39.4%)	2 (6.1%)	15 (50.0%)	13 (43.3%)	2 (6.7%)
≥ 2 cm in both lungs	2 (25.0%)	3 (37.5%)	3 (37.5%)	5* (41.7%)	1(8.3%)	6 (50.0%)

\*In sponsor's analysis, there were 4 subjects in this category. Some subjects had missing values at Week 24.

Of the 55 subjects in the TMC207 group, 29 subjects (52.7%) had no change in their cavitation category compared to baseline. An improvement at Week 24 compared to baseline was noted in

23 subjects (41.8%). Cavitation category became worse compared to baseline in 3 subjects (5.5%).

In the placebo group, 27 of the 52 subjects (51.9%) remained the same in their cavitation category compared to baseline. An improvement was observed in 21 subjects (40.4%). Cavitation category became worse compared to baseline in 4 subjects (7.8%).

Overall, there were no big differences in cavitation status changes between the two treatment groups.

## **Relapse**

Relapse was defined as having a confirmed positive sputum culture (or a single positive sputum culture after which the subject discontinued) during or after treatment after having been defined converted with isolation of a *M. tuberculosis* strain with the same genotype compared to baseline or with unknown genotype as compared to baseline. Therefore, the definition of relapse does not require either week 24 culture conversion or week 72 culture conversion.

Relapse was considered as having occurred when not followed by a subsequent culture conversion. This was not captured in the definition but was used in analysis.

*Comment: No genotype data were found from this NDA.*

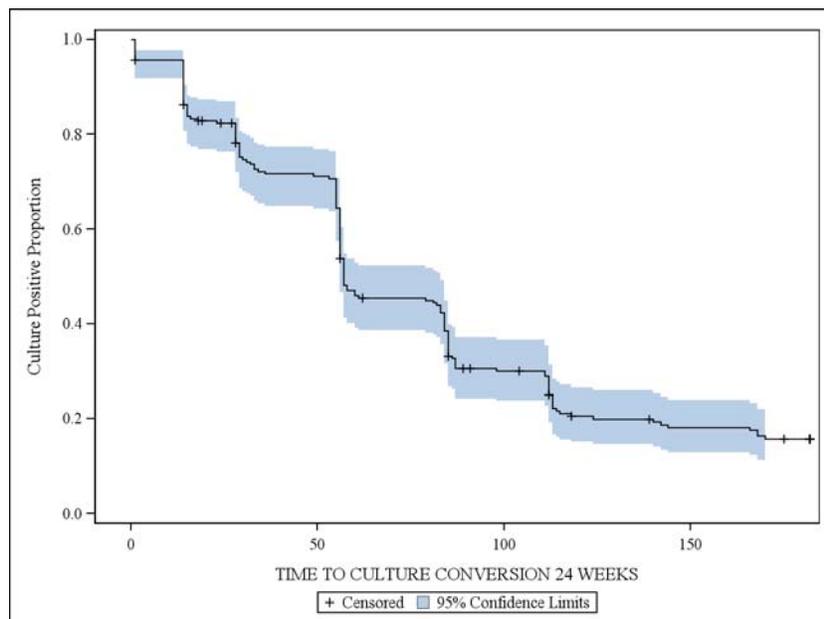
In the mITT population, 5 subjects (7.6%) in the TMC207 group and 8 subjects (12.1%) in the placebo group experienced relapse. There was one female (race: other) subject relapsed in each group. In the ITT population, there was one additional relapse subject in the placebo group who was male, discontinued and relapsed at Day 172.

*Comment: See reviewer's analysis section for additional analyses of the relapses.*

### **3.2.4.1.2 Study C209**

The Kaplan-Meier survival curve of the primary efficacy endpoint, time to sputum culture conversion by 24 weeks in the mITT population is depicted in the following graph. The survival times were more clustered around study visits because subjects were seen less often than in Study C208. Median time to culture conversion for the mITT population was 57 days.

**Figure 7: Kaplan-Meier Survival curve for time to culture conversion by Week 24 in mITT population, Study C209**



In the mITT population, 80% (163/205) of subjects achieved culture conversion at the end of Week 24, a secondary efficacy endpoint.

There were 16 deaths (16/233=6.9%) reported in C209. Twelve of these deaths occurred during the trial: 3 in the investigational treatment phase and 9 in the follow-up phase. Four deaths occurred during follow-up visits after discontinuation.

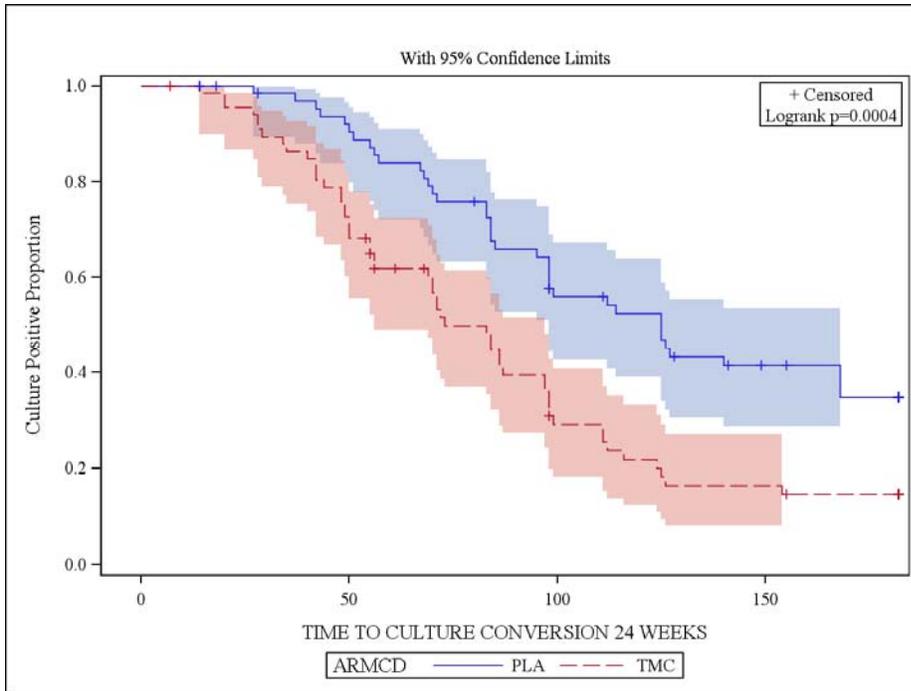
### **3.2.4.2 Reviewer's Analysis Results**

#### **FDA's additional analysis of the primary endpoint in Study C208 Stage 2**

We conducted additional analyses for the pivotal study C208 Stage 2. One subject (Subject 4135) in the TMC207 group had positive culture results at baseline but no culture results afterwards. This subject was excluded from the mITT population in the study report. In the reviewer's analysis, we included this subject in the mITT population as a failure (censored at Day 182).

The Kaplan-Meier survival curves by treatment group for this analysis are shown in the following graph. There was a significant difference in survival between the two groups and the p-value from the log-rank test was 0.0004, compared 0.0001 in the mITT population without Subject 4135.

**Figure 8: Kaplan-Meier survival curves: proportions of culture positive subjects over time by Week 24 in the mITT population, Study C208 Stage 2, FDA’s analysis**



The results from the Cox proportional hazards model including this subject are shown in the following table. The hazard ratio for treatment was 2.15 with a 95% confidence interval of [1.39, 3.31] and a p-value of 0.0005, showing a slightly smaller treatment effect, compared with the sponsor’s primary endpoint analysis. Compared with no cavitation or <2 cm category, the hazard for subjects with  $\geq 2$  cm cavitation was no longer statistically lower. Again, there were no significant interactions between treatment and other covariates in the model.

**Table 20: FDA’s estimates from Cox proportional hazards model for the primary endpoint in the mITT population, Study C208 Stage 2**

Parameter	Level	Estimate	SD	p-value	HR	HR 95% CI
<b>Arm</b>	TMC207	0.77	0.22	0.0005	2.15	1.39, 3.31
<b>Pooled Center</b> (South America as reference)	Asia	0.41	0.39	0.2930	1.51	0.70, 3.25
	Europe	-0.75	0.48	0.1230	0.47	0.18, 1.22
	South Africa 1	-0.57	0.34	0.0890	0.57	0.29, 1.09
	South Africa 2	-0.19	0.34	0.5693	0.83	0.43, 1.60
	South Africa Other	-0.43	0.37	0.2378	0.65	0.32, 1.33
<b>Cavitation</b> (no as reference)	$\geq 2$ cm in both lungs	-0.57	0.35	0.1038	0.57	0.28, 1.12
	$\geq 2$ cm in one lung only	-0.88	0.29	0.0021	0.41	0.24, 0.73

The following table shows the culture conversion rates at Week 24 for an analysis including this subject. Compared with the sponsor’s analysis, the cure rate in the TMC207 group was changed from 79% to 78% and the p-value from Chi-square test was changed from 0.009 to 0.0135, but still was statistically significant at the significance level of 0.05.

**Table 21: FDA’s culture conversion rates at Week 24 in the mITT population, Study C208 Stage 2**

<b>Microbiologic Status at Week 24</b>	<b>TMC207</b>	<b>Placebo</b>	<b>Difference [95% CI] p-value</b>
Treatment success	52 (78%)	38 (58%)	20% [ 4.5%, 35.6%] 0.0135
Treatment failure	15 (22%)	28 (42%)	

**FDA’s additional analysis of the end-censored endpoint in Study C208 Stage 2**

In the primary endpoint analysis, death and discontinuation were censored at the last MGIT visit. Censored subjects were not in the risk sets for calculation of culture conversion rates from the point of their censoring onwards, therefore the estimated culture conversion rates are higher with these subjects excluded as opposed to considering them as events. During the review of the protocol the division considered this issue and on 1/23/08 we sent the following comment to the sponsor:

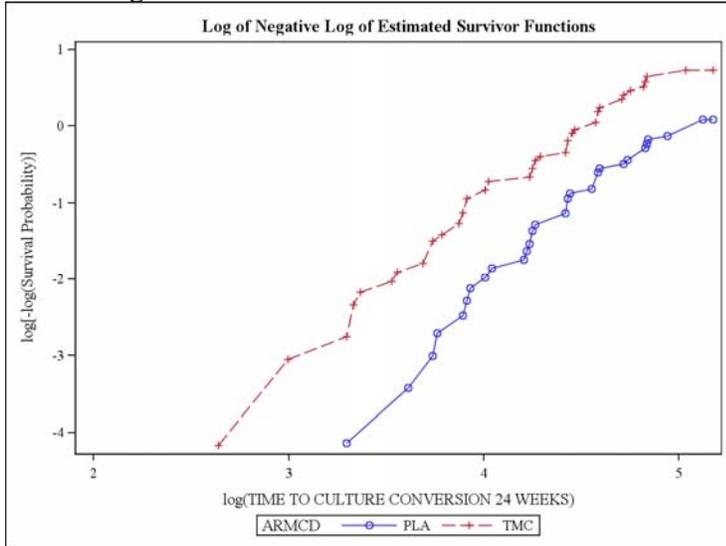
Comment on censoring subjects who drop out. Currently patients who drop out prior to finalizing their treatment with TMC207 or placebo will be censored at their last visit. We would be equally interested in an analysis that carries them forward as not converting through the 24 week treatment period.

We were interested in considering death and discontinuation as failure, consistent with the approach in calculating culture conversion rates. The sponsor’s first sensitivity analysis (interim Missing=Failure, end-censored) was in alignment with this consideration and all subjects who died, failed, or discontinued by week 24 was censored at day 182 in the time to conversion analysis. Therefore we conducted an analysis using the FDA mITT analysis population. The relative risk from a Cox proportional hazards model including Subject 4135 was 2.04, with a 95% CI [1.32, 3.14] and p-value of 0.0012. The culture conversion rates based on this endpoint was the same as in Table 21.

**Check the Assumption of Proportional Hazards**

The following plot shows the log of negative log of estimated survivor functions for the primary endpoint, which did not show a violation of the proportional hazard assumption.

**Figure 9: Log of negative log of estimated survival functions in the mITT population, Study C208 Stage 2**



**Time on Background Regimen by Treatment Group, Disposition Type, and Week 24 Culture Conversion Status**

The time on background regimen in weeks by treatment group, disposition type, and sputum culture conversion status at Week 24 is summarized in the following table. On average, the completed subjects had the longest time on background regimen (91.4 weeks and 92.7 weeks for subjects completing study with culture conversion in the TMC207 and placebo, respectively). Discontinued subjects had a shorter time on the background regimen than ongoing subjects. In addition, discontinued subjects with culture conversion had a longer time on background regimen than those with no culture conversion in each treatment group.

**Table 22: Time on background regimen in weeks by treatment group, disposition type, and culture conversion at Week 24 in the ITT population, Study C208 Stage 2**

	TMC207 N=79		Placebo N=81	
	Conversion	No Conversion	Conversion	No Conversion
<b>Completed</b>				
N	17	1	16	4
Mean (SD)	91.4 (19.8)	106	92.7 (27.1)	99.7 (12.2)
[Range]	[26.0, 116.0]		[26.1, 124.9]	[87.6, 111.9]
<b>Discontinued</b>				
N	8	19	6	21*
Mean (SD)	44.6 (21.7)	23.2 (30.8)	48.0 (32.7)	27.0 (23.4)
[Range]	[18.6, 73.0]	[0.0, 105.0]	[19.1, 99.0]	[2.4, 97.1]
<b>Ongoing</b>				
N	31	3	22	8
Mean (SD)	69.8 (23.3)	72.7 (40.2)	65.4 (26.2)	90.9 (17.3)
[Range]	[27.3, 108.3]	[26.3, 96.0]	[17.6, 105.0]	[65.1, 118.1]
<b>Rollover</b>				
N				1
Mean				64.7

\*additional 3 subjects had missing values

### Culture Conversion Rate by Compliance

The following two tables show the conversion status at Week 24 by treatment compliance status in the investigational stage (first two weeks and Weeks 3-24). Compliance was defined by the percentage of number of doses taken during the actual observation period for each subject (i.e. actual number of doses taken divided by planned number of doses during the observation period). Note compliance is not the same as the total number of doses taken, nor duration of treatment.

In the first two weeks, 61 and 62 subjects in the TMC207 and Placebo groups had 100% compliance and only a few subjects were in other compliance categories. Therefore, it is not possible to compare the effect of compliance in the first two weeks on culture conversion in each treatment group. Compliance seems not related with disposition type (completed, ongoing, discontinued, rollover).

In Weeks 3 to 24, only 7 and 10 subjects in the TMC207 and placebo took less than 95% of doses. When the compliance rates were higher than 80%, TMC207 showed a consistent treatment result. Discontinued subjects were less likely to have 100% or higher compliance.

Since the sample size was small, it is not worthwhile to tabulate the conversion rates by compliance and disposition type.

**Table 23: Culture conversion at Week 24 by compliance during Weeks 1 to 2 in the mITT population, Study C208 Stage 2**

<b>COMPLIANCE</b> <b>First two weeks</b>	<b>TMC207</b>	<b>Placebo</b>
<b>100%</b>	48/61 (78.69%)	37/62 (59.68%)
<b>80% to 95%</b>	4/4 (100%)	1/2 (50%)
<b>50% to &lt;80%</b>	0/1	0/2
<b>Total</b>	52/66	38/66

**Table 24: Culture conversion at Week 24 by compliance during Weeks 3 to 24 in the mITT population, Study C208 Stage 2**

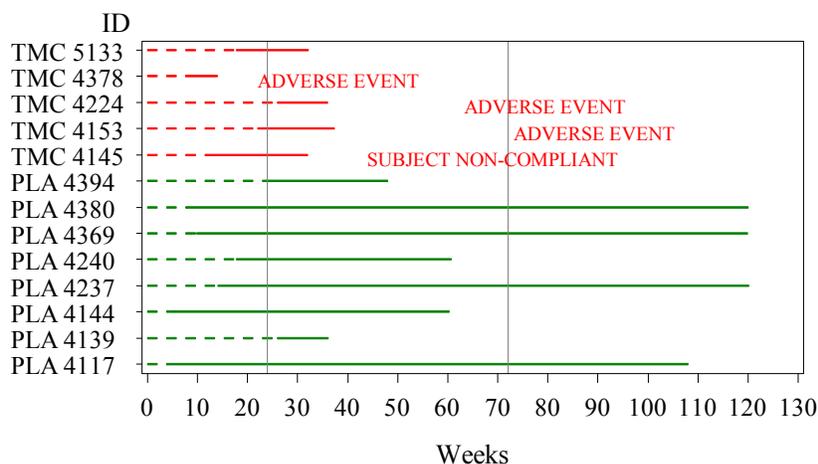
<b>COMPLIANCE</b> <b>Weeks 3 to 24</b>	<b>TMC207</b>	<b>Placebo</b>
<b>&lt;50%</b>	0	0/2
<b>50% to &lt;80%</b>	0/1	0/2
<b>80% to &lt;95%</b>	4/6 (66.67%)	2/6 (33.33%)
<b>95% to &lt;100%</b>	9/13 (69.23%)	2/6 (33.33%)
<b>100%</b>	15/17 (88.24%)	16/23 (69.57%)
<b>&gt;100% to 105%</b>	22/25 (88.00%)	18/24 (75.00%)
<b>&gt; 105%</b>	2/3 (66.67%)	0/1
<b>Total</b>	52/65	38/64

One TMC207 subject and two placebo subjects had missing compliance values.

### **Additional Analyses with Relapsed Subjects in Study C208 Stage 2**

The time from onset of treatment to culture conversion (broken line) and time from culture conversion to relapse (solid line) in the mITT population is shown in the following figure.

**Figure 10: Time to culture conversion and time from culture conversion to relapse for subjects with relapse in the mITT population, Study C208 Stage 2**



As can be seen from the figure, the subjects in the placebo group appear to take a longer time from culture conversion to relapse than those in the TMC207 group. However, the four subjects who relapsed at Week 108 or Week 120 in the placebo group were based on only one positive result at the last visit with microbiological assessment rather than two positive culture results. The results could have been overruled if more visits had been available and if the subsequent results were negative. If these four subjects were excluded, the two treatment arms become more comparable with respect to relapse with 5 relapses on TMC207 and 4 on placebo.

The relapse definition did not require culture conversion at either or both of Week 24 or Week 72. Not all subjects with relapse were culture converted at either Weeks 24 or 72 or both visits. Table 25 shows the culture conversion status at Week 24 and 72 for those relapsed subjects. Two subjects on TMC207 (4224 and 4378) and 1 subject on placebo (4139) were not culture negative at Week 24 or 72, but were converted at other times. Subject 4224 was culture negative at Weeks 28 and 32 and considered as relapse at Week 32; Subject 4378 in the TMC207 was culture negative at Weeks 8, 10, 12; then was positive until dropout at Week 21, considered as relapse at Week 14. Both subjects had a censored conversion time of 22 weeks (155 days) in the primary analysis.

Time on background regimen by treatment group for relapsed subjects is shown in Table 26. As more subjects in the TMC207 group discontinued, the average time on background was much shorter.

**Table 25: Culture conversion status at Week 24 and 72 for those subjects with relapse, Study 208 Stage 2**

	Conversion		TMC207	Placebo
	Week 24	Week 72		
<b>All</b>	No	No	2*	1†
	Yes	No	3	3
	Yes	Yes		4
<b>Disposition type</b>				
Completed	Yes	No		1
	Yes	Yes		4
Discontinued	No	No	2*	
	Yes	No	2	
Ongoing	No	No		1†
	Yes	No	1	2
<b>Total</b>			5	8

\*Those 2 subjects did not have microbiological results at Week 24 visit.

†Subject 4139 described in the text above.

**Table 26: Time on background regimen in weeks for relapsed subjects by treatment group, Study C208 Stage 2**

Time on Background Regimen	TMC207	Placebo
N	5	8
Mean (SD)	53.7 (24.5)	79.3 (33.9)
[Range]	[20.1, 76.3]	[26.1, 115.7]

### Additional Analysis of Sputum Culture Conversion from Week 24 to Week 72

Since the treatment phase was 24 weeks, we explored the proportion of subjects who had no positive culture results from Week 24 to Week 72 which was the end of the complete data collection for the NDA submission. In the sponsor's analysis, two positive culture results were needed to overrule a culture conversion. We did an analysis where even one positive result will overrule a culture conversion, a more strict definition. In this analysis, if a subject was culture converted by week 24, there were four categories for the period from Week 26 to Week 72 (the first visit after Week 24 is at Week 26):

- No positive culture among available visits from week 26 to 72, including unscheduled visits.
- Positive culture: any positive culture from the period
- Discontinuation with negative culture
- No data available

The following table shows the results of this analysis. The first row is the numbers of treatment failures, those who did not culture convert or who discontinued by Week 24. We will focus on

the results for those who converted by Week 24. More subjects in the TMC207 group remained culture negative. The number of subjects with positive culture in the TMC207 group was smaller. Five subjects (including 1 death) in the TMC207 group discontinued with negative culture.

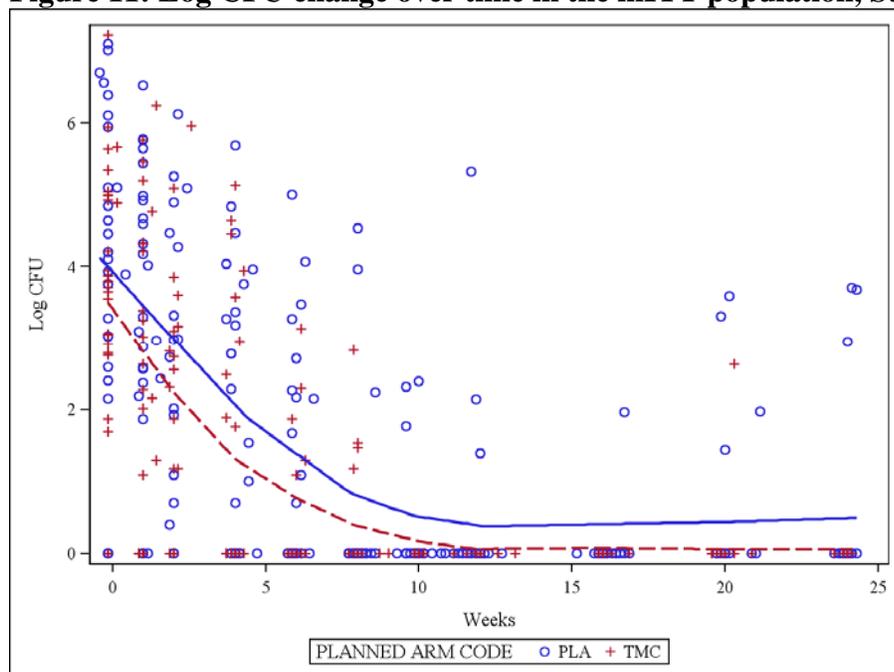
**Table 27: Sputum Culture Results from Week 26 to Week 72 in mITT population, Study C208 Stage 2**

	<b>TMC207 N=66</b>	<b>Placebo N=66</b>
No conversion at Week 24	14	28
Culture conversion at Week 24	52	38
No positive culture	37	18
$\geq 1$ positive culture	10	16
Discontinued with all negative culture results	5 (1 death)	2
No data available	0	2

### Log CFU Change over Time

$\text{Log}_{10}\text{CFU}$  and Loess smooth curves are plotted in the following figure (red dash line for TMC207). At baseline, the TMC207 group had a lower mean  $\text{log}_{10}\text{CFU}$  value, although the difference was not statistically significant. As time increased, the difference remained during the entire investigational treatment period. Since Week 10, all subjects except for one subject in the TMC207 groups had 0 CFU (so  $\text{Log}_{10}\text{CFU}$  was coded as 0). The plot looks slightly different from the sponsor's plot of means and SDs over time, because we used all available data, including 0 values.

**Figure 11: Log CFU change over time in the mITT population, Study C208 Stage 2**



The selected sites for CFU counts were South Africa 1 and 2. The majority of subjects from the two sites had CFU data. A logistic regression of culture conversion at Week 24 on  $\log_{10}$ CFU and treatment group did not show any significant results.

The culture conversion rates at Week 24 by whether or not a subject had baseline CFU data in the mITT population are shown in the following table. Among subjects with baseline CFU available, there was no statistically significant difference in culture conversion rates at Week 24 between the two treatment groups. This might explain why there was no difference in  $\log_{10}$ CFU change over time between the two treatment groups. Among those subjects without baseline CFU available, there was a statistically significant difference (Chi-square test p-value 0.002). Again, among those with CFU data in South Africa 2, a higher conversion rate was observed in the placebo group.

**Figure 12. Culture conversion rates at week 24 by presence of baseline CFU in the mITT population, Study C208 State 2**

	TMC207	Placebo
<b>All</b>		
Yes	18/25 (72%)	17/25 (68%)
No	34/41 (82.9%)	21/41 (51.2%)
<b>South Africa 1</b>		
Yes	10/13 (76.9%)	7/14 (50%)
No	1/1	0/3
<b>South Africa 2</b>		
Yes	8/12 (66.7%)	10/11 (90.9%)
No	1/1	1/2

**Figure 13. Kaplan-Meier curves for culture conversion by presence of baseline CFU in the mITT population, Study C208 State 2**

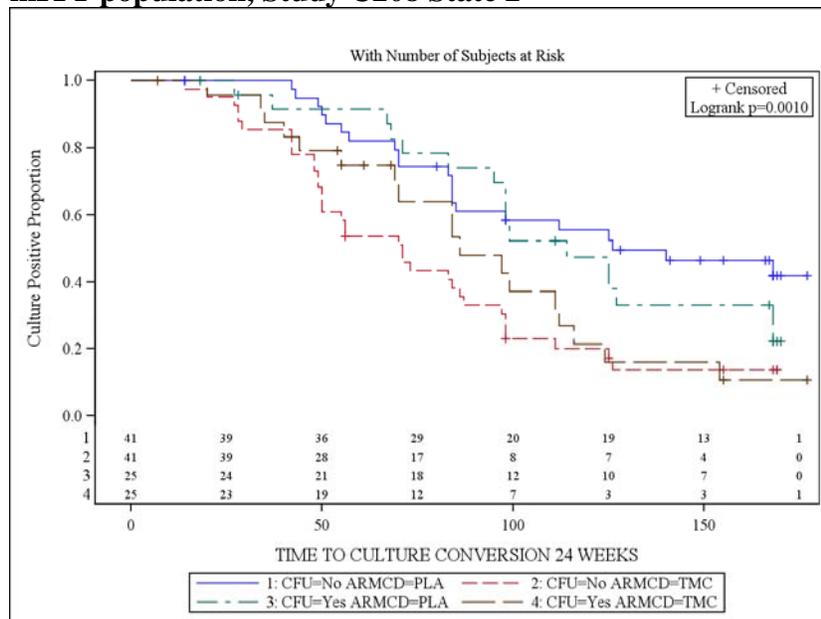


Figure 13 shows the Kaplan-Meier curves for the primary endpoint by presence of baseline CFU and treatment group. Among those with CFU counts, the difference in culture conversion between the two treatment groups was not as big as that among those without CFU. Overall, a log-rank test shows a statistically significant difference among these four groups.

The log<sub>10</sub>CFU data for two South Africa regions are shown in the following table. At baseline, the log<sub>10</sub>CFU means were slightly higher in the placebo group for the two regions.

**Table 28: Mean (SD) and sample size (N) of Log<sub>10</sub>CFU for two South Africa regions, Study C208 Stage 2**

	<b>TMC207</b>	<b>Placebo</b>
South Africa 1	3.3 (1.8) 13	3.4 (2.3) 14
South Africa 2	4.3 (1.5) 13	5.1 (1.4) 11

### **Culture Conversion at Week 24 by baseline MIC**

Baseline minimal inhibitory concentration (MIC) values to TMC207 determined in solid medium (Agar proportion method) were available for 114 subjects in the mITT population, 50 of which had a value of 0.06 ug/mL, 45 of which had a value not greater than 0.03 ug/mL, and 16 of which had values of 0.12, 0.24, or 0.48 ug/mL. The following table shows the Week 24 culture conversion rates by baseline MIC. The distribution of MIC values was balanced in the two treatment groups. TMC207 worked well compared to placebo among subjects with a MIC less than 0.06 ug/mL, but was similar to placebo among subjects with MIC ≥0.06 ug/mL.

**Table 29: Culture conversion rate at Week 24 by baseline minimal inhibitory concentration in solid medium (Agar) in the mITT population, Study C208 Stage 2**

<b>MIC (ug/mL)</b>	<b>TMC207</b>	<b>Placebo</b>
<0.06	21/23 (91.3%)	10/22 (45.5%)
≥0.06	22/34 (64.7%)	21/35 (60.0%)
Missing	9/9 (100%)	7/9 (77.8%)

There appears to be no imbalance in MIC to TMC207 at baseline by region.

Results for TMC207 MIC determination (liquid REMA method) at baseline were available for 112 of the 132 subjects (84.8%) in the mITT population. The culture conversion rates were not so clearly correlated with baseline liquid MIC values in the two treatment groups. In all MIC categories, TMC207 showed a consistent treatment effect.

**Table 30: Culture conversion rate at Week 24 by baseline minimal inhibitory concentration in liquid medium (REMA) in the mITT population, Study C208 Stage 2**

<b>MIC (ug/mL)</b>	<b>TMC207</b>	<b>Placebo</b>
≤0.0156	11/13 (84.6%)	9/16 (56.3%)
=0.0313	20/28 (71.4%)	15/23 (65.2%)
≥0.0625	13/16 (81.3%)	6/15 (40.0%)
Missing	8/9 (88.9%)	8/12 (66.7%)

The Pearson correlation coefficient between the baseline values from the Agar and REMA methods was 0.54 with a p-value < 0.0001, indicating a statistically significant but moderate correlation.

### Body Temperature in Study C208 Stage 2

At baseline, mean body temperature was 36.54°C and 36.60°C in the TMC207 and placebo group, respectively, with a range of 34.8°C to 38.4°C in the TMC207 group and of 35.0°C to 38.0°C in the placebo group. One and five subjects had a temperature >37.5 °C at baseline in the TMC207 group (38°C) and placebo group (37.6°C for 2 subjects and 38°C for 3 subjects), slightly different from the results in the study report. No obvious difference was seen in temperature change over time.

### 3.3 Evaluation of Safety

In this review we only reviewed safety data from Study C208 Stage 2. For safety evaluation of Study C208 Stage 1 and Study C209, please see the medical review.

#### Summary of Adverse Events

The numbers of subjects with any AEs are listed in the following table. For safety analysis, investigational treatment phase was from date of first TMC207 or placebo intake until date of last TMC207 or placebo intake + 1 week; overall treatment phase was from date of first TMC207 or placebo intake until date of database cut-off (10 June 2011) (for rollover: until last day before switch, for discontinuation: until date of last medication intake (TMC207, placebo or BR) + 1 week). All events were coded using the Medical Dictionary for Regulatory Activity (MedDRA version 10.0). The sponsor did not conduct any statistical comparisons using statistical tests such as Fisher's exact test or Chi-square test.

**Table 31: Summary of numbers of subjects with adverse events in the ITT population, Study C208 Stage 2**

	TMC207		Placebo	
	Investigational treatment phase N = 79	Overall treatment phase N = 79	Investigational treatment phase N = 81	Overall treatment phase N = 81
Any AE	77 (97.5)	78 (98.7)	77 (95.1)	79 (97.5)
Any AE at least grade 2	51 (64.6)	63 (79.7)	56 (69.1)	65 (80.2)
Any AE at least grade 3	22 (27.8)	34 (43.0)	19 (23.5)	29 (35.8)
Any AE grade 4	5 (6.3)	11 (13.9)	3 (3.7)	6 (7.4)
Any SAE	6 (7.6)	19 (24.1)	1 (1.2)	15 (18.5)
Any AE leading to a permanent stop of any study medication	4 (5.1)	4 (5.1)	5 (6.2)	5 (6.2)
Any AE of at least grade 3 or leading to a permanent stop of any study medication or an SAE	22 (27.8)	34 (43.0)	21 (25.9)	31 (38.3)

Almost all subjects experienced at least one AE. In the investigational treatment phase, more than 64% of subjects in each group experienced AEs with at least grade 2. The numbers of subjects with at least grade 3 or with grade 4 were balanced between the two treatment groups. However, more subjects in the TMC207 groups experienced serious AEs (SAEs), especially in the investigational treatment phase. The SAEs were alcohol intoxication (fatal), suicidal thoughts, haemoptysis, right bronchiectasis and right (lung) empyema worsening, right ear severe conductive hearing loss and left ear mild conductive hearing loss in the TMC207 group, and spontaneous abortion in the placebo group.

### Adverse Events by Body System or Organ Class

The following table shows the number of subjects with adverse events by body system or organ class in >5% subjects in overall treatment phase. In the investigational treatment phase, more subjects in the TMC207 than in the placebo group had blood and lymphatic system disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, nervous system disorders, and respiratory, thoracic and mediastinal disorders. But the differences were not statistically significant (the p-value for nervous system disorder was 0.05 from Chi-square test and 0.065 from the Fisher's exact test).

**Table 32: Number of subjects with adverse events by body system or organ class in the ITT population, Study C208 Stage 2**

	TMC207		Placebo	
	Investigational Treatment phase N=79	Overall treatment phase N=79	Investigational treatment phase N=81	Overall treatment phase N=81
Blood and lymphatic system disorders	8 (10.1)	11 (13.9)	4 (4.9)	6 (7.4)
Cardiac Disorders	5 (6.3)	6 (7.6)	8 (9.9)	13 (16.0)
Ear and labyrinth disorders	24 (30.4)	26 (32.9)	26 (32.1)	29 (35.8)
Eyes disorders	10 (12.7)	18 (22.8)	14 (17.3)	20 (24.7)
Gastrointestinal disorders	50 (63.3)	53 (67.1)	50 (61.7)	53 (65.4)
General disorders and administration site conditions	23 (29.1)	31 (39.2)	23 (28.4)	27 (33.3)
Immune system disorders	1 (1.3)	1 (1.3)	3 (3.7)	5 (6.2)
Infections and infestations	25 (31.6)	44 (55.7)	28 (34.6)	43 (53.1)
Injury, poisoning and procedural complications	5 (6.3)	11 (13.9)	8 (9.9)	15 (18.5)
Investigations	17 (21.5)	21 (26.6)	17 (21.0)	24 (29.6)
Metabolism and nutrition disorders	30 (38.0)	33 (41.8)	31 (38.3)	35 (43.2)
Musculoskeletal and connective tissue disorders	35 (44.3)	39 (49.4)	32 (39.5)	40 (49.4)

	TMC207		Placebo	
	Investigational Treatment phase N=79	Overall treatment phase N=79	Investigational treatment phase N=81	Overall treatment phase N=81
Nervous system disorders	32 (40.5)	39 (49.4)	21 (25.9)	32 (39.5)
Psychiatric disorders	15 (19.0)	17 (21.5)	11 (13.6)	17 (21.0)
Renal and urinary disorders	2 (2.5)	5 (6.3)	2 (2.5)	3 (3.7)
Reproductive system and breast disorders	7 (8.9)	11 (13.9)	10 (12.3)	15 (18.5)
Respiratory, thoracic and mediastinal disorders	25 (31.6)	29 (36.7)	23 (28.4)	35 (43.2)
Skin and subcutaneous tissue disorders	19 (24.1)	25 (31.6)	21 (25.9)	28 (34.6)
Vascular disorders	2 (2.5)	5 (6.3)	3 (3.7)	6 (7.4)

Due to the possible effect of TMC207 on ECG, we list the cardiac disorders in detail in the following table. It was noticed that there were 4 subjects in the TMC207 group, each with one of the following disorders in the investigational treatment phase: arrhythmia, atrioventricular block, bundle branch block left, or conduction disorders, but there were no subjects with these disorders in the placebo group. The numbers were too small to make meaningful conclusion. Medical reviewers have reviewed the safety data in detail.

**Table 33: Number of subjects with cardiac disorders in the ITT population, Study C208 Stage 2**

	TMC207		Placebo	
	Investigational treatment phase N=79	Overall treatment phase N=79	Investigational treatment phase N=81	Overall treatment phase N=81
<b>Cardiac Disorders n (%)</b>	<b>5 (6.3)</b>	<b>6 (7.6)</b>	<b>8 (9.9)</b>	<b>13 (16.0)</b>
Angina Pectoris	0	0	1	1
Arrhythmia	1	1	0	0
Arrhythmia supraventricular	0	0	1	1
Atrioventricular block	1	1	0	1
Bradycardia	0	0	0	2
Bundle branch block left	1	1	0	1
Conduction disorder	1	1	0	0
Palpitations	0	0	1	1
Sinus Bradycardia	0	0	1	1
Sinus Tachycardia	1	1	2	3
Tachycardia	0	1	2	3

Adverse events considered related to TB by the investigator were reported in 40.5% (32/79) of subjects in the TMC207 group and in 42.0% (34/81) in the placebo group during the investigational treatment phase; in 45.6% (36/79) of subjects in the TMC207 group and in 56.8% (46/81) in the placebo group in the overall treatment phase.

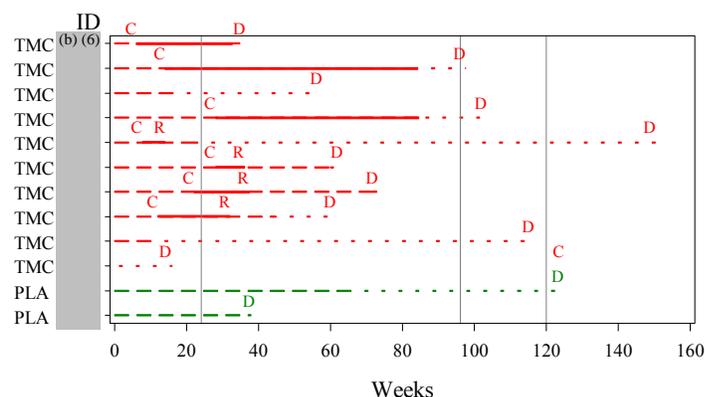
In the investigational phase, the most frequently reported TB-related AEs were hemoptysis (17.7% (14/79) and 11.1% (9/81) of subjects in the TMC207 and placebo group, respectively), chest pain (7.6% (6/79) and 4.9% (4/81), respectively), pyrexia (6.3% (5/79) and 6.2% (5/81), respectively), and cough (5.1% (4/79) and 2.5% (2/81), respectively). All other TB-related AEs occurred in less than 5.0% of subjects in the TMC207 group during the Investigational Treatment phase.

## Death

Four subjects (5.1%) in the TMC207 group and one subject (1.2%) in the placebo group died during the trial in the original submission. Causes of death were coded as tuberculosis (2 subjects; verbatim “worsening of TB condition” and “MDR-TB relapse”), alcohol poisoning, hepatitis and hepatic cirrhosis (1 subject each) in the TMC207 group and hemoptysis in the subject in the placebo group.

Based on a 4-month safety update submitted on October, 25, 2012, there were 10 deaths in the TMC207 group and 2 deaths in the placebo group in Stage 2. The difference of 10.2% (an exact 95% confidence interval [2.1%, 19.7%]) was statistically significant with a Fisher’s exact p-value 0.0167. The following figure shows the time of culture conversion, relapse, and death for these 12 deaths. The dashed line represents the time when a subject was culture positive, the solid line represents time as being culture negative. C’s refer to conversion, R’s refer to relapses and D’s refer to deaths. The dotted lines signify the time a subject has discontinued the trial. Note that 4 of the TMC207 deaths occurred after a subject had relapsed. All but one subject (ID 4464) were in the mITT population. We explored the race for these deaths and found 7 out of 12 were listed as “other” race. Among these 7 deaths, 5 were in the TMC207 group. For more information on causes of death, please see the medical review.

**Figure 14: Time of culture conversion, relapse, and death for 12 deaths in C208**



### 3.4 Benefit-Risk Assessment

TMC207 is a new class of medication for potential use on top of an optimized regimen in the treatment of MDR-TB. TMC207 has showed a significant treatment effect from Study C208 Stage 2 and the results from Study C208 Stage 1 and Study C209 are supportive. Considering MDR-TB is a severe medical condition with profound public implications (transmission of MDR-TB), the benefit of employing this medication is obvious. However, there was a statistically elevated mortality risk observed in Study C208 Stage 2 (10/79 (12.7%) versus 2/81 (2.5%)). The difference of 10.2% (an exact 95% confidence interval [2.1%, 19.7%]) was statistically significant with a Fisher's exact p-value 0.0167. If this drug is approved, this major safety concern should be clearly labeled.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

The majority of the subgroup analyses will be done for Study C208 Stage 2, but not for Stage 1 and C209 due to the small sample size for Stage 1 and single treatment group for Study C209. The following table shows the culture conversion rates at Week 24 by gender. The trend was similar across the two subgroups with the males reaching statistical significance. The possible reason is that the sample size for female was small.

**Table 34: Culture conversion rates at Week 24 by gender in the mITT Population, Study C208 Stage 2**

	<b>TMC207</b>	<b>Placebo</b>	<b>Difference [95% CI] p-value</b>
Male	35/45 (77.8%)	23/40 (57.5%)	20.3% [0.7%, 39.8%] <b>0.0450</b>
Female	17/21 (81.0%)	15/26 (57.7%)	23.3% [-2.1%, 48.6%] 0.1208*

\* Exact method.

The following table shows the culture conversion rates at Week 24 by race. In all races, except for Black, TMC207 demonstrated a consistently higher culture conversion rate than the placebo, although the treatment effects varied among difference races. Among Hispanic subjects and subjected with "Other" race, the treatment effect was statistically significant. In Black subjects, the two treatment groups had similar conversion rates.

*Comment: In Stage 2 of this study, Black subjects from one site (one investigator) had a lower conversion rates at Week 24 in the TMC207 group than in the placebo group, as shown in the reviewer's subgroup analysis section. In this stage, in the same center 87.5% (7/8) and 71.4% (5/7) of Black subjects in the TMC207 and placebo groups had culture conversion at Week 24. The direction of treatment effect in this subgroup was in agreement with the overall treatment effect. However the sample sizes for Black subjects from this site were small.*

**Table 35: Culture conversion rates at Week 24 by race in the mITT population, Study C208 Stage 2**

	<b>TMC207</b>	<b>Placebo</b>	<b>Difference [95% CI] p-value</b>
Black	17/24 (70.8%)	18/25 (72.0%)	-1.2% [-26.5%, 24.1%] 0.93
Caucasian/White	4/6 (66.7%)	4/8 (50.0%)	16.7% [-37.8%, 64.1%] 0.64*
Hispanic	12/12 (100%)	5/10 (50.0%)	50.0% [15.0%, 81.3%] <b>0.006*</b>
Oriental/Asian	8/9 (88.9%)	5/6 (83.3%)	5.6% [-36.3%, 53.0%] 0.89*
Other	11/15 (73.3%)	6/17 (35.3%)	38.0% [2.1%, 67.7%] <b>0.037*</b>

\*Exact method

As shown in the following table, Black subjects from South Africa-2 region had a numerically much lower culture conversion rate in the TMC207 group than in the placebo group. In Black subjects from other regions TMC207 showed a numerically consistent treatment effect. However these differences were not statistically significant. All Black subjects in South Africa 2 were treated by one doctor. The reason for this treatment effect discrepancy is unclear. It is noticed that the sample size in each group was small. Further investigations by demographic factors, HIV status, TB types, and lung cavitation did not provide any discernable patterns. The high conversion rate in this placebo group contributed to a smaller overall treatment effect between the two treatment groups. Therefore, the result was not concerning to this reviewer.

**Table 36: Conversion Rates at Week 24 in Black Subjects in the mITT population, Study C208 Stage 2**

	<b>TMC207</b>	<b>Placebo</b>
South-Africa 2	8/12 (66.7%)	11/12 (91.7%)
Black in other regions	9/12 (75.0%)	7/13 (53.8%)

One doctor from 'South Africa-2'

The following table shows the culture conversion rates by region in the mITT population. Except for Asia and South Africa 2 regions, TMC207 showed consistent results at least numerically if not statistically. However, in South-Africa 2, the culture conversion rate was numerically higher in the placebo group than in the TMC207 group. Twenty-four subjects (12 in each group) in this region were Black. As discussed before, TMC 207 had a low conversion rate among Black subjects in this center.

**Table 37: Culture conversion rate at Week 24 by pooled center in the mITT population, Study C208 Stage 2**

<b>TB type</b>	<b>TMC207</b>	<b>Placebo</b>	<b>Difference [exact 95% CI] exact p-value</b>
Asia	8/8 (100%)	4/4 (100%)	
Eastern Europe	3/6 (50.0%)	3/7 (42.9%)	7.1% [-50.2%, 59.2%] 0.93
South Africa 1	11/14 (78.6%)	7/17 (41.2%)	37.4% [1.3%, 66.7%] <b>0.042</b>
South Africa 2	9/13 (69.2%)	11/13 (84.6%)	-15.4% [-48.5%, 19.5%] 0.53
South Africa Other	7/10 (70.0%)	6/12 (50%)	20.0% [-23.4%, 58.4%] 0.46
South America	14/15 (93.3%)	7/13 (53.9%)	39.5% [6.6%, 69.0%] <b>0.019</b>

One doctor from South Africa-1 and one doctor from South Africa-2

HIV status by region is listed in the following table. All HIV positive subjects were from South Africa, and in South Africa 2, there was a higher proportion of HIV positive subjects in the placebo group than in the TMC207 group.

**Table 38: HIV status by region in mITT population, Study C208 Stage 2**

Region	TMC207	Placebo
South Africa 1	0/14	1/17 (6%)
South Africa 2	2/13 (15%)	8/13 (62%)
South Africa Other	3/10 (30%)	5/12 (42%)

As discussed previously, there were more HIV positive subjects in the placebo group, and almost all subjects in this region were Black subjects. The sample size was small and all these factors were confounded and it is difficult to determine which of these factors if any can explain the observed difference in South Africa 2.

The following table shows the culture conversion rates at Week 24 by age group. The age group 30 to <50 years had a higher difference between the TMC207 and Placebo groups. In all age groups, TMC207 showed consistently better results than the placebo.

**Table 39: Culture conversion rate at Week 24 by pooled center in the mITT population, Study C208 Stage 2**

Age group in yrs	TMC207	Placebo	Difference [95% CI] p-value
18 to <30	22/29 (75.9%)	17/28 (60.7%)	15.1% [-8.7%, 39.0%] 0.22
30 to <50	20/23 (87.0%)	16/30 (53.3%)	33.6% [11.1%, 56.2%] 0.009*
50 to 65	10/14 (71.4%)	5/8 (62.5%)	8.9% [-31.4%, 50.9%] 0.79
<b>Sponsor's analysis</b>			
≤45	39/47 (83.0%)	32/54 (59.3%)	
>45 to 65	13/19 (68.4%)	6/12 (50.0%)	

\*Exact method.

#### **Additional Analyses with Relapsed Subjects in Study C208 Stage 2**

The following table shows the relapses by age and race. Eight relapses were in age group 30 to <50 years of age. Seven relapses were among Black subjects.

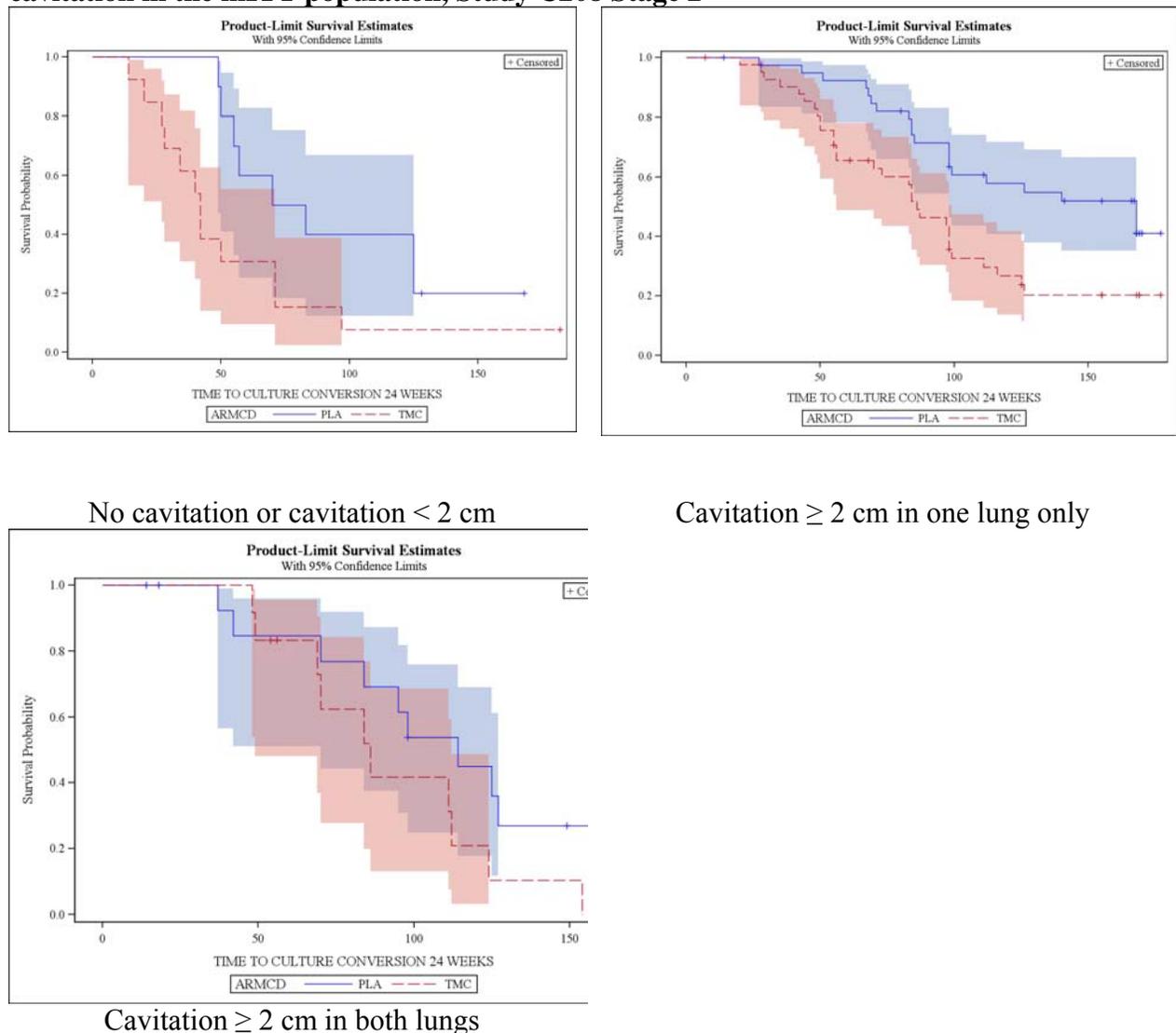
**Table 40: Age and Race for subjects with relapse, Study C208 Stage 2**

	TMC207	Placebo
Age		
<30	1	1
30 to <50	3	5
50 to 65	1	2
Race		
Black	2	5
Oriental/Asian	1	0
Other (non Caucasian/White or Hispanic)	2	3

## 4.2 Other Special/Subgroup Populations

We summarized the sponsor's additional subgroup analyses and conducted additional subgroup analyses for Study C208 Stage 2. The following figure shows the Kaplan-Meier survival curves by cavitation and treatment group in the mITT population. The difference in time to culture conversion between the two treatment groups was more visible among subjects with cavitation  $\geq 2$  cm in one lung only. The p-values from the Log-rank test were 0.0057, 0.0046, and 0.1311 for the three cavitation categories, no cavitation or cavitation  $< 2$  cm, cavitation  $\geq 2$  cm in one lung only, and cavitation  $\geq 2$  cm in both lungs, respectively. TMC207 demonstrated a significant treatment effect in subjects with no cavitation or cavitation  $< 2$  cm, or with cavitation  $\geq 2$  cm in one lung only. But the treatment effect in subjects with cavitation  $\geq 2$  cm in both lungs was not statistically significant.

**Figure 15: Kaplan-Meier survival curves for culture conversion by Week 24 by lung cavitation in the mITT population, Study C208 Stage 2**



The following table shows the culture conversion rates at Week 24 by cavitation type in the mITT population. The differences between the two treatment groups were not statistically significant for each lung cavitation type.

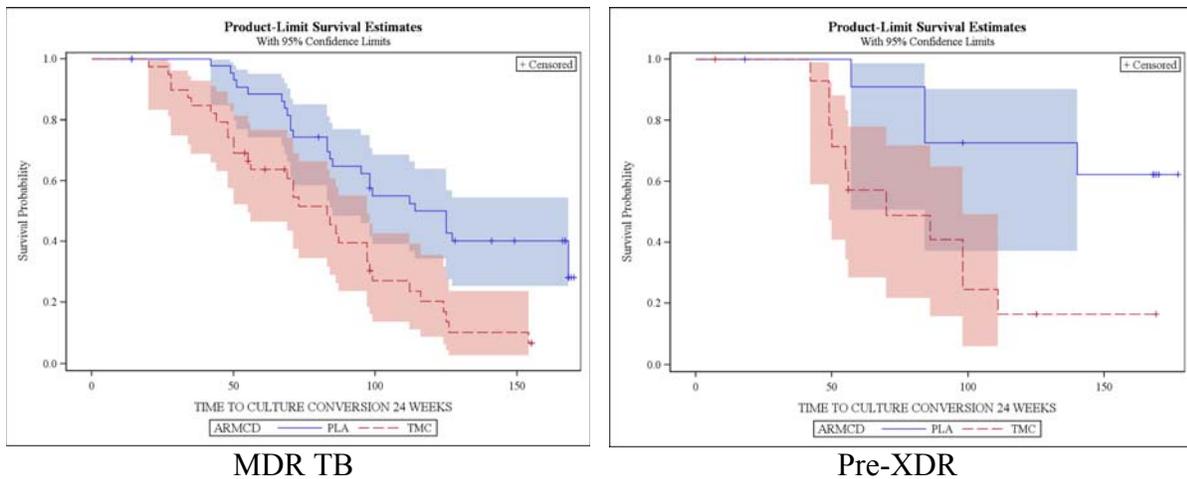
**Table 41: Culture conversion rates at Week 24 by lung cavitation in the mITT population, Study C208 Stage 2**

Lung cavitation	TMC207	Placebo	Difference [95% CI] p-value
No cavitations or cavitations < 2 cm	12/12 (100%)	8/10 (80.0%)	20.0% [-10.8%, 55.6%] 0.17*
Cavitations >= 2 cm in one lung only	30/42 (71.4%)	21/41 (51.2%)	20.2% [-0.3%, 40.7%] 0.059
Cavitations >= 2 cm in both lungs	10/12 (83.3%)	9/15 (60%)	23.3% [-13.7%, 56.5%] 0.24*

\*Exact method.

The following subgroup analysis shows the time to culture conversion by TB-type (MDR and pre-XDR TB) in the mITT population. The p-value from the Log-rank test was 0.0004 and 0.0097, respectively. TMC207 shows a consistent treatment effect in subjects with MDR-TB or pre-XDR-TB.

**Figure 16: Kaplan-Meier survival curves for culture conversion by Week 24 by baseline TB in the mITT population, Study C208 Stage 2**



Sample sizes for DS-TB and Pre-XDR were too small for Kaplan-Meier plotting.

The following table shows the culture conversion rates at Week 24 by baseline TB type. Again, the difference in culture conversion rates was statistically significant in MDR or pre-XDR TB subjects.

**Table 42: Culture conversion rates at Week 24 by baseline TB type in the mITT population, Study C208 Stage 2**

<b>TB type</b>	<b>TMC207</b>	<b>Placebo</b>	<b>Difference [95% CI] p-value</b>
MDR	32/39 (82.1%)	28/45 (62.2%)	19.8% [1.2%, 38.4%] 0.0448
Pre-XDR	11/15 (73.3%)	4/12 (33.3%)	40.0% [0.6%, 70.8%] 0.0467*
Missing values	9/12 (66.7%)	6/9 (66.7%)	

\*Exact method. Missing values were considered as MDR-TB based on medical history.

Additionally, analyses by baseline TB type (DS, MDR, pre-XDR, XDR, missing) for the ITT population also showed consistent results; however, the numbers of subjects with drug susceptible and XDR-TB were too small to make meaningful comparisons. Failures could be due to microbiological failure to culture conversion or discontinuation by Week 24. The numbers of subjects with failures due to discontinuation by baseline TB type were as follows: in the TMC207 group 15 out of 20 failures were due to discontinuation (3, 7, 3, 1, and 1 in the DS, MDR, Pre-XDR, XDR, and Missing TB type subgroups; in the placebo group 17 out of 35 failures were due to discontinuation (2, 7, 2, and 6 in the DS, MDR, Pre-XDR, and Missing TB type subgroups). Note in the DS-TB subgroup, all failures on TMC207 were due to discontinuation and 2 out 3 failures in the placebo group were due to discontinuation.

**Figure 17: Culture conversion rates at Week 24 by baseline TB type in the ITT population, Study C208 Stage 2**

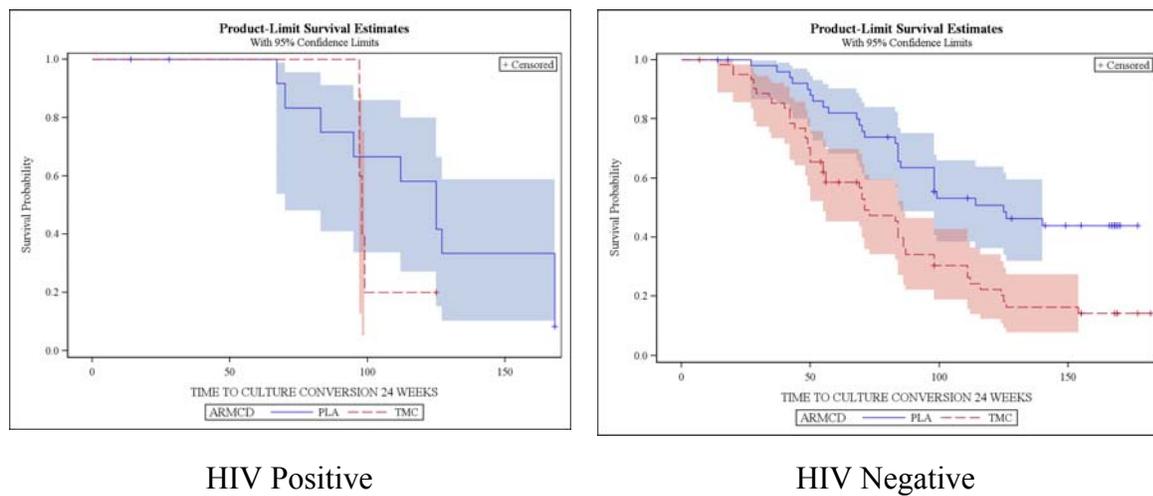
<b>TB type</b>	<b>TMC207</b>	<b>Placebo</b>
DS	1/4 (25.0%)	1/4 (25.0%)
MDR	32/40 (80.1%)	29/46 (63.0%)
Pre-XDR	12/16 (75.0%)	4/12 (33.3%)
XDR	2/3 (66.6%)	3/4 (25.0%)
Missing values*	12/16 (75.0%)	9/15 (60.0%)
Total	59/79 (74.7%)	46/81 (56.8%)

The following graphs show the survival curves by HIV status at baseline. The number of HIV positive subjects was too small to make a meaningful comparison. The p-value from the Log-rank test in HIV negative subjects in the mITT population was 0.0001.

The following table shows the culture conversion rates by HIV status at baseline. In the TMC207 group, the conversion rates were similar regardless of HIV status, though the sample size was very limited in HIV positive subjects. However, in the placebo group, HIV negative subjects had a lower conversion rate than HIV positive subjects. Therefore, the higher proportion of HIV negative subjects in the TMC207 (61/66 or 92.4%) group, compared with that in the placebo group (52/66, 78.8%) should not be a concern in assessment of TMC207 efficacy.

Among HIV negative patients, compared with the placebo group, the TMC207 group had a higher conversion rate. Among HIV positive, the conversion rates were similar. It is noticed that the sample size was small.

**Figure 18: Kaplan-Meier survival curves for culture conversion by Week 24 by baseline HIV status in the mITT population, Study C208 Stage 2**



**Table 43: Culture conversion rates at Week 24 by baseline HIV status in the mITT population, Study C208 Stage 2**

HIV status	TMC207	Placebo	Difference [95% CI] p-value
HIV negative	48/61 (78.7%)	27/52 (51.9%)	26.8% [9.7%, 43.8%] 0.0027
HIV positive	4/5 (80.0%)	11/14 (78.6%)	1.4% [-52.2%, 38.6%] 1*

\*Exact method.

Based on the protocol subjects were expected not to take antiviral treatment for HIV/AIDS. Therefore no additional analyses on antiviral treatment among HIV positive subjects were conducted.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

There are a few statistical issues in Study C208 Stage 2. The treatment effect in Black subjects in South Africa 2 was not shown at Week 24 culture conversion rate. The lack of treatment effect among Black subjects also affected the observed treatment effect in South Africa 2, because almost all subjects in this site were Black. However we noticed that the sample size in this group was small and we can not make a conclusion. The confounding of race, region, and HIV status could not be determined clearly from this study. The long-term treatment effect should be examined in detail in a future review of the final study report.

One subject with positive culture result at baseline was excluded from the mITT population because of no post-baseline culture results available. We conducted an additional analysis including this subject. The effect of this excluding on the overall estimate of treatment effect was minimal.

The definitions of primary endpoints were changed from the protocol to the statistical analysis plan. However, all changes were made prior to data lock and unblinding and this should not be a concern.

Another issue is the lack of complete study data. Study C208 was not completed with this NDA submission. A study report was submitted to the IND, but not included in this NDA. A full review of the final study will help to better understand the treatment effect, especially the long-term treatment effect and some effects in some subgroups, which can not be determined based on currently available data.

There was a statistically significant increase in mortality in the TMC207 group. Despite the observed treatment benefit in time to culture conversion, it did not lead to a benefit in patient survival. This was a major concern both for efficacy and safety.

## **5.2 Collective Evidence**

The two efficacy studies provided the following collective evidence:

- C208 demonstrated statistically significant treatment effects of TMC207 in the primary endpoints (time to sputum conversion) and culture conversion rates at corresponding time points (week 8 or 24) in both Stage 1 and 2.
- Treatment effects in Study C208 appear to be diminishing numerically over time.
- C209 efficacy results from Week 24 data were supportive. The median culture conversion time was 57 days and the conversation rate was 80%, comparable with the culture conversion rates observed in Study C208 Stage 2.
- There was a statistically elevated mortality risk in the Study C208 Stage 2.

## **5.3 Conclusions and Recommendations**

Based on the statistical review of this NDA, the efficacy in terms of a surrogate endpoint, sputum culture conversion, was supported by this pivotal study C208 and supportive study C209. There was a significantly elevated mortality risk in the TMC207 group. This should be considered in an approval decision and use of this regimen.

## **5.4 Labeling Recommendations**

As a statistically significantly increase mortality is observed and not well explained by available data, this message should be adequately conveyed in the labeling.

*Note that at the time of the writing of this review, the sponsor has completed study 208 stage 2 and has submitted the study report to the IND for this drug. This information along with the data should be submitted to the NDA either as a major amendment or a subsequent labeling supplement with clinical data in order to have the complete study results reported in the label.*

## 6 Appendix

### 6.1 Comparison of definition of endpoints in Study C208 Stage 2

The following table shows the similarities and differences among different efficacy endpoints and their corresponding analyses in Stage 2.

**Table 44: Comparisons of definition of endpoints, Study C208 Stage 2**

	Stage 2 Primary analysis	Interim Analyses		
		Primary	Sensitivity analysis	
			1 End-censored	2 No overruling
<b>Subjects with Week 24 complete information</b>				
Subjects with conversion	Time to culture conversion (2 consecutive negative cultures at least 25 days apart).			
Overruling conversion when followed by a confirmed positive result	Yes	Yes	Yes	Yes
Censoring time for Failures	Last MGIT visit	Day 182	Day 182	Day 182
<b>Discontinued subjects by Week 24</b>				
Time for discontinued subjects	Censored at last MGIT visit	Censored at last MGIT visit	Censored at Day 182	If culture converted at last MGIT visit: Time to culture conversion*  If not culture converted at last MGIT visit: Censored at last MGIT visit

\*The discontinuation information was not taken into account and culture conversion was evaluated based on microbiological information only: for a subject who converted but discontinued afterwards, the subject was considered converted and the actual time of conversion was used for analysis. Six additional subjects were considered as having culture conversion in this analysis.

### 6.2 Comparison of observed Week 24 time to culture conversion in Study C208 Stage 2

The sponsor conducted 4 analyses, the week 24 primary analysis, an update of this analysis referred to as interim primary, and two sensitivity analyses, Missing = Failure and one where a subject's last culture results was used (Sensitivity 2)."

We compared the different time-to-culture-conversion endpoints for Week 24. The following figure shows the differences in time to culture conversion in the mITT population between the Stage 2 primary endpoint, Week 24 interim primary endpoint, interim M=F endpoint, and interim sensitivity 2 endpoint.

There were changes for two responders (culture converters) in time to culture conversion between the primary Week 24 endpoint and the three interim time-to-conversion endpoints. For 2 responders the time to culture conversion was changed to a shorter time in the interim analysis; for Subject 4380 (placebo group) time to conversion shifts from 70 days in the primary efficacy analysis to 56 days in the interim Week 24 data selection of the current interim analysis. For Subject 4486 (TMC207 group) a shift from 84 days in the primary efficacy analysis to 72 days in the interim Week 24 data selection was noted. These subjects have samples with long times to growth of 42 days or longer for samples taken at Days 56 and 72, respectively, which might indicate that the sample was not a true positive. In the primary analysis this was considered positive, while in the interim analysis these samples were analyzed as negative.

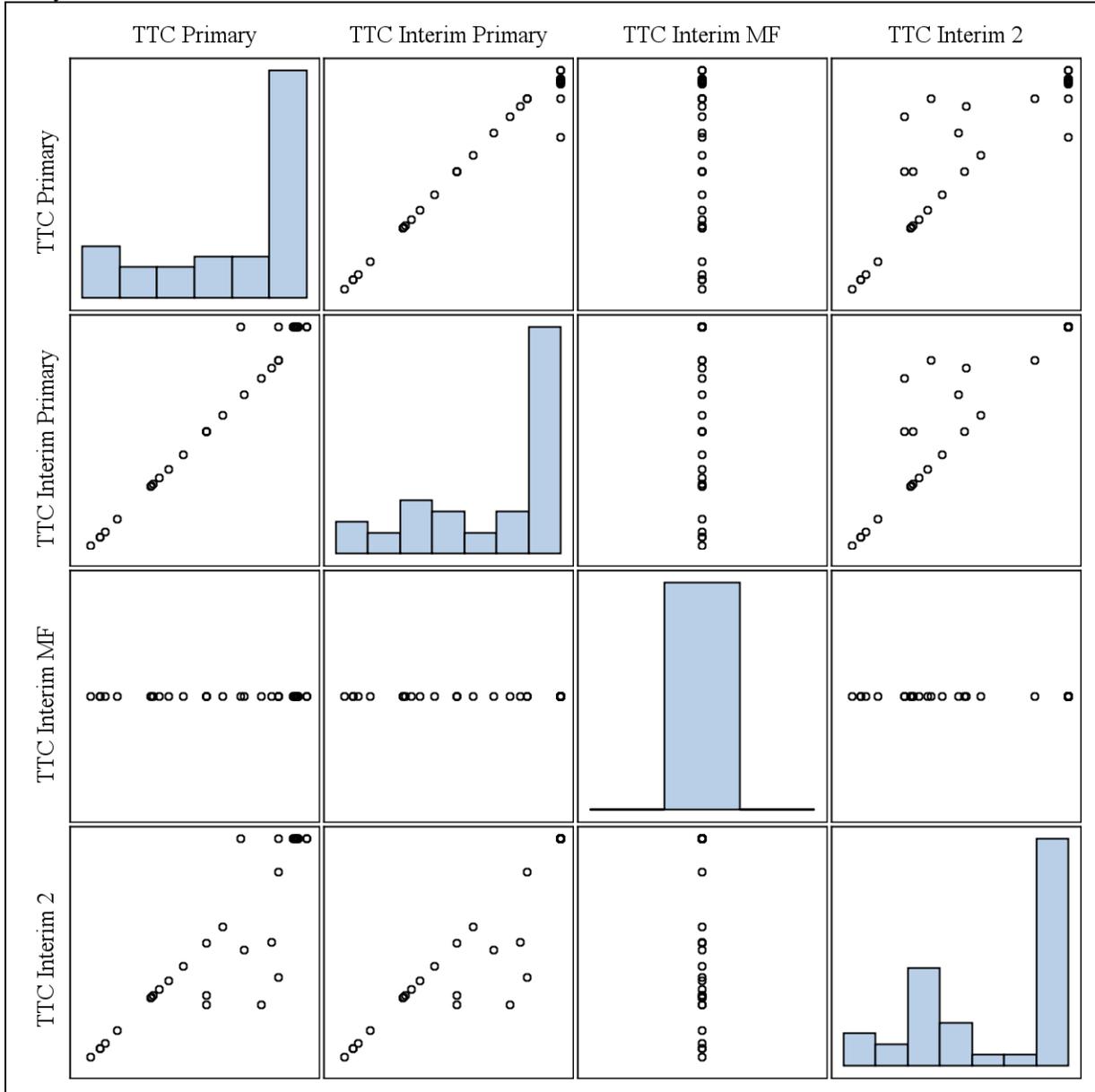
The main differences in those variables are for those non-responders (not converters), as shown in the following figure. A difference in time to culture conversion is noted for 21 non-responders between the Stage 2 primary endpoint (TTC Primary) and Interim Week 24 primary endpoint (TTC Interim Primary). The time to culture conversion for non-responders was the censored time for those subjects in the analysis. These were all subjects that were ongoing during the 24-week treatment period. In the primary analysis, these subjects were all censored at their last assessment visit up to week 24, while in the interim Week 24 analysis a more conservative approach considered by the sponsor was taken by censoring these subjects at the upper limit of the week 24 window (Day 182).

In addition, in interim Week 24 primary endpoint, only some, not all discontinued subjects (only 6 out of 18 in the placebo group and 5 out of 13 in the TMC207 group) had a censoring time of Day 182. Subjects who discontinued earlier than Week 24 were censored at the last MGIT time. One exception is Subject 4364 in the TMC207 group, who had a time of 125 days in the Stage 2 primary endpoint, but 182 in the interim Week 24 primary endpoint.

In Interim Week 24 M=F endpoint, not only discontinued subjects but all non-responders were censored at Day 182. Compared with Week 24 Primary endpoint, censoring time for 12 and 8 discontinued subjects in the placebo (IDs: 4118, 4124, 4130, 4248, 4293, 4366, 4376, 4390, 4453, 4460, 4475, and 4485) and TMC207 (IDs: 4039, 4041, 4101, 4127, 4143, 4238, 4246, and 4378) groups, respectively, was changed to Day 182.

Compared with the Stage 2 primary endpoint, 6 subjects (Subjects 4041 on TMC207 and Subjects 4376, 4390, 4453, 4475, and 4485 on placebo) had a shorter time in TTC Interim 2 because discontinuation was not considered and the time was based on microbiological results only; accordingly they became not censored for this sensitivity analysis.

**Figure 19:** Comparison of Week 24 time-to-culture-conversion endpoints in the primary analysis, mITT



Similarly for Interim Week 72 analyses, the censoring variable was the same for Week 72 interim primary and Week 72 interim M=F sensitivity analysis, but 19 subjects censored for the Week 72 primary analysis were not censored for Week 72 sensitivity analysis 2 and time to culture conversion in the sensitivity 2 analysis for those subjects was shorter.

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/s/  
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XIANBIN LI  
12/04/2012

KAREN M HIGGINS  
12/04/2012  
I concur.

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 204384

**Applicant:** Janssen

**Stamp Date:** 6/29/2012

**Drug Name:** TMC207  
(Bedaquiline)

**NDA/BLA Type:** NDA

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Subgroup analyses of time to culture/smear conversion and culture/smear conversion rates were conducted by extent of cavitation, pooled center (region), extent of resistance of tuberculosis strain, PZA susceptibility at baseline, and HIV status at baseline, etc; but not by gender, age, and race in the first submission. We requested this information on 7/19/2012 and received on 7/24/2012.  Phase IIb pooled safety subgroup analysis results are included.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?** \_\_\_ Yes \_\_\_

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

The following two studies are planned to be used for efficacy evaluation of this NDA:

1. Phase IIb Study C208 is a randomized, double-blind, placebo-controlled superiority trial with TMC207 in subjects with MDR-TB, which has been conducted in 2 consecutive stages with different subjects. Stage 1 was an exploratory stage. Stage 2 is an ongoing proof-of-efficacy stage. The primary efficacy endpoint was time to sputum culture conversion in MGIT during the 8-week (Stage 1) or 24-week (Stage 2) investigational treatment period (TMC207 or placebo in combination with background regimen).
2. Phase IIb Study C209 is a single-arm, open-label trial, which provides supportive data. The primary endpoint is time to culture conversion in MGIT during the 24-week investigational treatment period.

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/s/  
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XIANBIN LI  
07/25/2012

KAREN M HIGGINS  
07/26/2012