Janssen Research & Development

Clinical Study Report Synopsis
[TMC207-C209; Phase 2]

TMC207 (bedaquiline)

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- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Sirturo®
Name of Active Ingredient(s)	TMC207 (bedaquiline)

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Status: Approved

Date: 30 October 2013

Prepared by: Janssen Infectious Diseases-Diagnostics BVBA

Protocol No.: TMC207-TiDP13-C209

Title of Study: A Phase II, open-label trial with TMC207 as part of a multi-drug resistant tuberculosis (MDR-TB) treatment regimen in subjects with sputum smear-positive pulmonary infection with MDR-TB.

EudraCT Number: 2008-008444-25

NCT No.: NCT00910871

Clinical Registry No.: CR012352

Coordinating Investigator(s): [redacted], MD, [redacted] the Netherlands

Study Center(s): The study was conducted at 31 sites in 11 countries

Publication (Reference):

- Haxaire-Theeuwes M, the TMC207 Team, Diacon AH, et al, Phase 2 open-label trial of TMC207 in an MDR-TB treatment regimen [Abstract]. 42nd Union World Conference on Lung Health, Lille, France, October 2011; S57.
- Haxaire-Theeuwes M, the TMC207 Team, Diacon AH, et al, Use of bedaquiline (TMC207) for treatment of MDR-TB [Abstract]. 43nd Union World Conference on Lung Health, Kuala Lumpur, Malaysia, November 2012; S42

Study Period: date study initiated: 19-Aug-2009, date study completed: 07-February-2013

Phase of Development: Phase II

Objectives: The objectives of this study were:

- To evaluate safety, tolerability, and efficacy of TMC207 as part of a multi-drug regimen in the treatment of subjects with multidrug resistant (MDR)-tuberculosis (TB).
- To evaluate the pharmacokinetics (PK) of TMC207 and its primary metabolite M2, and pharmacokinetic/pharmacodynamic (PD) relationships for safety and efficacy.
- To explore the effect of TMC207 on the experience of TB symptoms as measured by the Tuberculosis Symptoms Profile (TSP), and to explore the measurement properties of the TSP.

Methodology:

This was a phase II, open-label, single-arm trial to evaluate the safety, tolerability, and efficacy of TMC207 as part of an individualized MDR-TB treatment regimen in subjects with pulmonary MDR-TB. MDR-TB is defined as infection with a strain of *Mycobacterium tuberculosis* that is resistant to at least both rifampin (RMP) and isoniazid (INH). Although the clinical definition of MDR-TB encompasses pre-extensively drug resistant (XDR)- and XDR-TB, in this document $MDR_{H\&R}$ will be used to refer to MDR excluding pre-XDR and XDR (eg, in descriptions of subgroups). Pre-XDR strains were defined as $MDR_{H\&R}$ strains with additional resistance to either any second-line injectable drug (kanamycin [KAN], amikacin [AMK], or capreomycin [CAP]) or any fluoroquinolone (FQ). XDR strains were defined as $MDR_{H\&R}$ strains with additional resistance to both a second-line injectable drug and a FQ.

This Clinical Study Report Synopsis presents data from the final analysis performed when all subjects had completed the study or had discontinued earlier.

Subjects received TMC207 for 24 weeks in combination with an individualized background regimen (BR) of antibacterial drugs used in the treatment of TB according to national and international guidelines and selected at the baseline visit. TMC207 dosage was 400 mg once daily (qd) for the first 2 weeks and 200 mg 3 times per week (tiw) for the following 22 weeks. Upon completion of the 24-week treatment with TMC207, all subjects continued to receive their BR under the care of their physician and in accordance with national TB program (NTP) treatment guidelines.

Safety, tolerability, and efficacy of treatment with TMC207 as part of an individualized MDR-TB treatment regimen were evaluated. Additionally, the PK of TMC207 and M2, and PK/PD relationships for safety and efficacy were assessed. A pharmacokinetic substudy was done at selected sites in China with the necessary technical and logistical capabilities. For the pharmacokinetic results, please refer to the Interim Clinical Study Report.

All subjects were followed up for 24 months after their last intake of TMC207. Subjects who prematurely withdrew (unless they withdrew consent) were also followed for this period or until the last follow-up visit for the last subject in the study. Investigators were asked to provide information about the survival/clinical outcome of these subjects throughout the follow-up period, approximately every 6 months.

Number of Subjects (planned and analyzed): It was planned to enroll approximately 225 subjects with sputum smear-positive pulmonary MDR-TB infection. Actual subject disposition data are provided below. At study end, 179 of 233 subjects had completed the study and 54 subjects discontinued prematurely.

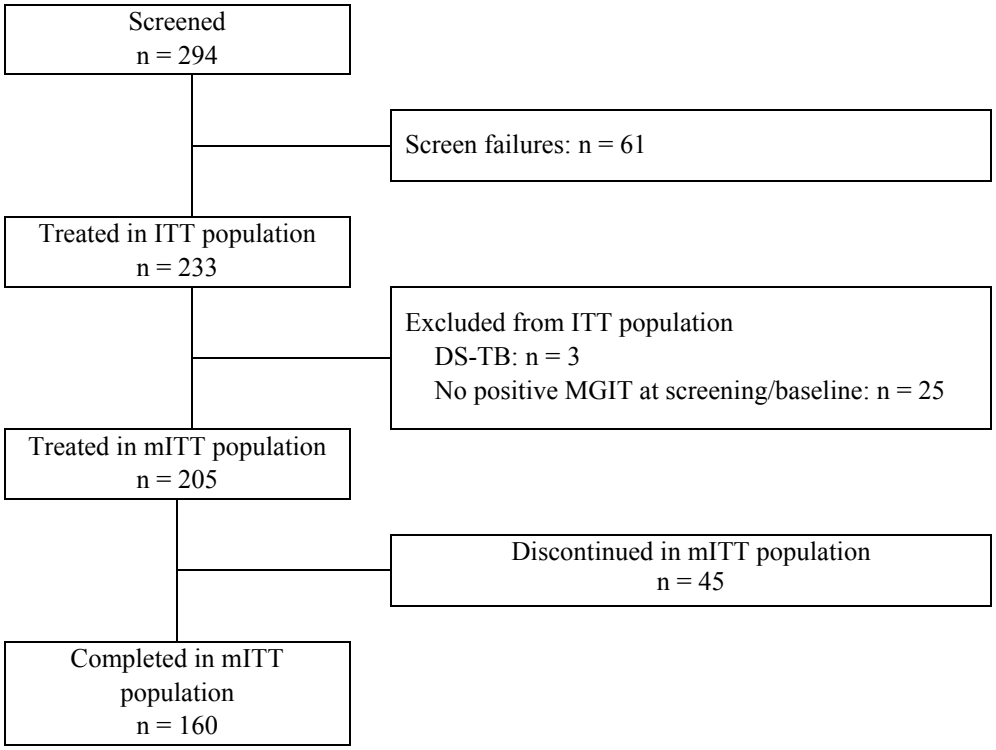
Populations in Analysis:

The intent-to-treat (ITT) population was defined as all subjects who had at least 1 intake of TMC207, regardless of their compliance with the protocol.

The modified intent-to-treat population (mITT) was defined as the subset of the ITT population excluding subjects:

- With drug susceptible (DS)-TB based on susceptibility results taken prior to baseline. Evaluation of drug susceptibility was based on the proportion method (7H11 agar) or resazurin microtiter assay (REMA) method if the previous was not available. If no central drug susceptibility test results were available, the subjects were included in the mITT, provided their Mycobacteria Growth Indicator Tube [MGIT] results were evaluable (see below).
- Whose MGIT results did not allow for primary efficacy evaluation (ie, subjects who did not have a positive MGIT at screening and/or baseline).

Subject Disposition:



Diagnosis and Main Criteria for Inclusion/Exclusion: Male or female; age ≥18 years; confirmed pulmonary MDR-TB infection; positive for acid-fast bacilli (AFB) on direct smear examination of expectorated sputum specimen or sputum culture positive for *M. tuberculosis* within the preceding 6 months; documented HIV-negative or -positive status at screening or within 1 month prior to study start; agree to comply with the NTP treatment guidelines.

Subjects which had a known or suspected hypersensitivity or serious adverse reaction to TMC207 or had previously received TMC207; were HIV-positive with CD4+ count <250 cells/µL; had cardiac arrhythmia requiring medication or specific QT/QTc interval characteristics; had complicated or severe extrapulmonary manifestations of TB, required surgical procedures for management of their TB or AIDS defining illnesses other than TB, were excluded from the study.

Disallowed Medication: The following medications were disallowed during administration of TMC207 and up to 1 month after the last dose of TMC207: systemic use of moderate and strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers; use of antiretroviral (ARV) medication (except for zidovudine/lamivudine/abacavir [AZT/3TC/ABC]).

The following medications were disallowed during administration of TMC207: medications of the statin class of compounds; tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine, clomipramine; nonsedating antihistamines astemizole and terfenadine; neuroleptics-phenothiazines thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole, and pimozide; prokinetic cisapride; quinoline antimalarials (eg, chloroquine and quinacrine); moxifloxacin and gatifloxacin.

Test Product, Dose and Mode of Administration, Batch No.: TMC207 tablets (F001; batch No 08K18/F001, 09D22/F001, 09E05/F001) containing 120.89 mg of the active fumarate salt of TMC207 (R403323), which is equivalent to 100 mg of the free base (R207910). TMC207 tablets are to be taken orally.

Criteria for Evaluation:

Efficacy evaluations: At every visit (also in case of withdrawal and at follow-up after withdrawal), triplicate spot sputum samples were collected to assess the presence or absence of *M. tuberculosis* by qualitative culturing (MGIT) and AFB smears. The MGIT based on triplicate spot sputum samples was used for the assessment of the primary efficacy parameter, time to culture conversion. *M. tuberculosis* identification was done on one of the spot sputum samples collected on Day -1 at a central laboratory.

Microbiology evaluations: drug susceptibility testing for TMC207 and the first- and second-line anti-TB drugs was done on one of the spot sputum samples collected on Day -1 (baseline), at the end of treatment period with TMC207 and was also performed on isolates from subjects who failed their MDR-TB treatment.

Pharmacokinetic evaluations: Predose pharmacokinetic (PK) sampling to determine plasma concentrations of TMC207 and M2 occurred at Weeks 2, 12, and 24. Plasma concentrations of TMC207 and M2 were determined using a validated liquid chromatography mass spectrometry/mass spectrometry (LC-MS/MS) method. The following parameters were determined using a population pharmacokinetic model: minimal plasma concentration (C_{0h}); area under plasma concentration-time curve from time of administration to the end of the dosing interval; average plasma concentration (C_{AVG}).

The majority of PK and PK-PD results obtained from the study have been described in the Interim Clinical Study Report (TMC207-C209-CSR-W24), Summary of Clinical Safety and Efficacy, and Overview of Deaths in the TMC207 Phase II Trials. Therefore, in this report only the following population PK and PK-PD results are presented:

- TMC207 C_{AVG} and its relationship towards safety (ie, deaths, hepatic safety)
- TMC207 C_{0h}, C_{AVG}, C_{AVG}/minimal inhibitory concentration (MIC), and C_{AVG} versus culture conversion

Metabolic evaluations: Feces samples were collected in a subset of 6 subjects enrolled at selected sites in South Africa at Day -1 and at the Week 24 visit. The results are described in a separate Non-clinical Pharmacokinetics Report.

Safety evaluations: Safety and tolerability were evaluated throughout the study. The evaluations of safety and tolerability included monitoring of adverse events (AEs), clinical laboratory tests (including urine test), electrocardiograms (ECGs), vital signs, and physical examination.

Patient-reported outcomes: Subjects completed the TSP questionnaire at screening, on Day -1, at Weeks 12 and 24, every 24 weeks during follow-up, and in case of withdrawal.

Chest x-ray: A postero-anterior chest x-ray was taken at screening (unless subject had taken the test within 1 month prior to the screening visit), at Weeks 12 and 24, every 12 weeks during follow-up, and in case of withdrawal and at follow-up after withdrawal.

Statistical Methods: This report describes the final analysis performed when all the subjects had completed the study or discontinued earlier. The interim analysis is described in a separate Interim Clinical Study Report.

Analyses were performed on the ITT and mITT population. The ITT population was the primary population for the safety analysis; the mITT population was the primary population for the efficacy and microbiology analysis. Descriptive statistics, frequency tabulations, population pharmacokinetic modeling, Kaplan-Meier, Cox proportional hazards model were performed.

The primary efficacy outcome parameter was time to sputum culture conversion during and beyond treatment with TMC207. This parameter was based on the qualitative assessment of culture growth in MGIT using spot sputum samples.

For analysis purposes, the study was subdivided into 4 phases: Screening phase, Investigational Treatment phase, Overall Treatment phase and Treatment-free Follow-up phase. Note that according to the phase definitions the Overall Treatment phase includes the Investigational Treatment phase.

Screening phase:	from signing of ICF until 1day before start of TMC207 intake
Investigational Treatment phase:	from date of first TMC207 intake until date of last TMC207 intake +1 week
Overall Treatment phase:	from date of first TMC207 intake until date of last medication intake (TMC207 or BR) +1 week
Treatment-free Follow-up phase:	from the day after end of the Overall Treatment phase until study termination date

RESULTS:

Study Population:

Study Termination

	TMC207/BR	
	ITT	mITT
Analysis Set: Number of Subjects	233	205
Completed	179 (76.8%)	160 (78.0%)
Discontinued	54 (23.2%)	45 (22.0%)
Adverse event or MDR-TB related event	17 (7.3%)	15 (7.3%)
Subject ineligible to continue the study	5 (2.1%)	3 (1.5%)
Subject lost to follow-up	8 (3.4%)	6 (2.9%)
Subject non-compliant	11 (4.7%)	11 (5.4%)
Subject withdrew consent	12 (5.2%)	9 (4.4%)
Other	1 (0.4%)	1 (0.5%)

n: number of subjects with that observation

In total 179 subjects completed the study of which 32 were still on BR at study end.
Major protocol deviations were noted in 33.0% of subjects in the ITT population. The most frequently reported major protocol deviation (19.3%) was an interruption of BR (defined as receiving less than 3 BR drugs for more than 2 weeks).

Demographic Data

	TMC207/BR	
	ITT	mITT
Analysis Set: Number of Subjects	233	205
Gender, n (%)		
Female	83 (35.6%)	73 (35.6%)
Male	150 (64.4%)	132 (64.4%)
Age (years)		
Median Range	32.0 (18; 68)	32.0 (18; 68)
Race, n (%)[a]		
American Indian or Alaska Native	8 (3.4%)	6 (2.9%)
Asian	89 (38.2%)	84 (41.0%)
Black or African American	75 (32.2%)	67 (32.7%)
White	61 (26.2%)	48 (23.4%)
Ethnic origin, n (%)		
Hispanic or Latino	17 (7.3%)	13 (6.3%)
Not Hispanic or Latino	216 (92.7%)	192 (93.7%)
Body weight (kg)		
Median Range	57.0 (30; 113)	57.0 (30; 113)
Body height (cm)		
Median Range	169.0 (145; 203)	169.0 (145; 203)
BMI (kg/m^2)		
Median Range	19.9 (13; 37)	19.8 (13; 37)
Pooled centers, n (%)[b]		
Asia (Other)	33 (14.2%)	31 (15.1%)
China	51 (21.9%)	50 (24.4%)
Eastern Europe	52 (22.3%)	41 (20.0%)
South Africa	79 (33.9%)	70 (34.1%)
South America	18 (7.7%)	13 (6.3%)

N: number of subjects with data; n: number of subjects with that observation

[a] Classification is based on the race description in the CRF template, no [redacted] sites participated in this study.

[b] Individual centers with low numbers of randomized subjects were pooled together based on geographic region to account for possible differences in resistance patterns.

Baseline Disease Characteristics

	TMC207/BR	
	ITT	mITT
Analysis Set: Number of Subjects	233	205
HIV Status		
N	225	198
Negative	216 (96.0%)	190 (96.0%)
Positive	9 (4.0%)	8 (4.0%)
Lung Cavitations		
N	233	205
No Cavitations or Cavitations <2 cm	85 (36.5%)	70 (34.1%)
Cavitations ≥2 cm in one lung only	120 (51.5%)	108 (52.7%)
Cavitations ≥2 cm in both lungs	28 (12.0%)	27 (13.2%)
Extent of resistance of *M. tuberculosis* strain[a]		
N	233	205
DS-TB	3 (1.3%)	0
MDR-TB	230 (98.7%)	205 (100.0%)
$MDR_{H\&R}$-TB	93 (39.9%)	93 (45.4%)
pre-XDR-TB	44 (18.9%)	44 (21.5%)
pre-XDR-TB Fluoroquinolone Resistant	31 (13.3%)	31 (15.1%)
pre-XDR-TB Injectable Resistant	13 (5.6%)	13 (6.3%)
XDR-TB	38 (16.3%)	37 (18.0%)
Previous use of second line TB drugs		
N	233	205
No	30 (12.9%)	28 (13.7%)
Yes	203 (87.1%)	177 (86.3%)

N: number of subjects with data

[a] For 55 subjects in the ITT population and 31 subjects in the mITT population, no confirmation from the central laboratory of INH and RMP resistance was available. These subjects were considered MDR based on the subject's medical history (local results).

ITT subjects and reason for exclusion from mITT

	TMC207/BR
	ITT
Analysis Set: Number of Subjects	233
Included in mITT	205 (88.0%)
Excluded from mITT	28 (12.0%)
DS-TB (not resistant to both INH and RMP)	3 (1.3%)
No Positive MGIT at Screening/Baseline	25 (10.7%)

Efficacy Results:

Primary efficacy analysis:

Median time to culture conversion (missing = failure) for the mITT population was 84 days. Median time to culture conversion for the end censored missing = failure and no overruling for discontinuation method for the mITT population was 85 and 57 days, respectively.

Major secondary efficacy analysis:

Data sets used in this analysis were: 24-Week data selection (taking into account all data up to and including Week 24) and Endpoint data selection (took all available data into account.).

Treatment with TMC207 as part of an individualized MDR-TB treatment regimen in subjects with pulmonary MDR-TB resulted in a MGIT culture conversion rate of 72.2% at endpoint.

Culture Conversion Rates; mITT

	Treatment	
	TMC207/BR	
	N	n (%)
Week 24		
Primary (M=F)[a]	205	163 (79.5%)
No Overruling[b]	205	167 (81.5%)
Endpoint		
Primary (M=F)[a]	205	148 (72.2%)
No Overruling[b]	205	172 (83.9%)

N: number of subjects with data, n: number of subjects with that observation

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

[b] Sputum culture conversion had occurred and was not followed by a confirmed positive MGIT result.

In total, 125 (61.0%) subjects were considered cured at the end of the study according to the WHO definition of cure defined as: an MDR-TB subject who completed the study and has been consistently culture-negative (with at least five consecutive negative cultures from samples collected at least 30 days apart) for at least the final 12 months of the study; if only one positive culture is reported during that time, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

Culture Conversion - Categorization by Week 24 Culture Conversion (M=F); mITT

	TMC207/BR	
	Response at Week 24	Non-Response at Week 24
Analysis Set: Number of Subjects	163	42
Response at Endpoint	139 (85.3%)	9 (21.4%)
Non-Response at Endpoint	24 (14.7%)	33 (78.6%)
Death - Total[a]	4 (2.5%)	10 (23.8%)
Death - Death BUT Converted	3 (1.8%)	0
Death - Failure to Convert	0	10 (23.8%)
Death - Relapse	1 (0.6%)	0
Discontinued BUT Converted	16 (9.8%)	5 (11.9%)
Failure to Convert	0	15 (35.7%)
Relapse[b,c]	4 (2.5%)	3 (7.1%)

n: number of subjects with that event
Deaths shown are those which occurred up to and including the week 120 analysis window. No deaths were reported beyond the Week 120 window.

[a] Two of the 16 subjects in the ITT population who died during the study or long term follow-up for survival were excluded from the mITT population and are therefore not presented in this table. Both subjects did not have a positive MGIT result at screening.

[b] Relapse: 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. Recurrence with isolation of an *M. tuberculosis* strain with a different genotype compared to baseline was considered reinfection.

[c] None of the subjects experiencing relapse were infected with an XDR-TB strain.

Confirmed culture conversion at endpoint was seen in 139 (85.3%) subjects that were responders at Week 24 (missing = failure) supporting that the surrogate marker of Week 24 culture conversion was both durable and predictive of the outcome at endpoint.

Culture Conversion Rates (Endpoint, Primary M=F) by Subgroups; mITT

	Treatment group	
	TMC207/BR	
	N	n (%)
Sex		
Female	73	54 (74.0%)
Male	132	94 (71.2%)
Age [years]		
≥18 - ≤45	160	115 (71.9%)
>45 - ≤65	43	31 (72.1%)
>65	2	2 (100.0%)
Race[a]		
American Indian or Alaska Native	6	5 (83.3%)
Asian	84	70 (83.3%)
Black or African American	67	39 (58.2%)
White	48	34 (70.8%)
Cavitation		
No cavitations or cavitations <2 cm	70	57 (81.4%)
Cavitations ≥2 cm in one lung only	108	73 (67.6%)
Cavitations ≥2 cm in both lungs	27	18 (66.7%)
Pooled Center		
Asia (Other)	31	24 (77.4%)
China	50	43 (86.0%)
Eastern Europe	41	31 (75.6%)
South-Africa	70	42 (60.0%)
South-America	13	8 (61.5%)
HIV Status at Baseline		
Negative	190	140 (73.7%)
Positive	8	3 (37.5%)
Extent of Resistance to *M. tuberculosis* Strain		
$MDR_{H\&R}$-TB	93	68 (73.1%)
Pre-XDR-TB	44	31 (70.5%)
Pre-XDR-TB Fluoroquinolone Resistant	31	23 (74.2%)
Pre-XDR-TB Injectable Resistant	13	8 (61.5%)
XDR-TB	37	23 (62.2%)
Previous use of Second Line Drugs		
Newly diagnosed	28	23 (82.1%)
Non-newly diagnosed	177	125 (70.6%)
Baseline PZA Susceptibility [MGIT960]		
Resistant	135	96 (71.1%)
Susceptible	38	25 (65.8%)
Number of active drugs in baseline BR (Validated critical concentrations)[b]		
0	8	7 (87.5%)
1	27	15 (55.6%)
2	20	11 (55.0%)
3	65	52 (80.0%)
4	35	26 (74.3%)
5	11	5 (45.5%)
6	1	0 (0 %)

Culture Conversion Rates (Endpoint, Primary M=F) by Subgroups; mITT

	Treatment group	
	TMC207/BR	
	N	n (%)
Baseline Albumin grades		
Grade 0	167	126 (75.4%)
Grade 1	15	10 (66.7%)
Grade 2	22	12 (54.5%)
Grade 3	1	0 (0%)
Baseline BMI		
<18	49	35 (71.4%)
≥18-<20	59	40 (67.8%)
≥20-<25	77	57 (74.0%)
≥25	20	16 (80.0%)
Baseline AFB score		
0	38	34 (89.5%)
0.5	60	44 (73.3%)
1	42	32 (76.2%)
2	34	22 (64.7%)
3	31	16 (51.6%)

N: number of subjects with data, n: number of subjects with that observation

[a] Classification is based on the race description in the CRF template, no [redacted] sites participated in this study.

[b] As drug susceptibility testing was not performed for all anti-TB drugs, some drugs are not accounted for. Drug susceptibility testing for drugs with validated critical concentrations was done for: INH, RMP, pyrazinamide (PZA), EMB, streptomycin (SM), KAN, CAP, ofloxacin (OFL), para-aminosalicylic acid (PAS)-C, and ETH.

Other subgroup analysis:

- Review of baseline linezolid use versus MGIT response at endpoint indicated that the response rate of subjects using linezolid at baseline (n=12) is comparable to the overall response rate seen in the study.
- Acknowledging relatively modest numbers, the limited follow-up period without treatment, and that some subjects were still on BR at endpoint, it is important to note that amongst the subjects infected with XDR-TB at baseline who converted their sputum at some point post baseline (n=26), none were classified as relapsers at endpoint. Seventeen of these 26 XDR-TB subjects had Treatment-free Follow-up (of median duration = 5.1 months). Medical review of baseline characteristics, BR, and major protocol violations related to BR or TMC207 intake suggests good compliance, and the individualized therapy based on central lab drug susceptibility results may have contributed to this favorable outcome. Therefore, at least in some subjects infected with XDR-TB, 6 months of TMC207 administration followed by continuation of an individualized BR was sufficient both to convert the sputum culture and prevent relapse.

Other secondary efficacy analyses:

- At baseline, mean (SE) time to signal was 15.03 (0.700) days. At Week 24, mean (SE) time to signal was 37.54 (0.774) days. Mean time to positive signal increased over time, mainly during the first 20 weeks.
- The median time to relapse was 382 days after baseline.
- Of the subjects in the mITT population with chest x-ray results at baseline (used as reference) and at endpoint, 101 (50.8%) subjects had no change in their cavitation category, 96 (48.2%) subjects had an improvement and 2 (1.0%) subjects had worsened at endpoint. The microbiological

outcomes for subjects who showed improvement were numerically better than for those who had no change in cavitation category.

- In general, few TSP symptoms were reported at baseline or they were low in severity. At baseline the most severe symptoms were cough, feeling unwell, mucus in throat and/or lungs, shortness of breath, and fatigue/weakness. Improvement (decrease of TSP score) was seen in 75.4% of subjects at the end of the study, 8.7% of subjects showed no change, and worsening (increase of TSP scores) was seen in 15.9% of subjects. The most frequently reported improvements were seen in the following symptoms: cough, fatigue/weakness, and feeling unwell.
- Clinical correlates of microbiology outcome:
    - Acknowledging the limitations of the data (low number of subjects in the non-responder group), no firm conclusions can be made about the TSP symptoms versus MGIT status. In responders with a symptom at baseline, symptom improvement was seen numerically more than worsening.
    - Stable weight was observed in 38.4% of subjects with MGIT culture conversion and in 46.9% of subjects without MGIT culture conversion. A weight increase of >5% was observed in 55.2% of subjects with MGIT culture conversion and in 31.3% of subjects without MGIT culture conversion while a weight decrease of >5% was observed in 6.4% of subjects with MGIT culture conversion and in 21.9% of subjects without MGIT culture conversion.

Microbiology (drug susceptibility testing):
TMC207 MICs were determined using 2 methods: on solid medium (7H11 agar) and in liquid medium (7H9 broth) using the REMA method. Only susceptibility results based on 7H11 agar are discussed in this report, the results of the REMA method and comparisons between the REMA and 7H11 agar results are described in a separate Microbiology Report.

- At baseline, the isolates from 162 (97.0%) subjects were inhibited at a TMC207 concentration of ≤0.12 µg/mL (7H11 agar). At endpoint, the isolates from 15 out of 24 subjects with paired MIC data had at least a 4-fold increase in TMC207 MIC (7H11 agar) compared to baseline. Of these 15 subjects, 11 subjects had a MIC value at endpoint of ≥0.24 µg/mL. No clear trend towards a correlation between baseline TMC207 MIC values (based on 7H11 agar) and response rate was noted.
- Susceptibility results for anti-TB drugs other than TMC207 at endpoint (7H11 agar or PZA in MGIT) indicated that the isolates from 17 of the 34 subjects with post-baseline drug susceptibility test results had developed resistance to at least 1 anti-TB drug at endpoint. Resistance to clofazimine had emerged in 10 subjects, to OFL in 4 subjects and to ETH, EMB, and thiacetazone each in 3 subjects. Resistance to other BR drugs occurred in less than 3 subjects: Augmentin, PAS-C, PZA each in 2 subjects, and CAP and linezolid each in 1 subject. The results indicate that acquired resistance to clofazimine is more common than for the other drugs tested and further investigation of this observation is warranted. However, it should be noted that no validated critical concentrations have been published for Augmentin, clofazimine, linezolid, and thiacetazone. Therefore, these results should be interpreted with caution. Three non-responders who were infected with a pre-XDR-TB strain at baseline developed XDR-TB at study end.
- Evaluation of possible cross-resistance between TMC207 and other anti-TB drugs indicated that isolates with at least a 4-fold increase in TMC207 MIC were more likely to be resistant to clofazimine. However, there is currently no evidence that less susceptibility to clofazimine is associated with high TMC207 MICs. Together, the above findings suggest that TMC207 and clofazimine may share a common resistance mechanism.

Pharmacokinetic/Pharmacodynamic Results:
Population PK data showed no clear relationship between TMC207 C_{0h}, C_{AVG}, or C_{AVG}/MIC (7H11 agar) and culture conversion rates.

Safety results:

Adverse events:

Summary Table of Adverse Events Reported During the Treatment Phases

	TMC207/BR	
	Investigational	Overall treatment
Analysis Set: Number of Subjects	233	233
AE category, n (%)		
in ITT	233 (100.0%)	233 (100.0%)
With at least one AE	212 (91.0%)	219 (94.0%)
With at least one SAE	15 (6.4%)	47 (20.2%)
With at least one AE of at least grade 2	130 (55.8%)	167 (71.7%)
With at least one AE of at least grade 3	45 (19.3%)	78 (33.5%)
With at least one AE of at least grade 4	5 (2.1%)	24 (10.3%)
With at least one AE leading to a permanent stop of TMC207	6 (2.6%)	6 (2.6%)
With at least one AE leading to a permanent stop of BR	49 (21.0%)	73 (31.3%)
With at least one AE considered at least possibly related to TMC207 by the investigator	77 (33.0%)	77 (33.0%)
With at least one SAE considered at least possibly related to TMC207	1 (0.4%)	1 (0.4%)
With at least one AE leading to a permanent stop of TMC207 considered at least possibly related to TMC207	1 (0.4%)	1 (0.4%)

n: number of subjects with 1 or more events
The Overall Treatment phase encompasses the Investigational Treatment phase.

Adverse Events Reported in >10% of Subjects During the Overall Treatment Phase (Regardless of Severity and Drug Relatedness) by Body System and Preferred Term; ITT

	TMC207/BR	
	Investigational	Overall treatment
Analysis Set: Number of Subjects	233	233
All events , n (%)	212 (91.0%)	219 (94.0%)
Body System or Organ Class		
Dictionary-derived term		
Gastrointestinal disorders	74 (31.8%)	91 (39.1%)
Nausea	27 (11.6%)	35 (15.0%)
Diarrhoea	18 (7.7%)	27 (11.6%)
Vomiting	21 (9.0%)	27 (11.6%)
Infections and infestations	48 (20.6%)	84 (36.1%)
Investigations	58 (24.9%)	83 (35.6%)
Metabolism and nutrition disorders	57 (24.5%)	71 (30.5%)
Hyperuricaemia	32 (13.7%)	36 (15.5%)
Musculoskeletal and connective tissue disorders	58 (24.9%)	69 (29.6%)
Arthralgia	29 (12.4%)	35 (15.0%)
Nervous system disorders	44 (18.9%)	61 (26.2%)
Headache	21 (9.0%)	31 (13.3%)
Skin and subcutaneous tissue disorders	45 (19.3%)	58 (24.9%)
General disorders and administration site conditions	43 (18.5%)	57 (24.5%)
Respiratory, thoracic and mediastinal disorders	30 (12.9%)	57 (24.5%)
Ear and labyrinth disorders	32 (13.7%)	41 (17.6%)

Adverse Events Reported in >10% of Subjects During the Overall Treatment Phase (Regardless of Severity and Drug Relatedness) by Body System and Preferred Term; ITT

	TMC207/BR	
	Investigational	Overall treatment
Eye disorders	28 (12.0%)	34 (14.6%)
Psychiatric disorders	24 (10.3%)	34 (14.6%)
Blood and lymphatic system disorders	14 (6.0%)	31 (13.3%)
Cardiac disorders	18 (7.7%)	25 (10.7%)

n: number of subjects with 1 or more events
The Overall Treatment phase encompasses the Investigational Treatment phase.

Overall, 16 (6.9%) subjects in the ITT population died during or after participation in the study. The median time to death for subjects who died is 443 days after baseline. Among the 12 subjects who died during the study, 10 died during the Overall Treatment phase (of which 3 died during the Investigational Treatment phase) and 2 died during treatment-free follow-up. Of these 12 subjects, 2 were excluded from the mITT population because they did not have a positive MGIT result at screening (subject [redacted] died during treatment-free follow-up, subject [redacted] died during the Overall Treatment phase). In addition, 4 deaths were reported during long term follow up for survival of subjects who prematurely discontinued the study. Of the 9 subjects that died of TB or TB-related illnesses as reported by the investigator (5 subjects who died during the study and 4 subjects who died during long term follow up for survival), all but one subject (CRF ID [redacted], excluded from mITT because of no positive MGIT result at screening) either failed to convert their sputum culture or relapsed. Serious adverse events (SAEs) leading to death during the study were tuberculosis (n=5), congestive cardiac failure, lung infection, pneumonia, renal impairment, hemoptysis, respiratory failure, and hypertension (n=1 each). All of the SAEs leading to death during the study were considered not related to TMC207 by the investigator, except for renal impairment which had developed after vomiting and dehydration and was judged doubtfully related to TMC207.

In total, 47 (20.2%) subjects were reported with SAEs during the Overall Treatment phase of which one was considered very likely related to TMC207 (ECG QT prolongation). One or more AEs led to permanent discontinuation of TMC207 in 6 (2.6%) subjects. By preferred term, no AE leading to discontinuation of TMC207 occurred in more than 1 subject.

During the Overall Treatment phase, 94.0% of subjects experienced at least 1 AE and this AE was considered at least possibly related to TMC207 by the investigator in 33.0% of subjects. The most frequently reported AEs (≥2.0%) considered at least possibly related to TMC207 by the investigator were vomiting, nausea, headache, arthralgia, pruritus, pain in extremity, insomnia, and diarrhea. One or more grade 3 or 4 AEs were reported in 33.5% of subjects during the Overall Treatment phase. The most frequently reported (≥1.0%) grade 3 or 4 AEs were hyperuricemia, blood uric acid increased, aspartate aminotranferrase (AST) increased, anemia, and tuberculosis.

Adverse events identified by the Standardized MedDRA Query (SMQ)[a] for rhabdomyolysis/myopathy were not observed during the Overall Treatment phase. Grade 3 or 4 adverse events identified by the SMQs for acute pancreatitis were reported in 3.0% of subjects: 1 event of hyperbilirubinemia was reported as grade 4. Adverse events identified by the SMQs for Torsade de Pointes/QT prolongation were observed in 4.3% of subjects. One grade 3 QT prolongation event was reported as SAE leading to permanent discontinuation of TMC207 and ECG QT prolonged was considered at least possibly related to TMC207 in 4 (1.7%) subjects, including the subject with the SAE. There were no reports of Torsade de Pointes or serious ventricular arrhythmias. There were no grade 3 or 4 severe cutaneous SMQ event during the Overall Treatment phase. Adverse events identified by the selected sub-SMQs from drug related hepatic disorders were reported in 42 (18.0%) subjects during the Overall Treatment phase and grade 3 or 4 events were reported in 16 (6.9%) subjects during the study. Two of the hepatic disorder sub-

SMQ events (hepatitis and liver disorder) were reported as SAEs during the Overall Treatment phase. Hepatic disorders sub-SMQs events were considered at least possibly related to TMC207 by the investigator in 4 (1.7%) subjects and in all but 1 resolved according to the investigator. For 1 subject with a reported AE of AST and alanine aminotransferase (ALT) increased, TMC207 intake was temporarily discontinued. For this subject AST and ALT values were already reported as grade 1 at screening and remained high (grade 3/4) until study end. Evaluation of this case was confounded by a diagnosis of hepatitis C.

[a] SMQs were used to identify similar medical concepts, from the same or different System Organ Classes, to ensure that each subject with an event included within an SMQ category was counted but counted only once

Clinical laboratory evaluations:
For the interpretation of all changes in laboratory parameters during the study, it should be noted that the majority of subjects were already receiving anti-TB drugs at baseline. In addition, subjects continued to receive their MDR-TB background regimen after completion of the 24-week Investigational Treatment phase with TMC207.

Most frequently observed (≥20%) treatment-emergent graded laboratory abnormalities during the Overall Treatment phase were increases in AST, hyperuricemia, hypernatremia, plasma prothrombin time, increases in ALT, gamma glutamyltransferase (GGT), and hyperglycemia. Most frequently (≥20%) observed treatment-emergent nongraded laboratory abnormalities during the Overall Treatment phase were CPK above normal, total cholesterol below normal, RBC count below normal, and gastrin, pepsinogen I and II, and neutrophils percentage above normal.

Treatment-emergent graded laboratory toxicities of grade 3 or 4 were observed in ≥3.0% of subjects during the Overall Treatment phase for hyperuricemia, and increases in AST, GGT, WBC increase, and increases in ALT, and hyperglycemia. Review of the 29 subjects with treatment-emergent grade 3 or 4 hyperuricemia showed that in each case PZA was part of the BR. Pyrazinamide is well known to be associated with increases in uric acid. Review of the medical history of the 7 subjects who had a grade 3 or 4 hyperglycemia AE during the Overall Treatment phase revealed that 6 subjects had a prior history of diabetes and the remaining subject (CRF ID [redacted]) had grade 4 hyperglycemia at screening.

One subject met the laboratory criteria for Hy's Law during the study (Week 32, 58 days after the end of TMC207 treatment) based on local laboratory data (source: CIOMS). The investigator considered the grade 3 and 4 AEs and grade 4 SAE reported for the abnormal liver function tests (preferred term liver disorder) not related to TMC207 and very likely related to BR. The subject recovered from liver disorder. Medical assessment of the case is complicated by the use of a background TB regimen which contained 4 hepatotoxic drugs (levofloxacin, protionamide, PZA, ETH), although a contribution of TMC207 to the event cannot be excluded. Abnormalities meeting laboratory criteria for Temple's Corollary were observed in 22 (9.4%) subjects with onset during (n=9) and after (n=13) the Investigational Treatment phase.

Electrocardiogram:
Mean absolute values in QT interval corrected for heart rate according to Fridericia (QTcF) increased during the Investigational Treatment phase, which was apparent as of the first on-study visit at Week 2, with mean increases from reference of more than 10 ms observed from Week 8 to Week 24. After Week 24 (ie, after stopping TMC207 treatment) mean absolute values in QTcF gradually decreased. No clinically relevant or consistent changes over time were observed for other ECG parameters.

Treatment-emergent abnormal QTcF values between 450 ms and 480 ms were reported during the Overall Treatment phase in 36 (15.5%) subjects. Five (2.2%) subjects had a treatment-emergent QTcF value between 480 ms and 500 ms; one subject with corresponding QTcF increases from reference of >60 ms. Two (0.9%) subjects had a treatment-emergent QTcF value of more than 500 ms while on a BR regimen containing clofazimine. (One subject had a QTcF value of 514 ms at Week 36 [after the Investigational

Treamtent phase]. Another subject had QTcF values of 516 ms on the last day of TMC207 treatment and 529 ms at Week 36 [after the Investigational Treatment phase]).

Physical examination and vital signs:
No clinically relevant or consistent changes over time were observed for vital signs-related parameters.

The number of subjects with post-baseline abnormal physical examination findings was comparable to that at baseline or decreased over time for all body system categories. A noteworthy decrease was observed for the incidence of abnormalities related to the respiratory system: from 65.2% of subjects at baseline to 33.7% at Week 24, 32.5% at Week 48, and 42.4% at Week 120. During follow-up, 15.3% of subjects had abnormalities related to the respiratory system.

Pharmacokinetic/pharmacodynamics relationship:
No relevant differences in median TMC207 C_{AVG} at Week 24 were observed for subjects who died (n=10) during or after the study (968.35 ng/mL) compared to the other subjects (1075.05 ng/mL). C_{AVG} of subjects who died ranged from 209.9 ng/mL to 1620.4 ng/mL while C_{AVG} of the other subjects ranged from 156.0 ng/mL to 2705.1 ng/mL. In addition, TMC207 C_{AVG} for subjects who experienced grade 3 or 4 hepatic related SMQ events (n=15) or SAEs (n=2) during the Overall Treatment phase are well within the range of C_{AVG} for subjects without these events.

Conclusion:

Treatment with TMC207 as part of an individualized MDR-TB treatment regimen in subjects with pulmonary MDR-TB resulted in a MGIT culture conversion rate of 79.5% after 24 weeks. At study end, the culture conversion rate was 72.2% and according to the WHO definition of cure, 125 (61.0%) subjects were considered cured at the end of the study. Confirmed culture conversion at endpoint was seen in 139 (85.3%) subjects that were responders at Week 24 (missing = failure) supporting that the surrogate marker of Week 24 culture conversion was both durable and predictive of the outcome at endpoint. MGIT culture conversion rates at endpoint in subjects with XDR-TB, pre-XDR-TB, and $MDR_{H\&R}$-TB were 62.2%, 70.5%, and 73.1%, respectively. In total 179 of 233 subjects completed the study of which 32 were still on BR at study end.
Acknowledging relatively modest numbers, the limited follow-up period without treatment, and that some subjects were still on BR at endpoint, it is important to note that amongst the subjects in the mITT population infected with XDR-TB at baseline who converted their sputum at some point post baseline (n=26), none were classified as relapsers at endpoint. Seventeen of these 26 XDR-TB subjects had Treatment-free Follow-up (of median duration = 5.1 months). Medical review suggests good compliance, and the individualized therapy based on central lab drug susceptibility results may have contributed to this favorable outcome. Therefore, at least in some subjects infected with XDR-TB, 6 months of TMC207 administration followed by continuation of an individualized BR was sufficient both to convert the sputum culture and prevent relapse.
Overall safety of TMC207 in combination with an individualized MDR-TB treatment regimen was consistent with observations from previous clinical studies with TMC207. Overall, 16 (6.9%) subjects in the ITT population died during or after participation in the study. The median time to death for subjects who died was 443 days after baseline. Four of the 16 deaths were reported during long term follow up for survival of subjects who prematurely discontinued the study. Of the 9 subjects that died of TB or TB-related illnesses as reported by the investigator all but one subject either failed to convert their sputum culture or relapsed. Grade 3 or 4 hepatic disorders identified by the selected sub-SMQs from drug-related hepatic disorders were reported in 16 (6.9%) subjects during the study. One subject met the laboratory criteria for Hy's Law during the study (58 days after the end of TMC207 treatment). The investigator considered the grade 3 and 4 AEs and grade 4 SAE reported for the abnormal liver function tests (preferred term: liver disorder) not related to TMC207 and very likely related to BR. The subject recovered from liver disorder. Medical assessment of the case is complicated by the use of a background TB regimen which contained 4 hepatotoxic drugs, although a contribution of TMC207 to the event cannot be excluded. Abnormalities meeting laboratory criteria for Temple's Corollary were observed in 22

(9.4%) subjects based on AST/ALT values during the Overall Treatment phase. Mean QTcF increased during the period of TMC207 administration with mean increases from reference of more than 10 ms observed from Week 8 to Week 24. The selected TMC207 dosing regimen for 24 weeks was generally safe and well tolerated as part of a multi-drug MDR-TB therapy. Treatment discontinuation due to AEs was infrequent (2.6%). Most AEs were mild or moderate in severity and were considered not related to TMC207 by the investigator.

Individual symptoms reported at baseline in the Tuberculosis Symptoms Profile as assessed by the subjects improved during treatment, although in general few symptoms were reported and their severity was low.

Apart from a trend towards a positive correlation of TMC207 plasma concentration and QTcF change from baseline observed in male and female subjects (based on interim data, see Interim Clinical Study Report), which was not considered clinically significant, no clear relationships were observed between TMC207 pharmacokinetics and safety or efficacy outcome parameters in the overall study population.