# SYNOPSIS

## Trial Identification and Protocol Summary

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|---|---|
| **Company**: Tibotec BVBA<br>**Trade Name**: -<br>**Indication**: Multi-drug resistant tuberculosis (MDR-TB) | **Drug Substance**: TMC207<br>**Trial no**.: TMC207-TiDP13-C112<br>**Clinical Phase**: I |
| **Title**: Pharmacokinetics, safety and tolerability of TMC207 in subjects with moderately impaired hepatic function. | |
| **Investigator**: E. Wittenberg, M.D., APEX GmbH, Landberger Strasse 476, 81241 Munich, Germany | **Country**: Germany |
| **Trial Period**: Start: 1-Feb-2010<br>End: 5-Jan-2011 | **No. of Investigators**: 1<br>**No. of Subjects**: 16 |
| **Objectives**: The objectives of this study were to assess the pharmacokinetics of TMC207 and its *N*-monodesmethyl metabolite (M2) after single-dose administration of TMC207 400 mg, and to assess the safety and tolerability of single-dose TMC207 400 mg in subjects with moderate hepatic impairment and in matched healthy controls. | |
| **Design**: This was a Phase I, open-label study of TMC207 in healthy subjects and subjects with moderate hepatic impairment.<br>A total of 16 subjects were enrolled in this study, i.e., 8 subjects with moderate hepatic impairment (Child-Pugh B, Panel A) and 8 healthy subjects (Panel B) matched for sex, age (± 5 years), and body mass index (BMI; ± 15%). Subjects received a single dose of TMC207 400 mg after a standardized breakfast on Day 1. Study participation was for approximately 4 weeks, screening not included. The end of the study was defined as the date of the last study-related visit of the last subject who completed or discontinued the study (last patient last visit).<br>Pharmacokinetic profiles of TMC207 and M2 were determined up to approximately 672 hours postdose (Day 29). Safety and tolerability were assessed at regular intervals throughout the study period. | |
| **Subject Selection**<br>Inclusion Criteria<br>1. Man or woman between 18 and 65 years of age, inclusive.<br>2. Otherwise healthy on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there were abnormalities, they had to be stable and controlled.<br>3. Otherwise healthy on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis were outside the normal reference ranges, the subject could be included only if the investigator judged the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination had to be recorded in the subject's source documents and initialed by the investigator.<br>4. Women had to be postmenopausal for at least 2 years, OR be surgically sterile (having had a total hysterectomy or bilateral oophorectomy, tubal ligation/bilateral tubal clips without reversal operation, or otherwise be incapable of pregnancy).<br>5. All women had to have a negative serum pregnancy test at screening.<br>6. Willing/able to adhere to the prohibitions and restrictions specified in the protocol.<br>7. Subjects had to have signed an informed consent document indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study.<br>8. A BMI (weight in kg divided by the square of height in meters) of 18.0 to 30.0 $kg/m^2$, extremes included.<br>**Only for subjects with moderate hepatic impairment (Panel A):**<br>9. History of hepatic disease, such as alcoholic liver disease, chronic infection with hepatitis viruses (hepatitis B virus [HBV], hepatitis C virus [HCV]), primary biliary cirrhosis and primary sclerosing cholangitis, nonalcoholic steatohepatitis (NASH).<br>10. Documented liver cirrhosis (e.g., biopsy report, computerized tomography, magnetic resonance imaging, ultrasound, liver scan, or laparoscopy).<br>11. Moderate liver function impairment defined by the Child-Pugh classification (Child-Pugh score of 7 to 9).<br>12. General medical condition, in the investigator's opinion, did not interfere with the assessments and the completion of the study.<br>**Only for matched healthy controls (Panel B):**<br>13. Matched to a subject with hepatic impairment with regards to sex, age (± 5 years), and BMI (± 15%). | |

Exclusion Criteria

1. History of and/or clinically relevant, currently active or underlying gastrointestinal (with the exception of liver cirrhosis in the hepatically impaired subjects), cardiovascular, nervous system, psychiatric, metabolic, renal, respiratory, inflammatory, neoplastic, skin, immunological or infectious disease, which was not stable and controlled. If there were clinically relevant currently active or underlying diseases, they were not to compromise the safety of the subject or the ability to participate in the study as judged by the investigator. The investigator was encouraged to discuss concomitant illnesses with the sponsor.
2. Currently significant diarrhea, gastric stasis, or significant constipation that in the investigator's opinion could have influenced drug absorption or bioavailability.
3. Known allergies, hypersensitivity, or intolerance to TMC207 or its excipients.
4. Use of disallowed therapies as specified in the protocol.
5. Received an investigational drug (including vaccines) or used an investigational medical device within 60 days before the planned start of treatment or were currently enrolled in an investigational study.
6. Pregnant or breast-feeding.
7. Any condition that, in the opinion of the investigator, would have compromised the study or the well-being of the subject or prevented the subject from meeting or performing study requirements.
8. Employees of the investigator or study center with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator.
9. Positive tuberculin skin test indicating latent tuberculosis.
   *Note:*
   - If the subject had a single Bacillus Calmette-Guérin (BCG) vaccine only as a child (< 18 years of age), tuberculin skin test results had to be considered as independent of these results (i.e., did not factor the BCG into any consideration of the tuberculin skin test results).
   - If the subject had any BCG vaccination as an adult (≥ 18 years of age), regardless of childhood BCG status, but the vaccine was not within the last 5 years, the patient had to be excluded if the tuberculin skin test reaction was ≥ 15 mm.
   - If the subject had had a BCG within the past 5 years, he or she had to be excluded from the trial.
10. A positive human immunodeficiency virus - type 1 or 2 at screening.
11. Current alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the investigator's opinion would have compromised the subject's safety and/or compliance with the study procedures.
12. A positive urine drug test at screening. Urine was tested for the presence of amphetamines, benzodiazepines, cocaine, cannabinoids, and opioids.
13. Donation of blood or plasma in the 60 days preceding the first intake of study medication.
14. Having received TMC207 in a previous study.
15. Subjects with QTcF interval > 450 ms at screening (and, if above the limit, confirmed by repeat single electrocardiogram [ECG]).
16. Subjects with any other clinically significant ECG abnormality at screening, such as arrhythmia, ischemia, or evidence of heart failure.
17. Subjects with a family history of Long QT Syndrome.
18. Vulnerable subjects (e.g., persons kept in detention).

**Only for subjects with moderate hepatic impairment (Panel A):**

19. Acute hepatitis (i.e., infection for less than 6 months).
20. Grade 3 or 4 encephalopathy (Child-Pugh classification).
21. Hepatic carcinoma.
22. Hepatorenal syndrome.
23. Mild or severe liver insufficiency defined as class A or C, respectively, according to Child-Pugh classification.
24. Active candidate for liver transplantation.
25. Any grade 3 laboratory abnormalities with the exception of laboratory abnormalities related to hepatic impairment.

**Only for matched healthy controls (Panel B):**

26. Acute hepatitis A infection (confirmed by hepatitis A antibody immunoglobulin M), hepatitis B infection (confirmed by hepatitis B surface antigen [HbsAg]), or hepatitis C infection (confirmed by hepatitis C virus antibody) at study screening.
27. Currently active hepatic disease.
28. Subjects with the following laboratory abnormalities at screening as defined by the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table and in accordance with the normal ranges of the clinical laboratory:
    - serum creatinine grade 1 or greater (> 1.0 x upper limit of laboratory normal range [ULN]);
    - pancreatic lipase grade 1 or greater (> 1.0 x ULN);
    - hemoglobin grade 1 or greater (≤ 10.5 g/dL);
    - platelet count grade 1 or greater (≤ 99999/$mm^3$);
    - absolute neutrophil count grade 1 or greater (≤ 1500/$mm^3$);
    - aspartate aminotransferase (AST) or alanine aminotransferase (ALT) grade 1 or greater (> 1.0 x ULN);
    - total bilirubin grade 1 or greater (> 1.0 x ULN);
    - any other laboratory abnormality of grade 2 or above, including proteinuria (spot urine) > 1+, and gross hematuria.

| **Treatment** | **TMC207** |
|---|---|
| Concentration<br>Dosage Form (F No.)<br>Usage | 100 mg<br>Tablet (F001)<br>Oral |
| Batch Number | 09D22 |
| Dose Regimen | A single dose of TMC207 400 mg on Day 1. |
| Duration of Treatment | TMC207: 1 single dose |
| Duration of Trial | Approximately 29 days excluding screening; no follow-up visits were foreseen |
| Disallowed Medication | **Only for subjects with hepatic impairment (Panel A):**<br>• any other medication than the regular medications for the management of their hepatic insufficiency (e.g., albumin, diuretics, lactulose, beta-blockers, and vitamins) had to be discussed prior to inclusion with the sponsor on a case-by-case basis, except for ibuprofen and acetaminophen;<br>• any herbal medications, including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the intake of study medication up to 28 days after the intake of study medication.<br>**Only for healthy control subjects (Panel B):**<br>• all over-the-counter medication at least 7 days before the intake of study medication (Day 1);<br>• all prescribed medication had to be discontinued at least 14 days before intake of study medication, except for ibuprofen and acetaminophen;<br>• any medication other than the study medication up to 28 days after intake of study medication, except for ibuprofen and acetaminophen;<br>• any systemic herbal medications or dietary supplements including products containing *Hypericum perforatum* (St. John's wort) from 14 days before the first intake of study medication up to 28 days after the intake of study medication.<br>**For all subjects (Panel A and B):**<br>• Ibuprofen and acetaminophen could be used up to 3 days before the intake of study medication. After that, the clinical investigator could permit the use of ibuprofen (maximum 800 mg per day) or acetaminophen (maximum 1000 mg per day). |

| **Assessments** | |
|---|---|
| Pharmacokinetics | Pharmacokinetic sampling to determine plasma concentrations of TMC207 and M2 was performed:<br>• on Day 1 (predose[a], at 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose), on Day 2 (i.e., 24 hours postdose), and on Days 3, 4, 6, 8, 10, 12, 15, 22, and 29 (i.e., 48, 72, 120[b], 168[b], 216[b], 264[b], 336[b], 504[b], and 672[b] hours postdose, respectively).<br>• at the time of discontinuation or the following morning.<br>[a] Immediately before intake of medication.<br>[b] A window of 2 hours before/after scheduled sampling time was allowed. |
| Safety | |
| Adverse Events | Adverse events (AEs) were monitored throughout the trial from signing of the informed consent form onwards until the last trial-related activity. |
| Clinical Laboratory | Blood samples for hematology and biochemistry[a] measurements and urine samples for urinalysis were taken:<br>• at screening;<br>• on Day 1[b], Day 2, Day 8, Day 15, and Day 29;<br>• at the time of discontinuation or the following morning, 7 or 8 days after discontinuation, and 30 to 32 days after discontinuation.<br>[a] Sample had to be taken after subject had fasted for at least 10 hours and before breakfast, except at the time of discontinuation when it was preferably taken fasted for at least 10 hours.<br>[b] Within 2 hours before intake of study medication. |
| Cardiovascular Safety | Vital signs[a] and ECG (triplicate) were recorded:<br>• at screening;<br>• on Day 1 (predose[b]);<br>• on Day 1 (2, 4, and 5 hours postdose) (ECG only);<br>• on Days 2, 8, and 15;<br>• on Day 22 (ECG only);<br>• on Day 29;<br>• at the time of discontinuation or the following morning and 7 or 8 days after discontinuation (vital signs only);<br>• 30 to 32 days after discontinuation (single ECG).<br>[a] Vital signs include systolic and diastolic blood pressure (SBP, DBP) and pulse rate that were measured supine after at least 5 minutes and standing after at least 1 minute.<br>[b] Within 1 hour before breakfast. |
| Physical Examination | A physical examination was performed:<br>• at screening;<br>• on Day -1;<br>• on Day 8;<br>• on Day 29;<br>• at the time of discontinuation or the following morning, 7 or 8 days after discontinuation, and 30 to 32 days after discontinuation.<br>At screening, on Day 8, and 7 or 8 days after discontinuation, physical examination also included a complete ophthalmologic examination with fundoscopy. |
| **Statistical Methods Performed** | Descriptive statistics, frequency tabulations, intent-to-treat analysis, linear mixed effects modeling, nonparametric test (for $t_{max}$) |

## Main Features of the Subject Sample and Summary of the Results

| **Baseline Characteristics - Subject Disposition** | **Healthy Subjects N = 8** | **Subjects With Moderate Hepatic Impairment N = 8** |
|---|---|---|
| Number of Subjects Entered (M/F) | 3/5 | 3/5 |
| Age: median (range), years | 57.0 (46-61) | 57.0 (48-61) |
| BMI: median (range), $kg/m^2$ | 26.00 (19.9, 30.1) | 26.35 (21.0, 29.1) |
| Completed | 8 | 8 |

| **Pharmacokinetics of TMC207** | **Healthy Subjects (reference)** | **Subjects With Moderate Hepatic Impairment (test)** |
|---|---|---|
| n | 8[b] | 8[c] |
| $C_{max}$, ng/mL | 5251 ± 1666 | 4854 ± 2182 |
| $t_{max}$, h[a] | 4.0 (2.0 - 5.12) | 5.0 (2.0 - 6.0) |
| $AUC_{72h}$, ng.h/mL | 59650 ± 18790 | 45960 ± 22540 |
| $AUC_{last}$, ng.h/mL | 90850 ± 31540 | 77550 ± 40180 |
| $AUC_{\infty}$, ng.h/mL* | 122300 ± 37550 | 123800 ± 54600 |
| $\lambda_{\alpha}$, 1/h | 0.09515 ± 0.01184 | 0.1050* ± 0.04506* |
| $t_{1/2t\alpha}$, h | 7.388 ± 0.9559 | 7.360* ± 2.194* |
| $\lambda_{\beta}$, 1/h* | 0.01347 ± 0.002134 | 0.01245 ± 0.002891 |
| $t_{1/2t\beta}$, h* | 52.84 ± 10.17 | 58.17 ± 12.94 |
| $\lambda_z$, 1/h* | 0.0008722 ± 0.0003026 | 0.001129 ± 0.0004095 |
| $t_{1/2term}$, h* | 890.4 ± 336.6 | 675.8 ± 221.5 |
| **LSmean Ratio (90% CI)** | | |
| | | **Test vs Reference** |
| n | | 8 vs 8 |
| $C_{max}$ | - | 0.86 (0.57 - 1.29) |
| $AUC_{72h}$ | - | 0.73 (0.52 - 1.03) |
| $AUC_{last}$ | - | 0.81 (0.56 - 1.17) |

* Accurate determination not possible

[a] mean ± SD, $t_{max}$: median (range)

[b] n = 6 for $AUC_{\infty}$, $\lambda_z$ and $t_{1/2term}$

[c] n = 5 for $AUC_{\infty}$, $\lambda_z$ and $t_{1/2term}$

| **Pharmacokinetics of M2** | **Healthy Subjects (reference)** | **Subjects With Moderate Hepatic Impairment (test)** |
|---|---|---|
| n | 8[b] | 8 |
| $C_{max}$, ng/mL | 36.43 ± 12.39 | 26.40 ± 9.640 |
| $t_{max}$, h[a] | 12.0 (5.12 - 24.0) | 12.0 (5.0 - 24.00) |
| $AUC_{72h}$, ng.h/mL | 1833 ± 601.3 | 1323 ± 578.0 |
| $AUC_{last}$, ng.h/mL | 10120 ± 2934 | 8617 ± 3999 |
| $AUC_{\infty}$, ng.h/mL* | 22040 ± 5048 | - |
| $\lambda_z$, 1/h* | 0.0009865 ± 0.0005276 | - |
| $t_{1/2term}$, h* | 845.3 ± 346.8 | - |
| Ratio $AUC_{last\ M2/TMC207}$, % | 11.62 ± 2.932 | 11.85 ± 3.452 |
| **LSmean Ratio (90% CI)** | | |
| | | **Test vs Reference** |
| n | | 8 vs 8 |
| $C_{max}$ | - | 0.73 (0.10 - 0.99) |
| $AUC_{72h}$ | - | 0.70 (0.50 - 0.98) |
| $AUC_{last}$ | - | 0.81(0.59 - 1.12) |

* Accurate determination not possible

[a] mean ± SD, $t_{max}$: median (range)

[b] n = 6 for $AUC_{\infty}$, $\lambda_z$ and $t_{1/2term}$

| **Safety** | **Healthy Subjects N = 8** | **Subjects With Moderate Hepatic Impairment N = 8** |
|---|---|---|
| Adverse Events | | |
| Most frequent AEs (reported in > 1 subject per panel), n (%) | | |
| Dizziness | 2 (25.0) | 0 |
| n (%) with at least 1 AE | 4 (50.0) | 5 (62.5) |
| n (%) with at least 1 grade 3-4 AE | 0 | 1 (12.5) |
| n (%) with at least 1 SAE | 0 | 0 |
| n (%) with at least 1 AE leading to discontinuation | 0 | 0 |
| n (%) of deaths | 0 | 0 |
| No deaths or other SAEs occurred in this trial. None of the subjects discontinued the trial due to an AE.<br>All AEs were reported in at most 1 (12.5%) subject per preferred term in any panel, except for dizziness which occurred in 2 (25.0%) healthy subjects.<br>Most AEs were grade 1 or 2 in severity. One (12.5%) subject with moderate hepatic impairment had grade 3 AEs. Subject 112-0004 had grade 3 muscle spasms and back pain starting on Day 14 and Day 21, respectively, which were also considered as Events of Special Interest in addition to grade 2 myalgia (starting on Day 15). No grade 3 or 4 AEs were reported following administration of TMC207 in healthy subjects. | | |
| Clinical Laboratory Tests | During the trial, one laboratory abnormality was reported as a AE, i.e., grade 1 blood creatine phosphokinase increased in a subject with moderate hepatic impairment. The same subject (CRF ID 112-0004) had coinciding muscle spasms.<br>Treatment-emergent grade 3 or 4 laboratory abnormalities were reported in 4 subjects (all subjects with moderate hepatic impairment). One subject had grade 4 hyperbilirubinemia and grade 3 elevated lipase, one subject had grade 3 hyperbilirubinemia and 2 subjects had grade 3 platelet count decreased. Note that for these subjects, the screening or baseline value of the corresponding laboratory parameter was already grade 3 increased (grade 4 hyperbilirubinemia) or grade 2 increased or decreased (for the grade 3 abnormalities). The 2 subjects with hyperbilirubinemia had abnormal indirect bilirubin levels at all assessments, including screening and baseline. In addition, the subject with grade 3 elevated lipase had grade 1 elevated amylase levels at the same timepoint as the grade 3 increase in lipase.<br>Graded treatment-emergent laboratory abnormalities were observed in at most 2 healthy subjects each. In subjects with moderate hepatic impairment, the most frequently observed (> 2 subjects) graded treatment-emergent laboratory abnormalities were in lipase (in 5 [62.5%] subjects), neutrophil count (in 4 [50.0%] subjects) and platelet count (in 3 [37.5%] subjects), which were not observed in healthy subjects. Nongraded laboratory abnormalities were observed in at most 2 (25.0%) subjects each in either panel, except for monocytes (%) and monocyte count below normal in each panel and CPK and LDH above normal in subjects with moderate hepatic impairment only. | |
| Cardiovascular Safety | Changes in median ECG parameters (heart rate, and PR, QRS, QT, QTcF and QTcB intervals) and vital signs parameters were generally minor and none of the observed changes were considered clinically significant. No treatment-emergent QTcF values larger than 500 ms were reported during the trial. One subject (subject with moderate hepatic impairment) had a treatment-emergent abnormal QTcF value (i.e., > 450 ms) of 472 ms with a corresponding increase from reference of 25 ms.<br>No AEs related to ECG or vital signs were reported. | |
| Physical Examination | An abnormal new finding upon physical examination was reported for 1 subject during the trial (subject with moderate hepatic impairment, pretibial edema), which was not reported as an AE. | |

N = number of subjects; n = number of observations

**Conclusions**
TMC207 exposure was lower in subjects with moderate hepatic impairment compared to healthy subjects. For TMC207, $C_{max}$, $AUC_{72h}$ and $AUC_{last}$ values were 14%, 27% and 19% lower, respectively, and for the *N*-monodesmethyl metabolite (M2), $C_{max}$, $AUC_{72h}$ and $AUC_{last}$ values were 27%, 30% and 19% lower, respectively, in subjects with moderate hepatic impairment as compared to healthy subjects.
The results of this trial demonstrate that TMC207 was generally safe and well tolerated.