CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204384Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA#	204384
Date of Original Submission:	June 29, 2012
Brand Name:	Sirturo®
Generic Name:	Bedaquiline (TMC207)
Strength and Formulation:	100 mg tablet
Sponsor:	Janssen R&D
Indication:	Treatment of Multidrug Resistant Pulmonary Tuberculosis (MDR-TB)
Submission Type:	Original NDA (NME), Priority.
Clinical Pharmacology Review Team:	Dakshina M. Chilukuri, Zhixia (Grace) Yan, Seong Jang, Fang Li, Justin Earp, Kevin Krudys, Kimberly Bergman, Philip Colangelo and Yaning Wang

EXECUTIVE SUMMARY

Bedaquiline (TMC207) is a diarylquinoline and a novel anti-mycobacterial agent proposed for the treatment of pulmonary tuberculosis due to multi-drug resistant *M. tuberculosis* (MDR-TB) in adults (≥ 18 years), as part of combination therapy. Bedaquiline should be administered by Direct Observation of Therapy (DOT) orally with food at a dose of 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks. Bedaquiline should only be used in combination with at least 3 drugs to which the patient's isolate has been shown to be susceptible in vitro. The clinical pharmacology review of the NDA was previously signed off in DARRTS on 12/03/2012.

The purpose of this review is to provide the proposed package insert with FDA edits (see Appendix-A) and also to outline the post-marketing commitment that the clinical pharmacology team is recommending. Given the long half-life of bedaquiline and its primary metabolite M2, and its expected long residence in the systemic circulation, it is possible that clinically significant interactions could occur with drugs that are substrates, inhibitors and inducers of certain transporters. Moreover, it is known that bedaquiline is primarily eliminated by the hepatic route. While the applicant has characterized the role of bedaquiline as a substrate and inhibitor of P-glycoprotein (PgP), the interaction between bedaquiline and other transporters such as OATP1B1 and OATP1B3 is unknown. Thus, the clinical pharmacology team is recommending that the applicant conduct an in vitro post-marketing study to characterize the potential of bedaquiline and M2 as a substrate, and as an inhibitor or inducer of the drug transporters such as OATP1B1 and OATP1B3. The applicant is referred to the FDA Draft Guidance on Drug Interactions entitled "*Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" for an extensive discussion on the evaluation of a drug as a substrate, inhibitor and inducer of drug transporters.

1.1. Recommendation
The clinical pharmacology information provided by the applicant in support of the accelerated application is acceptable and supports the use of the proposed dose regimen for bedaquiline for the treatment of MDR-TB.

1.2. Phase 4 Post-Marketing Commitment (PMC) to the Sponsor:

As a post-marketing commitment, please conduct an in vitro study to characterize the potential of bedaquiline and M2 as a substrate, inhibitor or inducer of the OATP1B1 and OATP1B3 drug transporters. . Please refer to the FDA Draft Guidance on Drug Interactions entitled "*Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" for further details on the evaluation of a drug as a substrate, inhibitor or inducer of drug transporters.

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Dakshina M. Chilukuri, PhD
Division of Clinical Pharmacology 4

Initialed by: _____

                                  Philip M. Colangelo, PharmD, PhD
                                  Team Leader - Division of Clinical Pharmacology 4

<u>APPENDIX A</u>

2. LABELING RECOMMENDATIONS (label agreed upon by DAIP as of 12/10/2012)

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3228191

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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Bedaquiline has a unique mechanism of action involving specific inhibition of mycobacterial adenosine 5'-triphosphate (ATP) synthase an enzyme that is essential for the generation of energy in mycobacteria. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating (dormant) tubercle bacilli.

The clinical evaluation of bedaquiline for the treatment of pulmonary tuberculosis due to multidrug resistant *M. tuberculosis* as part of combination therapy in adults is based on data from 1 proof-of-principle Phase IIa trial in Drug-Sensitive-TB (DS-TB) subjects (Trial C202), 2 independent sequential stages in a randomized placebo-controlled Phase IIb trial in MDR-TB subjects who were treatment-naïve for second-line anti-TB medication (Trial C208 Stage 1 and C208 Stage 2), and 1 uncontrolled Phase IIb trial in newly diagnosed or treatment-experienced MDR-TB subjects (Trial C209). In Stage 2 of Trial C208, the addition of TMC207 to a standardized MDR-TB treatment for 24 weeks resulted in a significantly shorter time to sputum culture conversion. The median time to mycobacteria growth indicator tube (MGIT) culture conversion was 73 days in the TMC207 group compared to 125 days in the placebo group (modified intent-to-treat [mITT]). The addition of TMC207 to a standardized MDR-TB treatment for 24 weeks also resulted in higher MGIT culture conversion rates; 78.8% of the subjects in the TMC207 group had culture conversion at Week 24 (mITT) compared to 57.6% in the placebo group. Furthermore, the results of the single- arm, open-label C209 trial in subjects with pulmonary MDR-TB, including pre-extensively drug resistant TB (XDR-TB) and XDR-TB, showed that the addition of TMC207 to an individualized MDR-TB treatment regimen for 24 weeks resulted in MGIT conversion rates of 79.5% (mITT) in the overall trial population; and in 55.6% in subjects with XDR-TB (mITT).

The clinical pharmacology program consisted of 16 trials that evaluated the PK, drug interactions, and PK/PD of bedaquiline. Bedaquiline exhibited dose-proportional PK in the dose range of 10 to 700 mg. When administered with food the systemic exposure of bedaquiline increased by 2-fold. The PK profile of bedaquiline is characterized by a short distribution phase followed by a very long terminal elimination phase ($T_{1/2}$ = 4-5 months). Although bedaquiline is highly protein bound to human plasma (>99%), the estimates of the apparent volume of distribution (~164 L) indicate that the drug distributes extensively into the tissues. Based on the results of the in vitro metabolism studies and drug interaction trials conducted, it appears bedaquiline does not inhibit or induce the cytochrome P450 enzymes. As a CYP3A4 substrate, the systemic exposure of bedaquiline was decreased by 50% in the presence of strong inducers such as rifampin and increased by 22% in the presence of strong inhibitors such as ketoconazole. The exposure-response relationship for efficacy indicated that no discernible relationship exists between systemic concentrations and sputum conversion. The exposure-safety relationship

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indicated that no strong relationship exists between exposure and incidence of most frequently reported adverse events that are likely related with bedaquiline treatment, such as nausea, headache, chest pain, and arthralgia.

1.1. Recommendation

The clinical pharmacology information provided by the applicant in support of the accelerated application is acceptable and supports the use of the proposed dose regimen for bedaquiline for the treatment of MDR-TB.

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreements with the sponsor.
Proposed dose regimen for general population	☒ Yes ☐ No ☐ NA	400 mg QD for 2 weeks followed by 200 mg three times a week for 22 weeks
Pivotal BE	☐ Yes ☐ No ☒ NA	A biowaiver was requested by the applicant
Labeling	☒ Yes ☐ No ☐ NA	Pending satisfactory agreement with the sponsor.

1.2. Phase 4 Commitments

There are no Phase 4 committments.

1.3. Summary of Important Clinical Pharmacology Findings

Table 1. Important PK properties of bedaquiline

PK Property	PK Parameter	
Dose-proportionality	PK dose-proportional for doses 10 – 700 mg	
Absorption	Tmax (median)	~5 hr
	Food Effect	High fat meal increased Cmax and AUC by 2-fold.
Distribution	Protein Binding,	> 99%
Metabolism	Pathways	Metabolized to M2 and M3 by CYP3A4.
Excretion	Fecal excretion is the major route of elimination	
	$T_{1/2\,term}$ ~ 4-5 months	

- TMC207 is orally bioavailable, with the C_{max} achieved around 5 hours after administration. In healthy subjects and DS-TB infected subjects, the exposure to TMC207 increases in an approximately dose-proportional manner, indicating linear pharmacokinetics after repeated dosing to 400 mg q.d. The mean terminal elimination half-life ($t_{1/2,term}$) of TMC207 is around 4-5 months, which is likely a result of the cationic

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amphiphilic characteristics of TMC207 and its propensity for accumulation in tissues; however, the effective half-life of TMC207 is approximately 24 hours, based on the approximately 2-fold accumulation after 2 weeks of q.d. dosing.

- The exposure to TMC207 increases approximately 2-fold when administered under fed conditions. TMC207 should therefore be administered with food in order to maximize systemic exposure in patients with MDR-TB. All clinical trials were conducted with bedaquiline administration with food.

- TMC207 is on average > 99% bound to proteins in human plasma. The apparent volume of distribution of bedaquiline in the central compartment was estimated to be around 164 L.

- TMC207 is metabolized primarily to the N-monodesmethyl metabolite, M2 (4- to 6-fold less active against *M. tuberculosis* than TMC207) and *N*-didesmethyl TMC207 (M3, formed by further *N*-demethylation of M2, which is virtually inactive against *M. tuberculosis*). CYP3A4 is the major CYP isoenzyme involved in TMC207 metabolism. Based on urine concentrations of bedaquiline in 2 Phase 1 trials, it appears that there is negligible renal excretion of unchanged TMC207. Creatinine clearance (CL_{CR}) was not associated with TMC207 exposure in the population pharmacokinetic analysis. The sponsor has suggested that no dose modification is required in patients with mild or moderate renal impairment and bedaquiline should be used with caution in patients with severe renal impairment or end-stage renal disease. However, the clinical pharmacology team is recommending that the confirmatory trial (C210) should include a cohort of 6-8 patients with severe renal impairment and PK evaluations should be conducted in those patients to evaluate if the exposure in these patients is different from patients with normal renal function.

- No dose adjustment of TMC207 is needed in patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the exposure to TMC207 was not studied. Given that bedaquiline is metabolized by hepatic enzymes, it is important to evaluate the PK in severe hepatic impaired patients. Thus, the clinical pharmacology team is recommending that the confirmatory trial (C210) should include a cohort of 6-8 patients with severe hepatic impairment and PK evaluations should be conducted in those patients to evaluate if the exposure in these patients is different from patients with normal hepatic function.

- There is no clinically relevant effect of age, sex, body weight, human immunodeficiency virus (HIV) co-infection, or extent of *M. tuberculosis* resistance on the pharmacokinetics of TMC207. Population pharmacokinetic modeling indicated that the exposure to TMC207 is 34% lower in African-American (Black) patients compared to other race categories. With no clear relationship between TMC207 exposure and efficacy seen in Phase IIb trials, the lower exposures are not considered to be clinically relevant.

- TMC207 has either no potential, or only a weak potential, to induce or inhibit CYP isoenzyme activity, thus TMC207 is unlikely to affect the exposure of coadministered drugs. Coadministration of TMC207 with CYP3A4 inducers may decrease TMC207 exposure, as observed in a drug-drug interaction trial with rifampin, and therefore coadministration of TMC207 with CYP3A4 inducers is not recommended.

- Coadministration of TMC207 with CYP3A4 inhibitors may increase TMC207 exposure, as observed in drug-drug interaction trials with ketoconazole and lopinavir combined with low-dose ritonavir (LPV/rtv), and therefore coadministration of TMC207 with

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moderate or strong CYP3A4 inhibitors for more than 2 weeks is not recommended. There was no considerable effect of TMC207 on the exposure to background regimen (BR) drugs for TB (ethambutol, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone).

- There is no clear relationship between exposure to TMC207 and efficacy in MDR-TB infected subjects within the range of exposures observed with the proposed therapeutic regimen. The exposure-safety relationship indicated that there exists no strong relationship between exposure and incidence of most frequently reported adverse events, such as nausea, headache, chest pain, and arthralgia.

- The single-dose Thorough QT (TQT) trial with 800 mg bedaquiline showed no significant QTc prolongation effect of bedaquiline. The largest upper bound of the 2-sided 90% confidence intervals for the mean difference between bedaquiline and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. However, the single-dose TQT trial was insufficient to characterize the potential of bedaquiline/M2 to prolong the QTc interval. Since this was a single dose trial, M2 exposure never achieved clinically relevant concentrations (C_{max} and AUC values of M2 in the thorough QT trial were 5.4- and 6.4-fold lower following single-dose administration of 800 mg bedaquiline compared with 400 mg bedaquiline after 2 weeks of q.d. administration in Trial C208. In addition, the finding of a positive concentration-QTc relationship suggests that M2 concentrations are responsible for the QTc prolongation observed in Trial C208.

- The QT-IRT recommended that ECGs should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval. Caution is recommended when prescribing bedaquiline concomitantly with medications with a known risk of QT prolongation. In the event that co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended. Concomitant administration of bedaquiline with fluoroquinolone antibiotics that have a potential for significant QT prolongation (e.g., gatifloxacin, moxifloxacin, sparfloxacin) should be avoided.

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2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

TMC207 is a diarylquinoline and a novel anti-mycobacterial agent. The molecular formula of the free base form is $C_{32}H_{31}BrN_2O_2$, the molecular weight is 555.50 Dalton. For the fumarate salt, this is $C_{32}H_{31}BrN_2O_2.C_4H_4O_4$ and 671.58 (555.50 + 116.07) Dalton, respectively. The structural formulas are provided in Figure 1.

Figure 1 Chemical Structure of TMC207 as Free Base (left) and as Fumarate Salt (right).
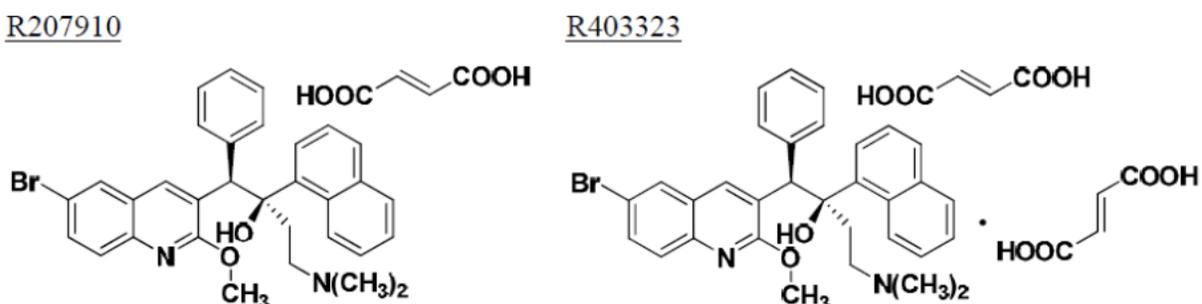
Solubility

The drug substance is practically insoluble in aqueous media over a wide pH range and very slightly soluble in 0.01 N HCl. The drug substance is soluble in a variety of organic solvents.

The drug product is an uncoated, immediate release tablet for oral administration, containing 120.89 mg of bedaquiline fumarate drug substance, equivalent to 100 mg bedaquiline free base, which is produced by means of _____ (b) (4).

Component	Quality Reference	Function	Weight per Tablet (mg)	(%)
Bedaquiline Fumarate	Company specification	Active ingredient	120.89	26.28
Lactose Monohydrate	Ph. Eur./NF			(b) (4)
Maize Starch[a]	Ph. Eur./NF			
Hypromellose 2910 15 mPa.s	Ph. Eur./USP			
Polysorbate 20	Ph. Eur./NF			
Purified Water[b]	Ph. Eur./USP			
Microcrystalline Cellulose	Ph. Eur./NF			
Croscarmellose Sodium	Ph. Eur./NF			
Silica, Colloidal Anhydrous[c]	Ph. Eur./NF			
Magnesium Stearate	Ph. Eur./NF			
Total Tablet Weight:			460.00	100.00

[a] Called 'corn starch' in the NF.
[b] Removed during processing.
[c] Called 'colloidal silicon dioxide' in the NF.
NA = Not applicable

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2.1.2. What is the proposed mechanism of drug action and therapeutic indication?
TMC207 has a unique mechanism of action involving specific inhibition of mycobacterial adenosine 5'-triphosphate (ATP) synthase, an enzyme that is essential for the generation of energy in mycobacteria. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating (dormant) tubercle bacilli.

2.1.3. What is the proposed dosage and route of administration?
The proposed dosage and route of administration of TMC207 is 400 mg (4 x 100 mg tablet) orally once daily for 2 weeks followed by 200 mg (2 x 100 mg tablet) 3 times per week (t.i.w.) for 22 weeks. TMC207 is proposed to be administered as part of a multidrug resistant tuberculosis (MDR TB) regimen. The total duration of treatment with TMC207 is 24 weeks. TMC207 should be taken with food.

2.2.General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
The TMC207 dose selected for use in the Phase IIb trial C208 (400 mg q.d. for 2 weeks, followed by 200 mg t.i.w. for a further 6 weeks in Stage 1 of the C208 trial, and for a further 22 weeks in Stage 2 of the C208 trial. This was later also used in the C209 trial) was based on nonclinical safety and microbiology data, as well as results from the previous clinical trials with TMC207, i.e., Phase I trials (providing safety and pharmacokinetic data) and the Phase IIa trial C202 in subjects with DS-TB (providing safety, pharmacokinetic, and antimycobacterial activity data of TMC207).

The primary efficacy endpoint was time to sputum culture conversion in MGIT during the 8-week (Stage 1, N=47) or 24-week (Stage 2, N=161) investigational treatment period (TMC207/placebo in combination with a background regimen (BR) in Trial C208 in patients with MDR-TB. At the end of TMC207 (or placebo) intake, the BR was continued until a total of 18 to 24 months (72 to 96 weeks) of therapy was reached. This period could be shortened provided that at least 12 months (48 weeks) of BR therapy was given after the confirmed negative culture. Regardless of the duration of the BR treatment period, subjects were to be followed for a total of 96 weeks after the last dose of TMC207 (or placebo) in both Stage 1 and Stage 2 of the C208 trial. This 96-week follow-up period, including the BR treatment period and a subsequent treatment-free follow-up period, allows for evaluation of long-term safety of TMC207 and evaluation of relapse or re-infection (see Figure 2). For Stage 2 of the C208 trial, interim data up to the last available time point (i.e., up to at least Week 72) were used to calculate the number of subjects with relapse/re-infection. The primary efficacy endpoint of Stage 2 of the C208 trial, i.e., time to culture conversion in MGIT during the 24-week investigational treatment period, was evaluated after all subjects had completed the 24-week investigational treatment period or discontinued earlier.

The second Phase IIb trial in the TMC207 program with MDR-TB subjects is the single-arm, open-label trial C209, which provided supportive data. The C209 trial is performed in 233 subjects with MDR-TB, including pre-XDR-TB (44 subjects) and XDR-TB (37 subjects), to further assess the safety and efficacy of TMC207 when added to an individually optimized

MDR-TB treatment regimen according to national and international guidelines, and to collect data in non-newly diagnosed MDR-TB subjects. The C209 trial is ongoing, but all subjects have completed at least the Week 24 visit of the trial or discontinued earlier, which allowed analysis of the primary efficacy endpoint, i.e., time to culture conversion in MGIT during the 24-week investigational treatment period (similar to the C208 trial). The C209 trial included 233 subjects with either newly diagnosed or treatment-experienced MDR-TB infection. In contrast to the C208 trial, subjects with XDR-TB infection were allowed to enter the C209 trial, provided they had at least 3 drugs in their anti-TB regimen to which their *M. tuberculosis* isolate was likely to be susceptible. All subjects received TMC207. TMC207 was administered as 400 mg q.d. for the first 2 weeks and 200 mg t.i.w. for the following 22 weeks, as was done in Stage 2 of the C208 trial. After 24 weeks, subjects continued to receive their BR under the care of their physician and in accordance with national TB program (NTP) treatment guidelines (usually for a total of 72 to 96 weeks or a minimum of 48 weeks after sputum conversion in most national and international treatment guidelines; see Figure 2). The trial is ongoing and all subjects are to be followed up for a total of 96 weeks after their last intake of TMC207, comprising the BR treatment period and a subsequent treatment-free follow-up period of at least 24 weeks (6 months), to allow for evaluation of relapse/re-infection.

Figure 2: Overview of Trial Design and Treatment Periods in Phase IIb Studies C208 and C209

§ 8 weeks in C208 Stage 1 and 24 weeks in C208 Stage 2 and C209.
# Placebo was administered in Stage 1 and Stage 2 of the C208 trial, and not in the C209 trial.
* Could be shortened provided at least 12 months (48 weeks) of BR therapy was given after the first confirmed negative culture.
† At least 8 weeks in C208 Stage 1 and 24 weeks in C208 Stage 2 and C209, if treatment is stopped before Week 96.

2.2.2. *What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?*

The primary efficacy endpoint in the Phase IIb trials was time to sputum culture conversion measured by the mycobacteria growth indicator tube liquid culture system (MGIT 960; performed by local laboratories). This microbiology endpoint is based on the qualitative assessment of culture growth in MGIT using spot sputum samples (samples can be positive, negative, or contaminated) and is a surrogate marker for clinical outcome. Time to sputum culture conversion is more sensitive than the proportion of subjects who convert and is considered an important interim indicator of the efficacy of anti-TB treatment as it has a strong correlation with treatment outcome. This endpoint is evaluated using microbiological methods using solid and liquid media culture. For additional details please see the reviews from the clinical and microbiological disciplines.

2.2.3. Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety bedaquiline was appropriately identified and measured in plasma by a validated LS-MS/MS assay. Please see Section 2.6 for details regarding the bioanalytical methods.

2.2.4. Exposure-Response

2.2.4.1. What are the characteristics for exposure-response relationships (dose-response, concentration-response) for efficacy?

Overall, PK/PD analyses did not identify clear exposure-response relationship for efficacy, suggesting that the proposed dosing regimen may lie at the top of the exposure-response curve.

In the pivotal trial C208 Stage 2, the sponsor submitted full PK profiles obtained at Week 2 and Week 24 in a subgroup of 51 patients following daily administration of 400 mg for two weeks and 200 mg three times per week for additional 22 weeks. Time-to-conversion was used as the primary endpoint for efficacy. With this data, the reviewer explored the relationship between measured PK parameters at week 2 (such as C_{max}, AUC, and the ratio of AUC to MIC) and the corresponding time to sputum conversion. The Kaplan-Meier estimate of the survival curves of bedaquiline subjects were stratified by quartiles of the measured PK parameters. After ruling out the imbalance of potential risk factors, higher exposure (only AUC_{24h} is shown below) was found not to be strongly associated with fewer days to conversion. (Figure 3).

Figure 3: Kaplan-Meier plot by AUC_{24h} (at week 2) quartiles for C208 Stage II (24-week Data selection and Primary Missing=Failure Analysis Method) -ITT
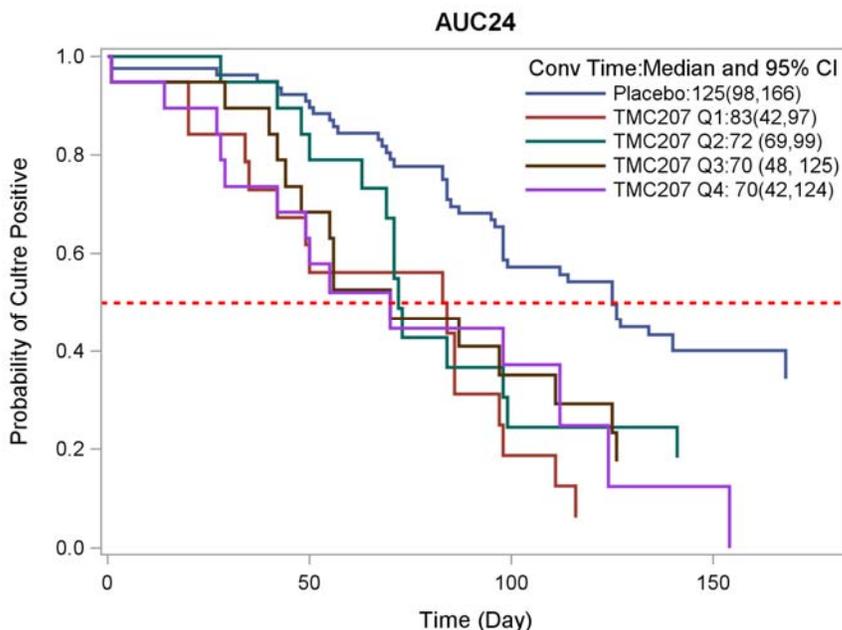
Relationship between culture conversion rate (MGIT) and PK metrics (AUC_{24h}, AUC_{24h}/MIC at week 2) was also examined. No clear and consistent relationship between TMC207 plasma AUC_{24h} or AUC_{24h}/MIC and culture conversion rates was observed (Figure 4).

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Figure 4: Culture Conversion rate (No Overruling, all available data selection) vs. AUC$_{24h}$/MIC quartiles– mITT
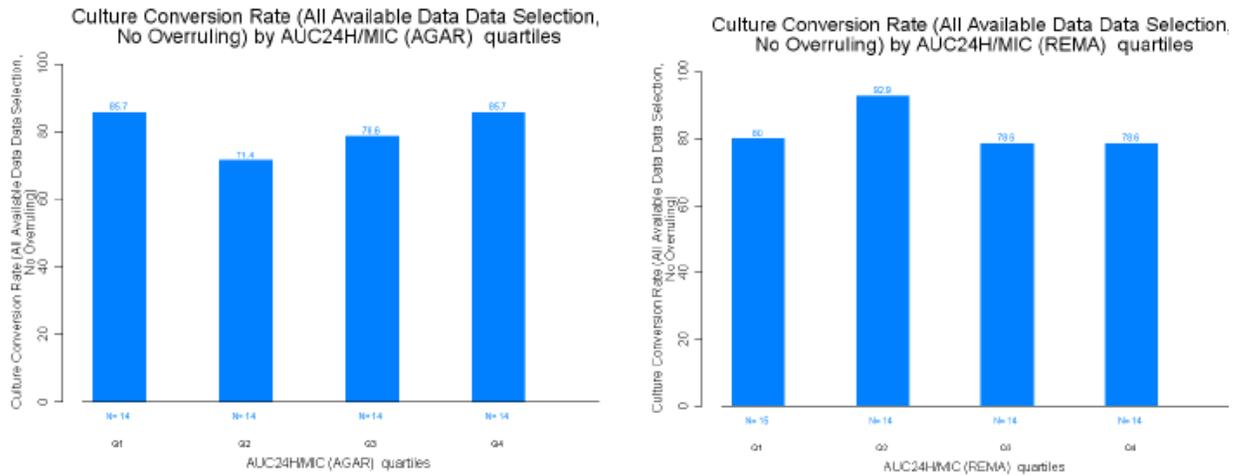

Agar: Q1: <= 416.432; Q2:] 416.432; 560.668]; Q3:] 560.668; 1114.016]; Q4: > 1114.016
REMA: Q1: <= 637.802; Q2:] 637.802; 952.886]; Q3:] 952.886; 1577.271]; Q4: > 1577.271

2.2.4.2.What are the characteristics for exposure-response relationships (dose-response, concentration-response) for safety?

No clear and consistent relationship between exposure and AE incidence was identified for the most frequently observed adverse events. However, this finding should be interpreted with caution. The reviewer first examined adverse events that are likely related to TMC207 treatment and then explored the potential association between drug exposure and incidence of these events. As demonstrated in Figure 5, the most frequently reported AEs (>15% of subjects) after TMC207/BR treatment in Study C208 Phase IIb with incidence consistently higher than the Placebo/BR arm were nausea (38%), arthralgia(32.9%), headache (27.8%), and hemoptysis (17.7%). Despite a small trend for arthralgia, no significant relationship between the AE incidence and TMC207 exposure (C$_{max}$ and AUC$_{24}$) was identified (Figure 6). However, as we only have a limited safety database and a portion of patients with full PK profiles, we cannot rule out the possibility of undetected significant relationship, and the finding here should be interpreted with caution.

Figure 5: Incidence of mostly reported (> 15%) adverse events after TMC207/BR and Placebo/BR treatment
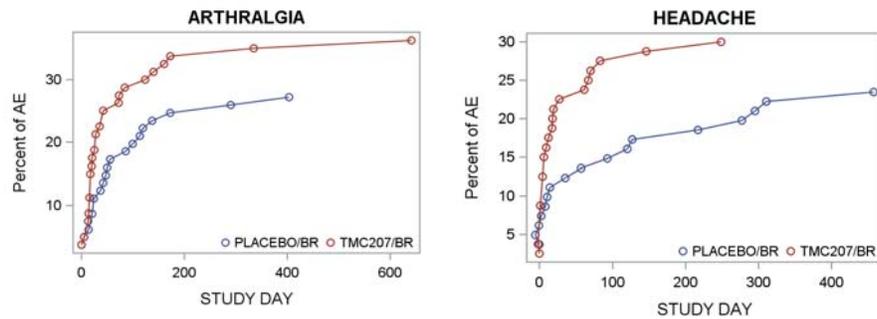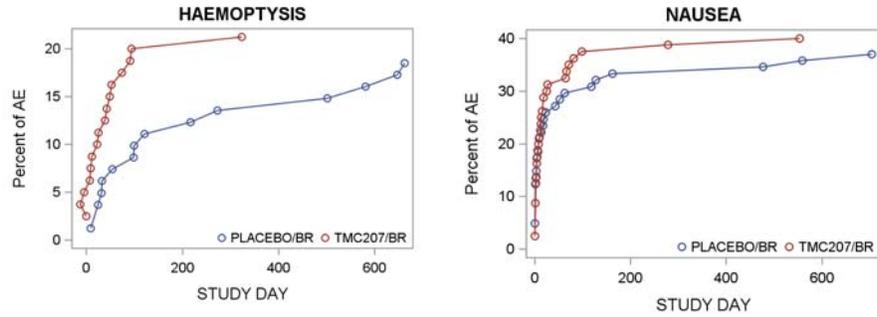
Figure 6: Relationship between AE incidence and AUC$_{24h}$ at Week 2. The blue points are observed quartile mean. The green shaded area is model-estimated 95% CI based on a logistic analysis
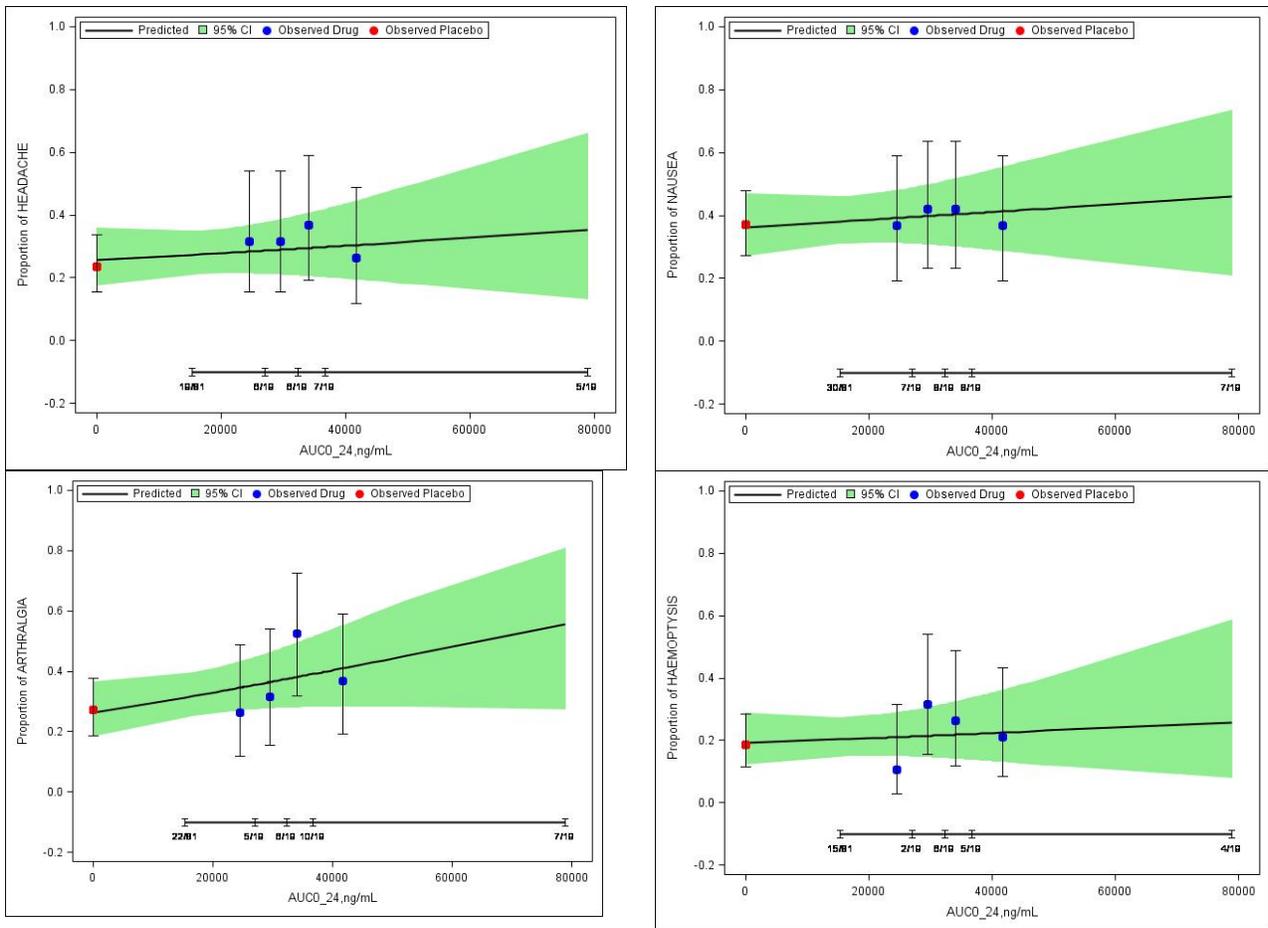
Thorough QT Trial:

The sponsor conducted a TQT trial per the ICH E14 Guidance. The results of the trial were evaluated by the Interdisciplinary Review Team. A brief summary of the findings are given below. For additional details the reader is referred to the IRT review.

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In this randomized, double-blinded, parallel study, 88 subjects with tuberculosis received either 800 mg TMC207 or a single oral dose of moxifloxacin 400 mg, and placebo. The overall summary of findings is presented in Table 1. No significant QTc prolongation effect of TMC207 was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between TMC207 and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms indicating that assay sensitivity was established.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for TMC207 and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time	ΔΔQTcF (ms)	90% CI (ms)
TMC207 800 mg	16	2.7	(0.2,5.2)
Moxifloxacin 400 mg*	10	12	(10.0, 14.0)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 9.3 ms.

The IRT noted that single-dose administration study design was insufficient to achieve exposures of the major metabolite that cover the high-exposure scenario in the clinical setting. Exposure response data from both study c208 and this dedicated QT study combined with the time course of QTcF compared with the time course of TMC207 and M2 concentrations suggest that an exposure-QTcF relationship exists for the metabolite M2. No exposure-QTcF relationship was evident with TMC207 exposure. The clinically relevant exposure of M2 occurs after 14 days of 400 mg q.d. dosing, owing to the long terminal half-life of the metabolite (5.3 months). QTcF assessment in the dedicated QT study was following a single dose of TMC207 and the Cmax and AUC values for M2 were 1/5.4- and 1/6.4- fold of the exposures to M2 observed in tuberculosis patients in the phase 2 study c208.

The relationship between ΔΔQTcF and bedaquiline concentrations is visualized in Figure 7 with no evident exposure-response relationship.

Figure 7: ΔΔ QTcF vs. bedaquiline concentration
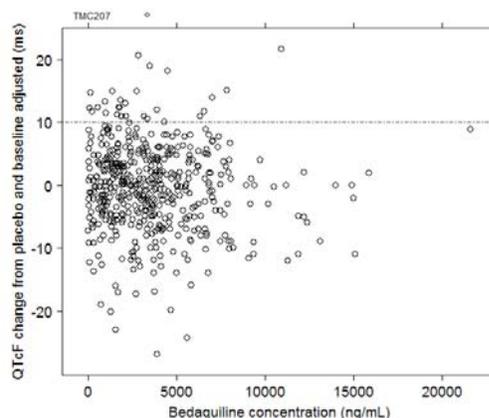
Evidence of an exposure-response relationship was determined for M2. The relationship between ΔΔQTcF and M2 concentrations is shown in Figure 8.

Figure 8: ΔΔQTcF vs. M2 concentration
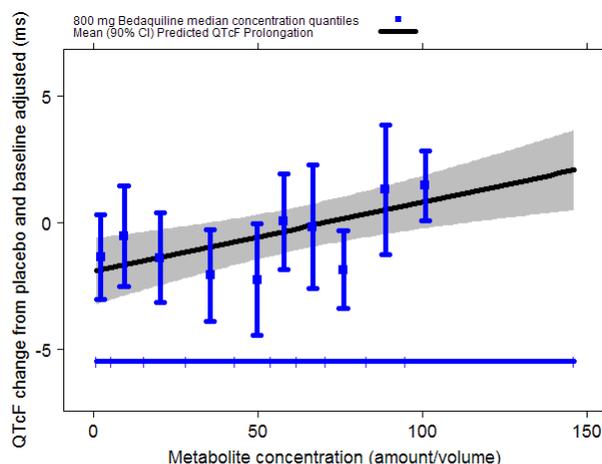
Data from the thorough QT study alone cannot inform of the QTcF prolongation at the clinically relevant concentrations of M2. Since this was single dose study, M2 exposures never achieved clinically relevant concentrations for the high-exposure scenario. Based on the sponsor's analysis after multiple dosing of 400 mg TMC207 q.d. for two weeks, a prolongation of ~10 ms may be expected for the mean C_{max} of 467 ng/mL for patients with tuberculosis. Further analyses of the exposure-QTc prolongation are under review.

> *2.2.4.3.Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?*

Nonclinical data suggested that TMC207 dosing should be in the range of linear pharmacokinetics to avoid over-proportional tissue distribution and potential toxicity. Furthermore, nonclinical toxicity studies showed that intermittent dosing of TMC207 was better tolerated than daily dosing of the same total weekly dose. This observation may be related to the lower tissue distribution of TMC207 and M2 during intermittent dosing versus daily dosing. Results from mouse efficacy studies also supported intermittent TMC207 dosing. In these preclinical studies, TMC207 could be dosed as infrequently as once weekly without loss of efficacy, provided the total weekly dose was the same.

Further, to help determine the dose to be used in the C208 trial, a population pharmacokinetic model for TMC207 was developed to simulate various dosing schedules that would (1) control continued increase of plasma concentrations inherent to the long terminal elimination half-life of TMC207and its main M2 metabolite, (2) maintain total exposure well below the safety threshold (i.e., total TMC207 + M2 AUC_{24h} < 100 μg-h/mL; determined in nonclinical studies), and (3) maintain a high enough dose to achieve antimycobacterial activity. The model was used to simulate various dosing regimens of TMC207 and pharmacokinetic profiles and corresponding pharmacokinetic parameters after 30 and 60 days of administration were predicted. All dosing regimens started with TMC207 400 mg q.d. for the first 2 weeks, followed by (1) 200 mg t.i.w.,

(2) 300 mg t.i.w., (3) 400 mg t.i.w., (4) 400 mg twice per week (b.i.w.), and (5) 200 mg q.d. for the next 6 weeks.

Based on the results of the population pharmacokinetic model and nonclinical data, the proposed dosing regimen for trial C208 started with a loading dose phase of 400 mg q.d. for 2 weeks. This dose was the highest dose tested during multiple-dose administration in several Phase I trials and was generally well tolerated during 2 weeks of daily dosing. Furthermore, a 400-mg dose is still within the range of linear pharmacokinetics in humans and a 400-mg daily dose administered as 7-day monotherapy to DS-TB infected subjects (i.e., the highest dose tested) in trial C202 showed statistically significant extended early bactericidal activity (eEBA) activity and was therefore further explored in the C208 trial. After the loading phase, 200 mg was to be dosed intermittently at 3 times/week (t.i.w.) during the subsequent investigational dosing period in order to restrict the continued increase in plasma concentrations and thus limit potential toxicity, while maintaining antimycobacterial activity.

Based on simulation of the pharmacokinetics of TMC207 in 2000 subjects using the population pharmacokinetic model, the intermittent dosing phase was predicted to result in a daily TMC207 AUC_{24h} of approximately 23 μg.h/mL towards the end of the 2-month treatment period. The highest predicted individual TMC207 AUC_{24h} associated with this intermittent regimen was approximately 40 μg.h/mL. After 2 weeks of TMC207 400 mg q.d., the exposure to M2 was approximately 20% of the TMC207 exposure in humans and hence the highest possible total AUC_{24h} (TMC207 + M2) would remain well below the threshold of 100 μg.h/mL, below which there was no relevant target organ toxicity in nonclinical studies, taking individual variability into account. Furthermore, the total simulated mean exposure during the intermittent dosing phase was not predicted to exceed the no observed adverse effect level (NOAEL) exposure after 6 months of daily dosing in the dog (AUC_{24h} of 37.0 and 39.6. μg.h/mL in males and females, respectively. Although the simulated mean TMC207 plasma concentration during the intermittent dosing phase (approximately 1000 ng/mL) was lower than the average TMC207 concentration associated with activity in trial C202 (i.e., mean average concentration of approximately 2700 ng/mL on Day 7, it remained well above the initially proposed target concentration of 600 ng/mL. The simulated median (90% CI) plasma TMC207 concentration time profile for the 8-week dosing regimen in trial C208, and part of the associated washout phase, is shown in Figure 9.

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Figure 9: Simulated TMC207 Plasma Concentrations for the Proposed 8-Week Dosing Regimen in Trial C208, Stage 1 (Simulation of 400 Subjects)
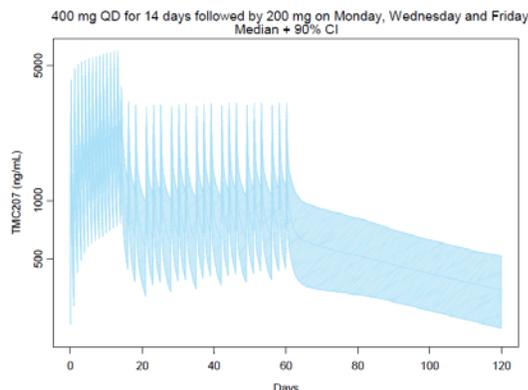
2.2.5.   What are the PK characteristics of bedaquiline?
Following escalating single doses, the plasma concentration-time profiles of TMC207 were characterized by a tri-exponential decline, which was slow in the terminal phase (Figure 10).

Figure 10: Mean Plasma Concentration-Time Profiles of TMC207 After Administration as Single Doses of 10 to 700 mg in Healthy Subjects (Trial CDE-101)
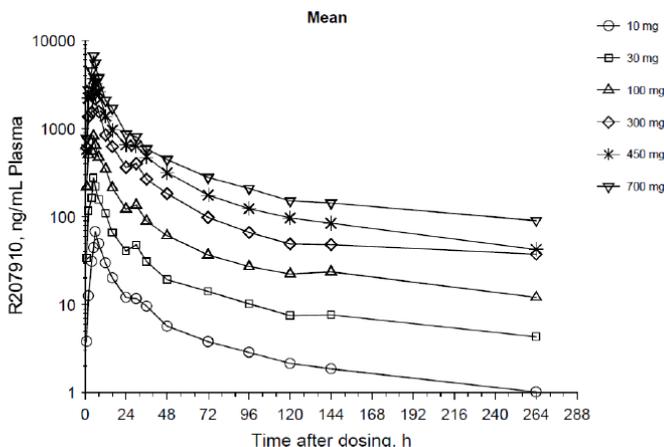
N = 6 in each treatment group, R207901 = TMC207

Further details on the PK of bedaquiline are discussed below.

2.2.5.1.   What are the single dose and multiple dose PK parameters?
Single Dose Pharmacokinetics of bedaquiline
The pharmacokinetics of TMC207 following single dose administration are summarized in Table 2. The median t_{max} ranged from 5 to 6 hours across the dose range tested. The mean C_{max}, AUC_{144h}, and AUC_{∞} values increased in an approximately dose-proportional manner. The mean apparent total clearance from plasma after dosing (CL/F) ranged from 5.35 to 6.32 L/h across the doses tested.

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Table 2: Pharmacokinetics of TMC207 in Plasma After Administration as Single Doses of 10 to 700 mg in Healthy Subjects (Trial CDE-101)

Parameter	Mean ± SD; t_{max}: Median (Range)					
	TMC207 10 mg	TMC207 30 mg	TMC207 100 mg	TMC207 300 mg	TMC207 450 mg	TMC207 700 mg
N	6	6	6	6	6	6
t_{max}, h	6.0 (6.0 - 8.0)	5.0 (5.0 - 5.0)	5.0 (2.0 - 6.0)	5.0 (2.0 - 6.0)	5.0 (2.0 - 5.0)	5.0 (5.0 - 6.0)
C_{max}, ng/mL	68.6 ± 14.8	276 ± 64	854 ± 283	2547 ± 1305	3755 ± 1165	6747 ± 2210
AUC_{144h}, ng.h/mL	1248 ± 233	4418 ± 1424	13604 ± 5115	38737 ± 14584	64530 ± 26927	97816 ± 38074
AUC_{∞}, ng.h/mL	1700 ± 291	6052 ± 1861	18134 ± 6577	53113 ± 17911	79179 ± 31794	133125 ± 44913
CL/F, L/h	6.05 ± 1.17	5.35 ± 1.63	6.19 ± 2.35	6.11 ± 1.70	6.32 ± 2.01	5.62 ± 1.29
$t_{1/2}$, h [a]	162 ± 84	143 ± 31	135 ± 24	169 ± 19	117 ± 19	172 ± 37

N = maximum number of subjects with data.
[a] Elimination $t_{1/2}$ as estimated over the sampling period, which does not represent the true elimination $t_{1/2,term}$.

Multiple Dose Pharmacokinetics of bedaquiline

The pharmacokinetics of TMC207 following multiple dose administration for 14 days are summarized in Table 3. On Day 1, the median t_{max} of TMC207 was 5 hours with the 50 and 150 mg doses, and 4 hours with the 400 mg dose. The mean C_{max}, C_{24h}, and AUC_{24h} values increased in an approximately dose-proportional manner.

The absorption rate of TMC207, as indicated by t_{max}, remained unchanged during the 14-day dosing period. On Day 14, the median t_{max} was 5 hours for all doses. The mean C_{max}, C_{24h}, and AUC_{24h} values increased in an approximately dose-proportional manner, suggesting linear pharmacokinetics up to a dose of 400 mg q.d. The mean CL/F ranged from 6.45 to 8.03 L/h across the doses tested. The mean elimination $t_{1/2}$ within the PK sampling period in this trial ranged from 167 to 173 hours. The mean accumulation index for C_{max} and AUC_{24h} was 1.42 to 1.68 and 1.90 to 2.44, respectively, across the doses studied.

Table 3: Pharmacokinetics of TMC207 in Plasma After Administration as Multiple Doses of 50 to 400 mg q.d. in Healthy Subjects (Trial CDE-102)

Parameter	Mean ± SD; t_{max}: Median (Range)		
	TMC207 50 mg q.d.	TMC207 150 mg q.d.	TMC207 400 mg q.d.
Day 1			
N	6	6	6
t_{max}, h	5.0 (5.0 - 6.0)	5.0 (5.0 - 5.0)	4.0 (2.0 - 5.0)
C_{max}, ng/mL	428 ± 112	1132 ± 401	3005 ± 493
C_{24h}, ng/mL	63.4 ± 10.0	180 ± 53.0	512 ± 114
AUC_{24h}, ng.h/mL	3989 ± 830	9922 ± 3199	27206 ± 5361
Day 14			
N	6	5	6
t_{max}, h	5.0 (5.0 - 6.0)	5.0 (5.0 - 5.1)	5.0 (3.0 - 6.0)
C_{max}, ng/mL	590 ± 116	1972 ± 559	4298 ± 1315
C_{24h}, ng/mL	187 ± 44.0	604 ± 147	1280 ± 309
AUC_{24h}, ng.h/mL	7914 ± 2009	24265 ± 5670	51525 ± 10123
CL/F, L/h	6.66 ± 1.66	6.45 ± 1.45	8.03 ± 1.68
$t_{1/2}$, h [a]	169 ± 77	167 ± 48	173 ± 35

N = maximum number of subjects with data.
[a] Elimination $t_{1/2}$ as estimated over the sampling period, which does not represent the true elimination $t_{1/2,term}$.

The multiple-dose pharmacokinetics of TMC207 when administered under fed conditions (standard meal) as the Phase II tablet were assessed in trial C208 in MDR-TB infected subjects, which was conducted in 2 stages (Stage 1 and Stage 2) with different subjects participating in each stage (Table 4). TMC207 was administered at a dose of 400 mg q.d. for the initial 2 weeks in both stages of the trial, which was then followed by administration of TMC207 at a dose of 200 mg t.i.w. for either a further 6 weeks (Stage 1) or a further 22 weeks (Stage 2).

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Table 4: Pharmacokinetics of TMC207 in Plasma After Administration of TMC207 400 mg q.d. (Week 2, Stages 1 and 2) Followed by 200 mg t.i.w. (Week 8 [Stage 1] or Week 24 [Stage 2]) in MDR-TB Infected Subjects (Trial C208, Stages 1 and 2)

| Parameter | Mean ± SD; t_{max}: Median (Range) | | | |
| | TMC207 400 mg q.d. + BR | | TMC207 200 mg t.i.w. + BR | |
	Week 2 (Stage 1)	Week 2 (Stage 2)	Week 8 (Stage 1)	Week 24 (Stage 2)
N	21	30	18	19
t_{max}, h	5.97 (2.97 - 8.00)	5.00 (2.33 - 6.17)	5.03 (2.75 - 8.33)	5.05 (3.07 - 6.77)
C_{0h}, ng/mL	1004 ± 657	792 ± 264	670 ± 532	454 ± 295
C_{max}, ng/mL	3270 ± 1144	2763 ± 1185	1659 ± 722	1267 ± 435
AUC_τ, ng.h/mL [a]	42500 ± 16810	32960 ± 12720	43370 ± 25740	28010 ± 9408
$C_{ss,avg}$, ng/mL	1770 ± 701	1371 ± 529	902 ± 535	584 ± 197
CL/F, L/h	10.7 ± 3.68	14.7 ± 8.52	6.00 ± 3.19	8.06 ± 3.51

N = maximum number of subjects with data.

[a] τ = 24 hours for Week 2 and 48 hours for Weeks 8 and 24.

Due to its long elimination $t_{1/2,term}$, steady-state concentrations of TMC207 were not achieved prior to full pharmacokinetic sampling at Week 2. Apparent steady-state concentrations were seen in most subjects by Week 8 of Stage 1 with no sign of further accumulation with the intermittent dosing regimen. A majority of subjects achieved average concentrations of TMC207 above the target of 600 ng/mL (i.e., the concentration estimated from nonclinical data to maintain the effective systemic exposure/MIC ratio) throughout the dosing period (Figure 11).

Figure 11: Individual Predose Plasma Concentrations of TMC207 After Administration of TMC207 400 mg q.d. (Week 1 to 2) and After Administration of TMC207 200 mg t.i.w. (Weeks 3 to 8) (Trial C208, Stage 1)

Δ Week 1 sample of subject 2083012 had an undetectable predose plasma concentration. Excluded from descriptive statistics
O Pharmacokinetic parameters of subject 2083057 and 2083125 were excluded due to no administration of TMC207 on Week 8
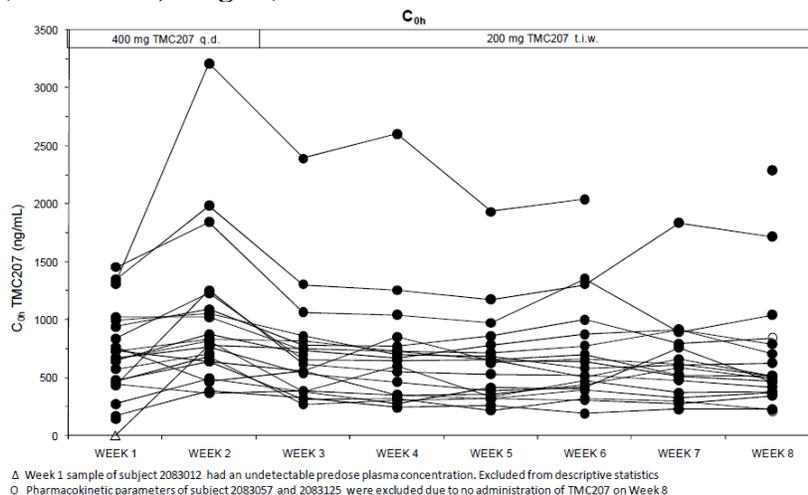
2.2.5.2.   *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

TMC207 Administered as Oral Solution

After multiple-dose administration of TMC207 as the oral solution at a dose of 400 mg q.d., the mean exposure (C_{max} and AUC_{24h}) to TMC207 was generally comparable between healthy subjects in trials CDE-102, C104, and C109, and DS-TB infected subjects in trial C202 (Table

5). The median t_{max} was 5 hours in all the trials in healthy subjects, and 4 hours in the TB infected subjects.

Table 5: Pharmacokinetics of TMC207 in Plasma After Multiple-Dose Administration of TMC207 400 mg q.d. as an Oral Solution in Healthy Subjects (Trials CDE-102, C104, and C109) and DS-TB Infected Subjects (Trial C202)

Parameter	Mean ± SD; t_{max}: Median (Range)			
	Healthy			DS-TB Infected
	CDE-102 Day 14	C104 Day 10	C109 Day 11	C202 Day 7
N	6	22	15	12
t_{max}, h	5.0 (3.0 - 6.0)	5.0 (3.0 - 6.0)	5.0 (2.0 - 6.0)	4.0 (2.05 - 6.02)
C_{max}, ng/mL	4298 ± 1315	4408 ± 1532	6400 ± 2096	5502 ± 2695
AUC_{24h}, ng.h/mL	51525 ± 10123	51360 ± 15750	77740 ± 26770	64750 ± 20700

N = maximum number of subjects with data.

2.2.5.3. *What are the characteristics of drug absorption?*

The absolute bioavailability of TMC207 has not been investigated in humans because an acceptable intravenous formulation was not available. In particular, an intravenous formulation of TMC207 is challenging to produce due to the poor solubility of the TMC207 drug substance.

In Vitro Absorption Studies

Human Caco-2 cells were used as an in vitro model to investigate the bi-directional transcellular permeability of TMC207 using unlabeled TMC207 and ^{14}C-TMC207. Furthermore, the transport of the major metabolite M2 was investigated using ^{3}H-M2. The P_{app} of TMC207 or its metabolite M2 was determined in both the apical to basolateral direction (absorptive transport) and the basolateral to apical direction (secretory transport). Despite having a low in vitro P_{app}, TMC207 is considered to be a moderate to high permeability compound because it was well absorbed after oral administration in animal studies. Both TMC207 and M2 were taken up by, or bound to, the Caco-2 cells, which may explain the apparent low in vitro P_{app} in this model. There was no indication that transport of the 2 compounds was affected by an apically located efflux transporter such as P-gp. Overall, inhibition of P-gp transport by TMC207 in vitro was only observed at concentrations far above therapeutic concentrations of TMC207, even when significant tissue accumulation of TMC207 and M2 is taken into account. Therefore, a relevant effect of TMC207 or M2 on P-gp transport is considered unlikely.

Clinical Trials Evaluating Effect of Food on TMC207 Absorption

In clinical trials, the effect of concomitant food intake on oral absorption of TMC207 was investigated in terms of the effect on relative bioavailability of TMC207. Irrespective of the TMC207 formulation administered (oral solution, capsule, or tablet formulations); concomitant food intake consistently increased the oral bioavailability of TMC207. The meal type used in these trials was the standard meal, which provided a total of 558 Kcal, 35% of which was derived from fat sources. The meal included 1 cereal (35 g) and 200 mL semi-skimmed milk, 2 slices granary toast, 2 x 10 g flora and 1x 21 g jam and 200 mL tea or coffee. The mean exposure to TMC207 increased 1.3-fold when administered under fed conditions as an oral solution (40 mg/mL, formulation F004) in trial CDE-101 (AUC_{144h}) or as a 100 mg capsule (formulation F006) in trial C108 (AUC_{last}). M2 was not measured in trial CDE-101.

When TMC207 was administered as the 100 mg Phase II tablet (formulation F001) under fed conditions in trials C108 (Table 6) and C111 (Table 7), the mean exposure to TMC207 increased 2.0-fold (AUC_{last}) and 2.4-fold (AUC_{672h}), respectively. Based on these results, it is recommended that TMC207 is administered with food, which is consistent with the dosing instructions in the Phase II trials.

Table 6: Pharmacokinetic Results of TMC207 in Trial C108

Pharmacokinetics of TMC207 Panel 2 (mean ± SD, t_{max} median (range))	Treatment A: Oral solution, fed	Treatment D: Fumarate salt in tablet, fed	Treatment E: Fumarate salt in tablet, fasted
n	12	12	12[a]
C_{0h}, ng/mL	4.828 ± 4.324	5.885 ± 6.829	7.748 ± 6.766
t_{max}, h	5.5 (3.0 - 8.0)	4.5 (3.0 - 6.0)	8.0 (4.0 - 12.0)
C_{max}, ng/mL	739.1 ± 220.3	732.8 ± 180.7	282.5 ± 90.20
AUC_{last}, ng.h/mL	17210 ± 4916	17580 ± 4944	9361 ± 3604
AUC_{∞}, ng.h/mL	20830[b] ± 5824[b]	20660[b] ± 6552[b]	11340[b] ± 5338[b]
$t_{1/2term}$, h	148.8[b] ± 54.56[b]	129.6[b] ± 19.77[b]	145.7[b] ± 52.62[b]

[a] n=9 for AUC_{∞} and $t_{1/2term}$
[b] accurate determination not possible

Table 7: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of TMC207 After Administration of TMC207 Formulated as Phase II Clinical Trial Tablet Under Fed Conditions (Treatment A) and Under Fasted Conditions (Treatment D) [Trial C111]

Parameter	LSmeans[a]		LSmeans ratio	90% CI
	Phase II clinical trial tablet (F001) under fasted conditions (reference 2)	Phase II clinical trial tablet (F001) under fed conditions (reference 1)		
C_{max}, ng/mL	296.5	1113	3.75	2.91 - 4.84
AUC_{72h}, ng.h/mL	6059	14760	2.44	1.91 - 3.10
AUC_{672h}, ng.h/mL[b]	10820	25730	2.38	1.77 - 3.20

[a] n=13 for reference 2 and n=12 for reference 1
[b] n=12 for reference 2

2.2.5.4. What are the characteristics of drug distribution?

The in vitro human plasma protein binding of TMC207, determined by equilibrium dialysis, was on average in excess of 99.99%, irrespective of the TMC207 concentration (up to 30 μg/mL). The protein binding of M2 was also high in human plasma (> 99.7% at M2 concentrations of 10 and 30 μg/mL. Data on the $R_{bl}/_{pl}$ for TMC207 are not available. The $R_{bl}/_{pl}$ ratios of M2 were independent of the concentration of M2 compound tested (ratio of approximately 1). The apparent volume of distribution of bedaquiline in the central compartment was estimated to be around 164 L.

Since *M. tuberculosis* is capable of surviving within phagocytes (e.g., infected macrophages, monocytes), the measurement of drug concentrations in phagocytes was of interest also in the context of the potential for TMC207 and M2 to induce phospholipidosis. This can promote the accumulation of drugs in tissues. After administration of TMC207 at single doses of 10 to 700 mg in Studies CDE-101 and CDE-102, the penetration of TMC207 from plasma to peripheral blood monocytes occurred with a median t_{max} of 4 to 6 hours, which was generally similar to the t_{max} values seen for plasma. The mean C_{max} and AUC of TMC207 in peripheral blood monocytes increased in an approximately dose-proportional manner in both trials, suggesting approximately linear pharmacokinetics up to a dose of 700 mg. The mean $t_{1/2}$ measured in Trial CDE-101 ranged from 83.6 to 99.4 hours, with no relationship to the dose administered, the mean

accumulation index on Day 14 ranged from 2.00 to 2.34 for C_{max} and 1.88 to 3.28 for AUC_{24h}. The mean elimination $t_{1/2}$ ranged from 99 to 150 hours, which was comparable with mean elimination $t_{1/2}$ in plasma in this trial. In both trials, there was a linear correlation between the concentration of TMC207 in peripheral blood monocytes and the concentration of TMC207 in plasma.

In Tables 8 and 9, the PK parameters of TMC207 in peripheral blood monocytes following single and multiple oral administration in healthy male subjects are presented.

Table 8: Pharmacokinetic Parameters of Bedaquiline in Peripheral Blood Monocytes Following Single Oral Administration in Healthy Male Subjects (Part 1)

Dose (mg)	t_{max} (h)	C_{max} (ng/sample)	AUC_∞ (ng·h/sample)	$t_{1/2}$ (h)
10	5.7 ± 0.8	0.76 ± 0.15	NA	NA
30	3.3 ± 1.0	1.87 ± 0.64	55.9 ± 7.40^a	83.6 ± 9.6
100	3.7 ± 1.5	10.4 ± 4.20	192 ± 51.0	93.9 ± 15.5
300	5.3 ± 1.6	19.9 ± 5.50	523 ± 171	91.1 ± 15.1
450	6.0 ± 0	43.6 ± 15.2	995 ± 269	99.4 ± 22.6
700	6.3 ± 2.9	53.7 ± 23.5	$1,389 \pm 229$	95.4 ± 23.1

Data are presented as mean ± SD; N=6 for each cohort unless specified; [a]N=5; h=hour; NA=not assessable; SD=standard deviation; Cross-reference: Attachment 3.4 (Part 1).

Table 9: Pharmacokinetic Parameters of Bedaquiline in Peripheral Blood Monocytes Following Once Daily Oral Dosing for 14 Days

Dose mg	t_{max} h	C_{max} ng/sample	AUC_τ ng·h/sample	$t_{1/2}$ h
Day 1				
50	4.0 ± 2.5	2.74 ± 0.88	34.8 ± 6.70^a	NA
150	6.8 ± 2.6	9.16 ± 4.78	114 ± 43.2^b	NA
400	4.7 ± 1.3	22.1 ± 8.30	171 ± 63.0	NA
Day 14				
50	7.3 ± 3.3	5.70 ± 2.17	73.6 ± 19.9^b	150 ± 67
150	5.4 ± 0.5^b	15.3 ± 4.70^b	175 ± 81.3^b	99.3 ± 40.7
400	5.2 ± 0.4	46.9 ± 16.2	523 ± 143	131 ± 73

Data are presented as mean±standard deviation. n=6 for each cohort unless specified; [a]n=4; [b]n=5; h=hours; NA=not available due to sampling period of 0 to 24 hours on Day 1; Cross-reference: Attachment 3.4

Both TMC207 and M2 have shown accumulation in various tissues in nonclinical species, which is likely, a result of the cationic amphiphilic characteristics of these moieties and may cause intracellular accumulation of phospholipids in association with drug accumulation (phospholipidosis). Phospholipidosis has been observed following administration of TMC207 and M2 in nonclinical studies. The phospholipidosis-inducing potential of TMC207, M2, and M3 towards human acute monocytic leukemia cell line (THP-1) cells, a human monocyte cell line, has been assessed in vitro in nonclinical studies. TMC207 as well as M2 and M3 induced phospholipidosis in THP-1 cells; the metabolites were stronger inducers of phospholipidosis than TMC207. Upon termination of drug intake, the phospholipidosis is generally reversible as the drug is eliminated from the tissues. The time course of reversal is dependent on the dissociation rate constant of the cationic amphiphilic drug (CAD) from the phospholipid and the elimination rate of the CAD from the tissue, which may result in a prolonged elimination $t_{1/2,term}$, as observed for TMC207 and M2.

Distribution of TMC207 and M2 to Sputum

In trial C202, in which DS-TB infected subjects were treated with TMC207 at doses of 25, 100, or 400 mg q.d. for 7 days, TMC207 and M2 were detected in sputum (which also contains cells) from Days 1 to 7. The mean concentrations of TMC207 and M2 in sputum increased in an approximately dose-proportional manner, and both analytes showed positive correlations between concentrations in plasma and sputum. However, the magnitude of exposure in sputum was lower than that in plasma with the increase in dose of TMC207. The mean sputum to plasma concentration ($C_{ss,avg}$) ratios for TMC207 on Day 7 were 1.22 for the 25 mg q.d. dose, 0.74 for 100 mg q.d., and 0.64 for 400 mg q.d. The corresponding values for M2 were 0.21, 0.35, and 0.58, respectively.

In Stage 1 of trial C208, the mean sputum concentrations of TMC207 were generally comparable at Weeks 1 (321 ±280 ng/g; CV 87%), 4 (313 ± 335ng/g; CV 101%), and 8 (381±572 ng/g; CV 150%), and higher at Week 2 (508 ±583 ng/g; CV 115%), but the inter-patient variability around the mean values was high. Sputum concentrations of M2 were highest at Week 8 (875 ng/g) and lowest at Week 1 (330 ng/g). As with TMC207, the inter-patient variability around the mean values was high. The mean concentrations of M2 in sputum exceeded those of TMC207 at all time points, which is consistent with the nonclinical findings of the tissue penetration of M2 being higher than that of TMC207, including the lung, due to M2 being a stronger phospholipidosis inducer, resulting in more pronounced binding to intracellular phospholipids. It should be noted, though, that the antimycobacterial activity of M2 is 4- to 6-fold lower than that of TMC207.

Follow-up samples from Stage 1 of trial C208 showed that TMC207 and M2 were still detectable in sputum for up to at least 16 weeks after treatment with TMC207 had been completed. At 2 weeks after the last dose of TMC207 200 mg t.i.w., TMC207 was quantifiable in the sputum of all subjects for whom samples were available (N=16). Sputum concentrations for individual subjects varied between 8.90 and 277 ng/g. At Week 24, reliable TMC207 sputum concentrations were available for only 6 subjects; for 3 of these subjects the concentrations of TMC207 were above LLOQ (3.52 ng/g). For M2, sputum concentrations at Week 10 ranged between 36.8 and 1170 ng/g. At Week 24, of the 6 subjects for whom sputum concentrations were available for TMC207, the concentrations of M2 were above LLOQ (4.07 ng/g) for 3 subjects, ranging between 17.4 and 58.5 ng/g.

In Stage 2 of trial C208, TMC207 and M2 sputum concentrations were higher at Weeks 1 and 2 (when TMC207 was dosed at 400 mg q.d.) compared to the concentrations at Week 8, 16, and 24 (when TMC207 was dosed at 200 mg t.i.w.). For TMC207, at Week 2 the mean sputum concentration was 309 ± 266 ng/g (N=16), with quantifiable individual sputum concentrations ranging between 26.3 and 980 ng/g. At Week 24, the mean TMC207 sputum concentration was 130 ± 114 ng/g, with individual values ranging between 12.9 and 359 ng/g. For M2, the mean sputum concentration was 969.3 ng/g (110 to 2920 ng/g) at Week 2 and 155.3 ng/g (17.4 to 456 ng/g) at Week 24, but data were available from only 4 subjects.

> *2.2.5.5.   Does the mass balance trial suggest renal or hepatic as the major route of elimination?*

A mass balance trial was not conducted for bedaquiline.

2.2.5.6. What are the characteristics of drug metabolism?

In vitro studies indicate CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline and the formation of the major metabolite, N-monodesmethyl bedaquiline (M2). The minor metabolite, M3, was formed by further N-demethylation of M2.

Across Phase 1 studies with single-dose (700 mg; Trial CDE-101) and multiple-dose (50-400 mg once daily for 14 days; Trial CDE-102) bedaquiline, M2 was the major metabolite detected in the plasma, which represented approximately 20% of the bedaquiline AUC and the mean $t_{1/2\ term}$ of M2 is ~5.5 months. The PK parameters of M2 observed in Stages I and II trial C208 are given below in Tables 10 and 11.

Table 10: Pharmacokinetic Results of M2 After Administration of TMC207 at 400 mg q.d. (Week 2) and After Administration of TMC207 at 200 mg t.i.w. (Week 8) [Stage I]

Pharmacokinetics of M2 (mean ± SD, t_{max}: median [range])	400 mg TMC207 q.d. + BR (Week 2)	200 mg TMC207 t.i.w. + BR (Week 8)
n	21	18[a]
t_{max}, h	6.00 (0 - 24.18)	6.99 (0 - 48.00)
C_{0h}, ng/mL	380.7 ± 156.8	262.3 ± 137.1
C_{min}, ng/mL	339.3 ± 141.5	217.4 ± 119.3
C_{max}, ng/mL	450.4 ± 167.3	300.7 ± 143.2
AUC_τ, ng.h/mL	9378 ± 3568	12240 ± 6665
$C_{ss,av}$, ng/mL	390.5 ± 148.1	254.5 ± 138.5
Fluctuatin index, %	29.71 ± 11.45	36.86 ± 15.98
Ratio $AUC_{\tau, M2/TMC207}$, %	22.92 ± 6.225	31.16 ± 12.72

τ = 24h for Week 2 and 48h for Week 8
[a] n = 17 for AUC_τ, $C_{ss,av}$, and fluctuation index

Table 11: Pharmacokinetic Results of M2 After Administration of TMC207 at 400 mg q.d. for 2 Weeks (Week 2), Followed by Administration of TMC207 at 200 mg t.i.w. for 22 Weeks (Week 24) [Stage II]

Pharmacokinetics of M2 mean ± SD, t_{max}: median (range)	400 mg TMC207 q.d. (Week 2)	200 mg TMC207 t.i.w. (Week 24)
n	26[a]	17[b]
C_{0h}, ng/mL	426.5 ± 135.1	162.4 ± 70.72
C_{min}, ng/mL	331.6 ± 121.7	120.3 ± 56.98
C_{max}, ng/mL	466.9 ± 156.8	177.9 ± 70.70
t_{max}, h	6.15 (1.10 - 24.17)	12.08 (5.00 - 48.08)
AUC_τ, ng.h/mL	9217 ± 3151	7270 ± 2532
$C_{ss,av}$, ng/mL	383.0 ± 129.9	151.6 ± 52.81
FI, %	40.63 ± 17.96	42.18 ± 18.21
Ratio $AUC_{\tau, M2/TMC207}$, %	31.08 ± 14.30	26.14 ± 4.494

τ = 24 h for Week 2 and 48 h for Week 24
[a] n = 30 for C_{0h} and C_{min}, n = 29 for C_{max} and t_{max}
[b] n = 18 for C_{0h} and C_{min}, n = 19 for C_{max} and t_{max}

2.2.5.7. What are the characteristics of drug excretion?

The renal elimination of bedaquiline as unchanged drug is not appreciable. In early Phase I trials the drug concentration in urine was measured in a few patients. In trial CDE-102, only negligible amounts of TMC207 (< 0.001% of the dose) were recovered as unchanged drug after repeated dosing in healthy subjects. TMC207 concentrations in urine on Day 1 were not measurable in the 50 and 150 mg dose groups, but were measurable in all subjects in the 400 mg group. On Day 14, TMC207 concentrations were not measurable with the 50 mg q.d. dose, but were measurable

in 2 out of 6 subjects with 150 mg q.d., and in all subjects (N=6) with 400 mg q.d. With 400 mg q.d., the amount of TMC207 excreted in urine during a dosing interval increased over time, with an accumulation index of 2.1 on Day 14. This magnitude of increase was comparable with the increase of AUC_{24h} in plasma (1.9- to 2.4-fold) over time, indicating that there was no alteration in renal clearance (CL_R) over the dosing period. On Day 14, the mean amount of TMC207 excreted in urine over the 24-hour dosing interval was 0.001 mg with 150 mg q.d. and 0.004 mg with 400 mg q.d., corresponding to $\leq 0.001\%$ of the orally administered dose.

For individuals who received the 400 mg q.d. dose, the estimated mean CL_R was 0.0009 L/h (0.015 mL/min). Because the mean oral clearance (CL/F) ranged from 6.5 to 8.0 L/h, the CL_R was only 0.01% of CL/F, even though steady-state had not been reached. Overall, these data indicate that the urinary excretion of the unchanged drug represents a negligible elimination pathway. Based on the data from those Phase I trials the extent of drug excreted in urine was determined to be <0.001%. Urinary concentrations were also measured in Trial BAC1003 (DDI trial with rifampin) and the results indicated that a majority of concentrations of both TMC207 and M2 were below the limit of assay quantitation in the urine.

>   *2.2.5.8.   Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

The dose-linearity of TMC207 PK was evaluated in Trials CDE-101 and CDE-102. As shown in Figures 12, 13 and 14, the systemic exposure increased in a dose-proportional manner. Also, as seen in Table 1 and 2, following single dose administration the clearance remains fairly constant across the range of doses tested indicating linearity.

Figure 12. Relationship between dose and systemic exposure on Day 1 and Day 14 (Trial CDE-101)
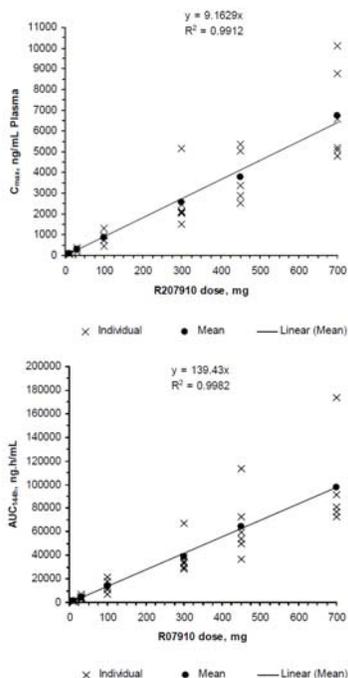
Figure 13. Relationship between dose and C$_{max}$ on Day 14 (Trial CDE-101)
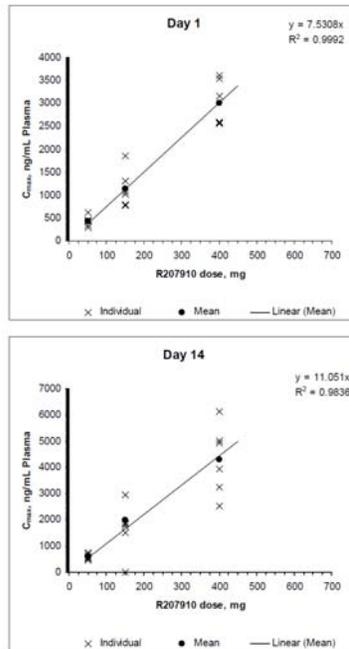
Figure 14. Relationship between dose and AUC on Day 1 and Day 14 (Trial CDE-102)

24
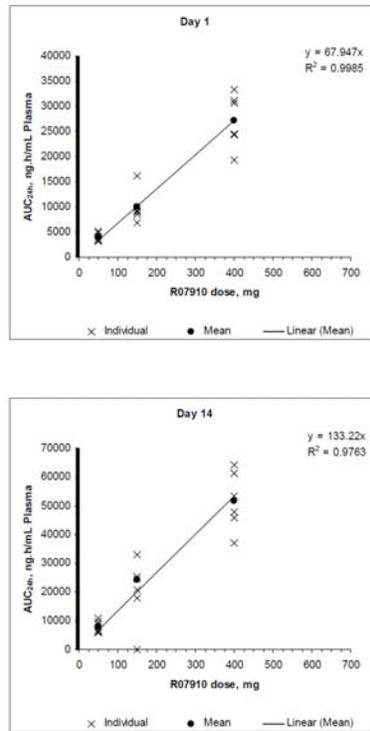
2.2.5.9.   How do the PK parameters change with time following chronic dosing?
Bedaquiline PK is characterized by a very long terminal elimination half-life (4-5 months).
However, the slow elimination of the drug is due to its extensive tissue penetration followed by
slow release from the tissues. The 'effective' half-life was calculated to be around 24-30 hours.
Given this long half-life, true steady-state was not reached during the course of the drug
administration over the 6-month period. Using the PK parameters generated in healthy
volunteers, simulations were conducted by the sponsor to predict the PK profile following
administration of the proposed clinical regimen. This is shown in Figure 9.

As seen in Figure 9, steady-state was not reached following repeat administration of the 400 mg
dose QD. However, the 200 mg t.i.w. regimen appears to result in steady-state after the 400 mg
QD regimen over a 14-day period.

*2.2.5.10.   What is the inter- and intra-subject variability of PK parameters in volunteers
and patients, and what are the major causes of variability?*
The interindividual variability of TMC207 pharmacokinetic parameters is generally moderate
and independent of the dose administered; in the final population pharmacokinetic analysis, the
interindividual variability was 50.5 and 39% for apparent clearance (CL/F) and central volume of
distribution, respectively.

2.3. Intrinsic Factors

*2.3.1.   What intrinsic factors influence exposure and/or response, and what is the impact of any
differences in exposure on efficacy or safety responses?*
Individual PK parameters were estimated by the sponsor's final population PK model. The
relationships between TMC207 oral clearance (CL/F) and selected covariates, including body
weight, age, sex, Cr_{CL}, albumin, and race were explored. As demonstrated in Figure 15 below,
there are no significant relationships between TMC207 clearance and the covariates of interest,
except race, where African-American patients were observed to have clearance that was 52%
higher compared to subjects of other race. Addition of African-American race to the reference
population PK model reduced inter-individual variations of apparent clearance (CL/F) by 5%.
Using the developed model, the sponsor projected that TMC207 exposure in African-American
patients would be 34.3% lower compared to other races. However, a subgroup analysis did not
identify a significant difference in efficacy of bedaquiline among races, suggesting that higher
clearance might not be clinically significant. The sponsor did not propose dose-adjustment in
African-American patients.

There were no significant relationship between central volume of distribution (Vc/F) and the
selected covariates (data not shown).

PK Parameter-Covariate Relationships

Figure 15: PK parameter-covariates relationships. The red lines are smoothed lines showing the trend. The box plots and black circles are based on empirical Bayesian individual estimates
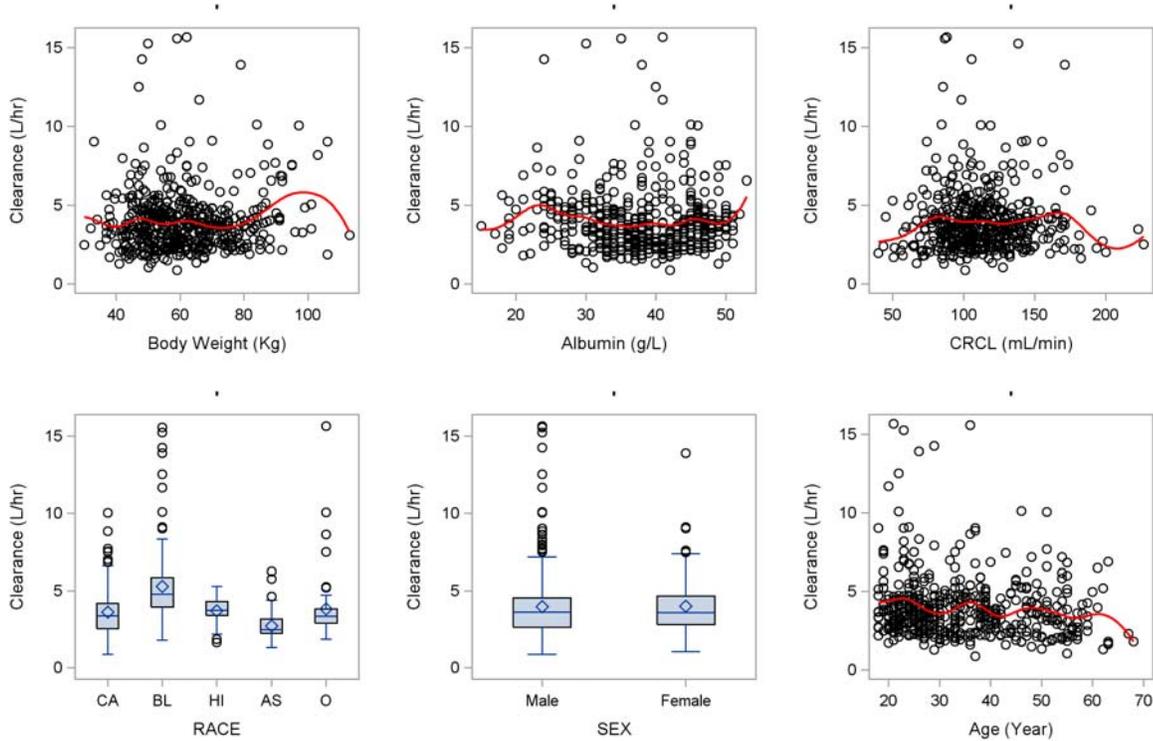
2.3.2. *Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

     2.3.2.1.*Weight*
No dose adjustment on body weight is needed. As demonstrated in section 2.5.10, body weight is not a significant covariate for clearance.

     2.3.2.2.*Elderly*
No dose adjustment for the elderly is recommended. The effect of age on clearance is small.

     2.3.2.3.*Pediatric patients*
Bedaquiline has not been studied in children (individuals under 18 years of age).

     2.3.2.4.*Gender*
No dose adjustment for gender is needed.

2.3.2.5.Race

No dose adjustment for race is recommended. While African-American patients have lower exposure than patients of other races, no difference in efficacy among races was identified.

2.3.2.6.Renal impairment

The effect of renal impairment on bedaquiline PK has not been investigated. A review of scientific literature did not indicate that renal impairment occurs commonly in MDR-TB patients. Based on urine concentrations of bedaquiline in 2 Phase 1 trials, it appears that there is negligible renal excretion of unchanged TMC207. Creatinine clearance (CL_{CR}) was not associated with TMC207 exposure in the population pharmacokinetic analysis. The sponsor has suggested that no dose modification is required in patients with mild or moderate renal impairment and bedaquiline should be used with caution in patients with severe renal impairment or end-stage renal disease. However, the clinical pharmacology team is recommending that the confirmatory trial (C210) should include a cohort of 6-8 patients with severe renal impairment and PK evaluations should beconducted in those patients to evaluate if the exposure in these patients is different from patients with normal renal function

2.3.2.7.Hepatic impairment

No dosage adjustment of TM207 is needed in subject with mild and moderate hepatic impairment (Child-Pugh Classes A and B, respectively). The sponsor is proposing to contraindicate the administration of TMC207 to subjects with severe hepatic impairment (Child-Pugh Class C) because no trial was conducted in those subjects. Given that bedaquiline is extensively metabolized in the liver and primarily eliminated from plasma by CYP3A4, it is expected that hepatic impairment will affect the PK characteristics of bedaquiline. The sponsor has provided the results of a PK trial in mild and moderate hepatic impairment (described below), but has not studied the effect of severe hepatic impairment on the PK of bedaquiline. Thus, it is also important to know the effect of severe hepatic impairment on the systemic exposure of bedaquiline to assess whether dosage adjustments are needed in these patients. Although there is no discussion in the scientific literature that addresses the expected frequency of hepatic impairment in TB patients, it is still important to understand the impact of hepatic impairment on the PK of bedaquiline. Thus, the clinical pharmacology team is recommending that the confirmatory trial (C210) should include a cohort of 6-8 patients with severe hepatic impairment and PK evaluations should be conducted in those patients to evaluate if the exposure in these patients is different from patients with normal hepatic function. If there are logisitical issues with enrolling these patients then a dedicated PK trial in severe hepatic impaired patients is recommended.

Trial TMC207-TiDP13-C112 was an open-label trial to investigate the pharmacokinetics of TMC207 when administered as a single dose of 400 mg in subjects with moderate hepatic impairment compared to control subjects with normal hepatic function. The trial population consisted of 16 subjects: 8 with moderate hepatic impairment (Child-Pugh Class B) and 8 healthy control subjects matched for sex, age (± 5 years), and BMI (± 15%). TMC207 was administered under fed conditions (standardized breakfast).

PK of TMC207: In subjects with moderate hepatic impairment, mean values of C_{max}, AUC_{72h}, and AUC_{last} for TMC207 were lower compared to in healthy subjects, while mean values of AUC_∞ were comparable for both subject groups. For subjects with moderate hepatic impairment, C_{max}, AUC_{72h} and AUC_{last} values of TMC207 were 14%, 27%, and 19% lower, respectively, as compared to healthy subjects, based on the ratios of the least square means (LSmeans) (Table 12). The ranges of individual values of C_{max}, AUC_{72h}, AUC_{last}, and AUC_∞ for TMC207 largely overlapped for both subject groups (Figure 16). The median time to reach the maximal plasma concentration of TMC207 was about 5 hours after intake for subjects with moderate hepatic impairment and about 4 hours after intake for healthy subjects, with comparable ranges for both panels. Mean values of terminal elimination half-lives ($T_{1/2}$) of TMC207 could not be determined accurately for both panels, but were about 890 hours and 676 hours for healthy subjects and subjects with moderate hepatic impairment, respectively.

Table 12. Summary of the statistical analysis of the pharmacokinetic parameters of TMC207 after administration of a single 400-mg dose of TMC207 under fed conditions to healthy control subjects and subjects with moderate hepatic impairment.

Parameters	LSmeans		LSmeans Ratio	90% CI[a]
	Healthy subjects (reference)	Subjects with moderate hepatic impairment (test)		
C_{max} (ng/mL)	5015	4311	0.86	0.57 - 1.29
AUC_{72h}, ng.h/mL	57110	41910	0.73	0.52 - 1.03
AUC_{last}, ng.h/mL	86240	69830	0.81	0.56 - 1.17

[a] 90% confidence intervals

There is no clear relationship between systemic exposure to TMC207 and efficacy. Thus, <27% lower exposure in patients with moderate hepatic impairment would not be expected to result in lower efficacy of TMC207. Accordingly, no dosage adjustment of TM207 is needed in subjects with mild and moderate hepatic impairment.

Figure 16. Scatter plot comparing individual values of C_{max} and AUC_{72h} of TMC207 between healthy control subjects and subjects with moderate hepatic impairment.

28
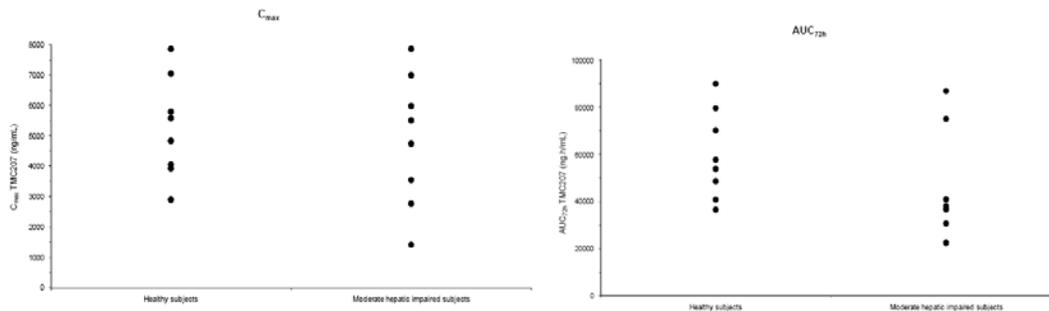
PK of M2: In subjects with moderate hepatic impairment, C_{max}, AUC_{72h}, and AUC_{last} values of M2 were 27%, 30%, and 19% lower, respectively, as compared to healthy subjects, based on the ratios of the LSmeans (Table 13). The median time to reach the maximal plasma concentration of M2 was about 12 hours after TMC207 intake, both for subjects with moderate hepatic impairment and for healthy subjects, with comparable ranges for both groups.

Table 13. Summary of the statistical analysis of the pharmacokinetic parameters of M2 after administration of a single 400-mg dose of TMC207 under fed conditions to healthy control subjects and subjects with moderate hepatic impairment.

| Parameters | LSmeans | | LSmeans Ratio | 90% CI[a] |
	Healthy subjects (reference)	Subjects with moderate hepatic impairment (test)		
C_{max} (ng/mL)	34.48	25.01	0.73	0.53 – 0.99
AUC_{72}h, ng h/mL	1748	1219	0.70	0.50 – 0.98
AUC_{last}, ng h/mL	9757	7921	0.81	0.59 – 1.12

[a] 90% confidence intervals

2.3.2.8. Pregnancy/Lactation

Bedaquiline has not been studied in pregnant or nursing women. It is not known if bedaquiline is excreted in human milk.

2.4. Extrinsic Factors

2.4.1. *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response? Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors?*

The effects of extrinsic factors such as herbal products, smoking and alcohol use have not been studied. The effect of co-administering other drugs with bedaquiline is addressed below.

2.4.2. *Drug-Drug Interactions*

2.4.2.1. *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

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In vitro studies show CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline, which suggests the potential for in vivo drug-drug interactions with inducers and inhibitors of CYP3A4.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
In vitro human liver microsomal studies show that bedaquiline is a substrate of CYP3A4. Genetic variants coding CYP3A4 appear to be relatively rare and not likely to influence bedaquiline metabolism. (b) (4)

2.4.2.3. Is the drug an inhibitor and/or an inducer of CYP enzymes?
Based on in vitro studies with human liver microsomes (FK4470), bedaquiline does not inhibit significantly the activity of any of the CYP isoenzymes tested (CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5 and CYP4A), as evidenced by high IC_{50}s of $\geq$91 μg/ml (>11 μg/ml for CYP2E1-mediated chlorzoxazone 6-hydroxylation due to limited solubility of bedaquiline in methanol).

Based on in vitro studies with human liver microsomes (FK5757), M2 shows marked inhibitory effect on CYP2B6, 2D6, 2C19, and 3A4 (IC_{50}s = 1.4-7.1 μg/ml); however, inhibition of CYP enzyme activity by M2 in vivo in humans may be limited because of the low exposure to M2 in humans (i.e., the mean C_{max} in plasma was < 0.5 μg/mL in trial C208, Stage 2) and high protein binding (>99.7%).

Based on in vitro studies with human hepatocytes (FK4372 and FK5329), bedaquiline shows little or no potential for induction of major CYP isoenzymes (including CYP1A2, CYP3A4, CYP2C9, and CYP2C19) compared to study controls at concentrations up to 5.55 μg/ml.

2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
TMC207 and M2 are not substrates of P-glycoprotein transport processes (see Section 2.2.5). At clinically relevant concentrations, TMC207 (<5 μg/mL) and M2 (<0.5 μg/mL) do not inhibit P-glycoprotein transport processes. At high concentrations (100 μM [~55 μg/mL]), TMC207 marginally inhibited P-glycoprotein transport of ^{3}H-paclitaxel. At high concentrations (100 μM [54.2 μg/mL]), M2 substantially inhibited P-gp dependent transport of ^{3}H-paclitaxel: the basolateral to apical over apical to basolateral paclitaxel transepithelial transport ratio was reduced from 55.7 to 8.58 with M2, compared with a ratio of 3.45 with verapamil (100 μM).

2.4.2.5. Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated? What co-medications are likely to be administered to the target patient population
In a placebo-controlled trial in patients with MDR-TB, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed. The likely co-medications in the target patient population include the background regimen drugs such as aminoglycosides (kanamycin, amikacin, etc.),

fluoroquinolones (ofloxacin, moxifloxacin, etc.), cycloserine, ethionamide, para-amino salicylic acid etc. Also, 1st line TB drugs such as pyrazinamide and ethambutol are likely to be co-administered.

2.4.2.6. *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

Rifampin: Co-administration with 600 mg rifampin (a potent CYP3A4 inducer) reduced bedaquiline C_{max} and AUC_{0-336h} by approximately 50% in healthy male volunteers receiving single oral dose of bedaquiline (300 mg). Therefore, the sponsor is recommending that co-administration of bedaquiline and rifamycins (rifampin, rifapentine, and rifabutin) or other potent CYP3A4 inducers used systemically should be avoided.

Ketoconazole: Co-administration with ketoconazole (a strong CYP3A4 inhibitor), 400 mg q.d. for 3 days, increased mean bedaquiline C_{max} and AUC_{0-24h} by 1.09- and 1.22-fold in healthy male volunteers receiving repeated doses of bedaquiline (400 mg q.d.). Given that bedaquiline has a long terminal half-life, and the impact of prolonged CYP3A4 inhibition on bedaquiline exposure is unknown, the sponsor is recommending that the combination of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided.

Isoniazid/Pyrazinamide: Co-administration of the combination of multiple-dose bedaquiline with multiple-dose isoniazid/pyrazinamide (300/2000 mg once daily) in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose adjustment of isoniazid or pyrazinamide is needed when co-administered with bedaquiline.

Nevirapine: Co-administration of multiple-doses of nevirapine (200 mg bid) with single-dose bedaquiline did not result in clinically relevant changes in the exposure to bedaquiline in HIV positive patients.

Kaletra: Following co-administration of a single-dose bedaquiline and multiple-dose lopinavir/ritonavir (400/100 mg bid), exposure (AUC) to bedaquiline was increased by 22% while the mean C_{max} remained comparable.

2.4.2.7. *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

There is no known mechanistic basis for pharmacodynamic drug-drug interactions.

2.4.2.7.1. *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?*

There are no other unresolved questions related to metabolism, active metabolites and drug interactions.

2.4.3. *What issues related to dose, dosing regimens, or administration are unresolved and represents significant omissions?*

It is recommended to evaluate the effect of severe renal impairment on the PK of bedaquiline to understand if there is the need to adjust the bedaquiline dose in severely renal impaired patients.

It is also recommended to evaluate the effect of severe hepatic impairment on the PK of bedaquiline to understand if there is the need to adjust the bedaquiline dose in severe hepatic impairment patients.

2.5.General Biopharmaceutics

2.5.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Based on the solubility and permeability data, the drug appears to belong to BCS Class II (low solubility and high permeability). The solubility and permeability data in support of this classification have been presented in earlier sections.

2.5.2. How is the proposed to-be-marketed formulation of bedaquiline linked to the clinically used formulation?

The proposed to-be-marketed (TBM) tablet formulation is different from the Clinical Trial Material (CTM). However, the sponsor submitted a waiver request based on in vitro dissolution data, which is being reviewed by the ONDQA.

2.5.3. What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

In clinical trials, the effect of concomitant food intake on oral absorption of TMC207 was investigated in terms of the effect on relative bioavailability of TMC207. Irrespective of the TMC207 formulation administered (oral solution, capsule, or tablet formulations); concomitant food intake consistently increased the oral bioavailability of TMC207. The mean exposure to TMC207 increased 1.3-fold when administered under fed conditions as an oral solution (40 mg/mL, formulation F004) in trial CDE-101 (AUC_{144h}) or as a 100 mg capsule (formulation F006) in trial C108 (AUClast). When TMC207 was administered as the 100 mg Phase II tablet (formulation F001) under fed conditions in trials C108 and C111, the mean exposure to TMC207 increased 2.0-fold (AUC_{last}) and 2.4-fold (AUC_{672h}), respectively. Based on these results, it is recommended that TMC207 is administered with food, which is consistent with the dosing instructions in the Phase II trials.

The food used in this trial is not the FDA recommended high fat breakfast. The sponsor used a 'standard breakfast' as the meal in the trial (see description below). Thus, this NDA application does not have a definitive food effect study as defined by the FDA Guidance. However the implication of this is minor given that the clinical trials were conducted with the standard meal. The product will be labeled to be given with food and a description of the meal type used in the clinical trials will be included in the label.

STANDARD BREAKFAST

1 x Cereal (35g) and 200 mL Semi Skimmed Milk
2 x Slices Granary Toast (54g), 2 x 10g Flora and 1 x 21g Jam
200 mL Tea or Coffee

Kcal	558
Fat	21.6 g (35 %)
Carbohydrate	80.9 g (54 %)
Protein	15.5 g (11 %)

2.6. Analytical Section

2.6.1. What bioanalytical methods are used to determine drug concentrations? Briefly describe the methods and summarize the assay performance.

During the clinical development of TMC207, changes were made to the original validated bioanalytical assay used for the determination of TMC207 in human plasma, so that a total of 3 assays were developed and validated to support the analysis of TMC207 in plasma in the TMC207 clinical program. These changes included the addition of M2 (the *N*-monodesmethyl metabolite of TMC207) as an analyte, improvements in the chromatographic conditions and switching to other instrumentation and validation for another laboratory. These assays were set up at 2 different laboratories and were all based upon the same method (high performance liquid chromatography [HPLC] coupled with tandem mass-spectrometry [LC-MS/MS]). The performance of these assays was characterized by means of a validation process, in line with internal procedures and international bioanalytical guidelines assay specifics. Validation characteristics for the bioanalytical methods for determination of TMC207 and M2 in plasma are summarized in Table 13. One LC-MS/MS-based assay was developed and validated to support the analysis of TMC207 and M2 in sputum homogenate samples. The validation characteristics for the determination of TMC207 and M2 in sputum are also summarized in Table 14.

Table 14: Bioanalytical Assay Validation Characteristics for Determination of TMC207 and M2 in Human Matrices

Report No. [Method] (Location)	Analyte (Internal Standard)	Range of Quantification	Recovery (%)	Compliance with Pre-specified Criteria		Permitted Dilution Ratio and Concentration	Specificity [c] (Interfering Peaks)
				Accuracy [a]	Precision [b]		
Human Plasma							
R207910/ BA161 [LC-MS/MS] (Module 5.3.1.4 /TMC207-R207910/ BA161)	TMC207 (R378290)	1.00 to 2000 ng/mL	5.00 ng/mL: 103.8 100 ng/mL: 100.2 2000 ng/mL: 103.1	1.00 ng/mL: ≤|20|% 2.89 ng/mL: ≤|15|% 50 ng/mL: ≤|15|% 1500 ng/mL: ≤|15|%	1.00 ng/mL: ≤|15|% 2.89 ng/mL: ≤|20|% 50 ng/mL: ≤|20|% 1500 ng/mL: ≤|20|%	Ratio: up to 1:10 Concentration: 10 to 20,000 ng/mL	Interference ≤20%
R207910/ BA602 [LC-MS/MS] (Module 5.3.1.4 /TMC207-R207910/ BA602)	TMC207 (R378290)	1.00 to 2000 ng/mL	5.00 ng/mL: 89.7 50.0 ng/mL: 87.3 2000 ng/mL: 89.1	1.00 ng/mL: ≤|20|% 2.79 ng/mL: ≤|15|% 52.7 ng/mL: ≤|15|% 1520 ng/mL: ≤|15|%	1.00 ng/mL: ≤|20|% 2.79 ng/mL: ≤|15|% 52.7 ng/mL: ≤|15|% 1520 ng/mL: ≤|15|%	Ratio: up to 1:10 Concentration: 10 to 20,000 ng/mL	Interference ≤20%
	N-mono-desmethyl TMC207 (M2) (R484173)	1.00 to 2000 ng/mL	5.00 ng/mL: 82.6 50.0 ng/mL: 80.1 2000 ng/mL: 84.5	1.00 ng/mL: ≤|20|% 2.79 ng/mL: ≤|15|% 52.7 ng/mL: ≤|15|% 1520 ng/mL: ≤|15|%	1.00 ng/mL: ≤|20|% 2.79 ng/mL: ≤|15|% 52.7 ng/mL: ≤|15|% 1520 ng/mL: ≤|15|%	Ratio: up to 1:10 Concentration: 10 to 20,000 ng/mL	Interference ≤20%
PBRL-RD-780 [LC-MS/MS] (Module 5.3.1.4 /TMC207-PBRL-RD-780)	TMC207 (R378290)	1.00 to 2000 ng/mL	Not determined	1.00 ng/mL: ≤|20|% 3.00 ng/mL: ≤|15|% 100 ng/mL: ≤|15|% 1600 ng/mL: ≤|15|%	1.00 ng/mL: ≤|20|% 3.00 ng/mL: ≤|15|% 100 ng/mL: ≤|15|% 1600 ng/mL: ≤|15|%	Ratio: up to 1:10 Concentration: up to 16,000 ng/mL	Interference ≤20%
	N-mono-desmethyl TMC207 (M2) (R484173)	1.00 to 2000 ng/mL	Not determined	1.00 ng/mL: ≤|20|% 3.00 ng/mL: ≤|15|% 100 ng/mL: ≤|15|% 1600 ng/mL: ≤|15|%	1.00 ng/mL: ≤|20|% 3.00 ng/mL: ≤|15|% 100 ng/mL: ≤|15|% 1600 ng/mL: ≤|15|%	Ratio: up to 1:10 Concentration: up to 16,000 ng/mL	Interference ≤20%

Report No. [Method] (Location)	Analyte (Internal Standard)	Range of Quantification	Recovery (%)	Compliance with Pre-specified Criteria		Permitted Dilution Ratio and Concentration	Specificity [c] (Interfering Peaks)
				Accuracy [a]	Precision [b]		
Human Sputum Homogenate							
PBRL-RD-909 (Module 5.3.1.4 /TMC207-PBRL-RD-909)	TMC207 (R378290)	1.50 to 3000 ng/g	Not determined	1.50 ng/g: ≤|20|% 4.50 ng/g: ≤|15|% 200 ng/g: ≤|15|% 2400 ng/g: ≤|15|%	1.50 ng/g: ≤|20|% 4.50 ng/g: ≤|15|% 200 ng/g: ≤|15|% 2400 ng/g: ≤|15|%	Ratio: up to 1:10 Concentration: up to 24,000 ng/g	Interference ≤20%
	N-mono-desmethyl TMC207 (M2) (R484173)	1.50 to 3000 ng/mL	Not determined	1.50 ng/g: ≤|20|% 4.50 ng/g: ≤|15|% 200 ng/g: ≤|15|% 2400 ng/g: ≤|15|%	1.50 ng/g: ≤|20|% 4.50 ng/g: ≤|15|% 200 ng/g: ≤|15|% 2400 ng/g: ≤|15|%	Ratio: up to 1:10 Concentration: up to 24,000 ng/g	Interference ≤20%

[a] Percent deviation from nominal concentration.
[b] Percent variability of replicates.
[c] Calculated as [(amount found − amount added) / amount added] × 100.

2.6.1.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The ranges for the standard curve were between 1.00-2000 ng/mL for plasma samples and 1.50-3000 ng/g for the sputum samples. The linearity of the assay and the adequacy of these standard curve ranges were evaluated for individual trials and are reported in the individual study reviews.

2.6.1.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Refer to Table 9 for the LLOQ and ULOQ for each assay.

2.6.1.3. What are the accuracy, precision, and selectivity at these limits?

Refer to Table 9 for the accuracy and precision for each bedaquiline assay.

2.6.1.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The stability of TMC207 and M2 in human matrices was considered proven if the analyte concentration remained between 85.0% and 115.0% of the concentration in the reference samples. The conditions under which stability was demonstrated are summarized in Table 15.

Table 15: Stability of TMC207 and M2 in Human Matrices

Matrix/ Analyte	37°C	Room Temperature	Refrigerator	Frozen (-20°C)	Freeze-Thaw Cycles
Human Heparin Blood					
TMC207 [a]	2 hours	24 hours	24 hours	ND	ND
M2 [b]	2 hours	24 hours	24 hours	ND	ND
Human Heparin Plasma					
TMC207 [c]	ND	72 hours	ND	723 days [c]	4
M2 [d]	ND	48 hours	ND	545 days	3
Human Sputum Homogenate					
TMC207 [e]	ND	24 hours	ND	364 days	3
M2 [e]	ND	24 hours	ND	364 days	3

ND = not determined.
[a] 5 and 925 ng/mL in R207910/BA161, and 5 and 930 ng/mL in R207910/BA602.
[b] 5 and 930 ng/mL in R207910/BA602.
[c] 5 and 1540 ng/mL in R207910/BA161, and 5 and 1520 ng/mL in R207910/BA602.
[d] 2.6 and 1520 ng/mL in R207910/BA602.
[e] 4.5, 2,400, and 24,000 ng/g in PBRL-RD-909.

Reviewer Assessment:
The validation and performance of the bioanalytical assay used for determination of parent drug, TMC207, and the main metabolite, M2, in plasma and sputum are deemed to be acceptable by the Clinical Pharmacology reviewer.

3. LABELING RECOMMENDATIONS

The label will be filed in DARRTS saeparately after agreement with the sponsor on the specific wording.

4. Individual Study Review
Available separately

5. Pharmacometric Review

<div align="center">

OFFICE OF CLINICAL PHARMACOLOGY
PHARMACOMETRIC REVIEW

</div>

1. Summary of Findings

1.1. Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1. What's the exposure-response relationship of TMC207 for efficacy?

Overall, PK/PD analyses did not identify clear exposure-response relationship for efficacy, suggesting that the proposed dosing regimen may lie at the top of the exposure-response curve. In the pivotal trial C208 Stage 2, the sponsor submitted full PK profiles obtained at Week 2 and Week 24 in a subgroup of 51 patients following daily administration of 400 mg for two weeks and 200 mg three times per week for additional 22 weeks. Time-to-conversion was used as the primary endpoint for efficacy. With this data, the reviewer explored the relationship between measured PK parameters at week 2 (such as C_{max}, AUC, and the ratio of AUC to MIC) and the corresponding time to sputum conversion. The Kaplan-Meier estimate of the survival curves of TMC207 subjects were stratified by quartiles of the measured PK parameters. After ruling out the imbalance of potential risk factors, higher exposure (only AUC_{24h} is shown below) was found not to be strongly associated with fewer days to conversion (Figure 1).

Figure 1: Kaplan-Meier plot by AUC_{24h} (at week 2) quartiles for C208 Stage II (24-week Data selection and Primary Missing=Failure Analysis Method) –ITT
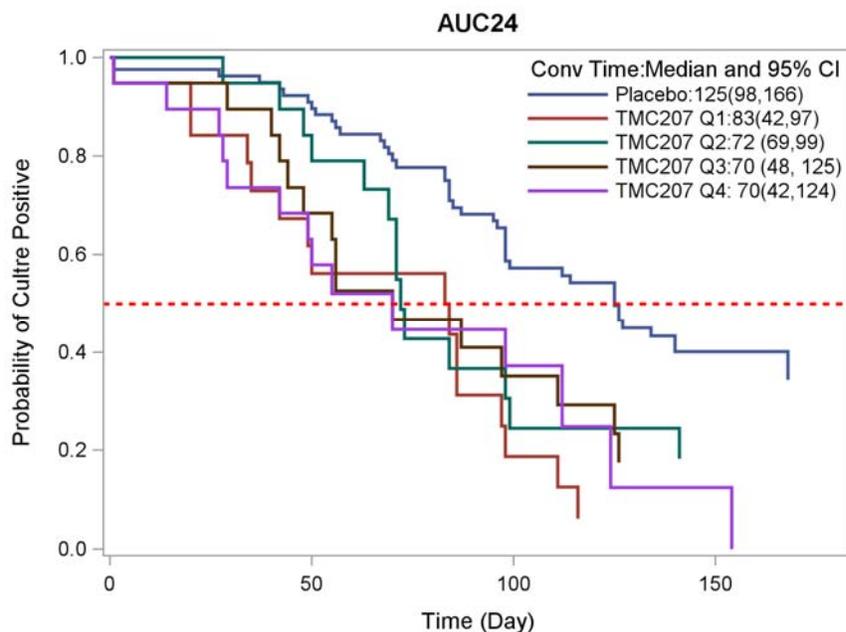
Relationship between culture conversion rate (MGIT) and PK metrics (AUC_{24h}, AUC_{24h}/MIC at week 2, only AUC24 shown here) was also examined. No clear and consistent relationship between TMC207 plasma AUC_{24h} or AUC_{24h}/MIC and culture conversion rates was observed (Figure 2).

**Figure 2: Culture Conversion rate (No Overruling, all available data selection) vs. AUC_{24h} quartiles– mITT**
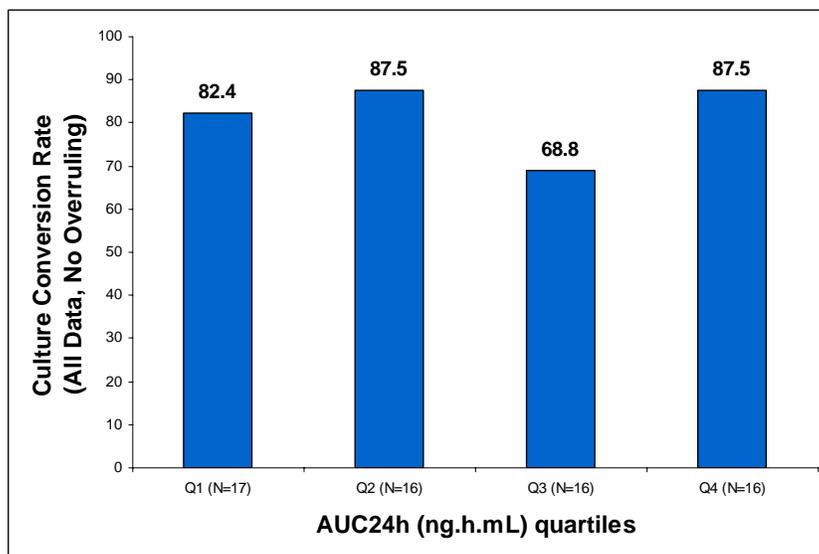
### 1.1.2. What's the exposure-response relationship of TMC207 for safety?

No clear and consistent relationship between exposure and AE incidence was identified for the most frequently observed adverse events. However, this finding should be explained with caution.

The reviewer first examined adverse events that are likely related to TMC207 treatment and then explored the potential association between drug exposure and incidence of these events. As demonstrated in Figure 3, the most frequently reported AEs (>15% of subjects) after TMC207/BR treatment in Study C208 Phase IIb with incidence consistently higher than the Placebo/BR arm were nausea (38%), arthralgia(32.9%), headache (27.8%), and hemoptysis (17.7%). Despite a small trend for arthralgia, no significant relationship between the AE incidence and TMC207 exposure (C_{max} and AUC_{24}) was identified (Figure 4). However, as we only have a limited safety database and a portion of patients with full PK profiles, we cannot rule out the possibility of undetected significant relationship, and the finding here should be interpreted with caution.

Figure 3: Incidence of mostly reported (> 15%) adverse events after TMC207/BR and Placebo/BR treatment
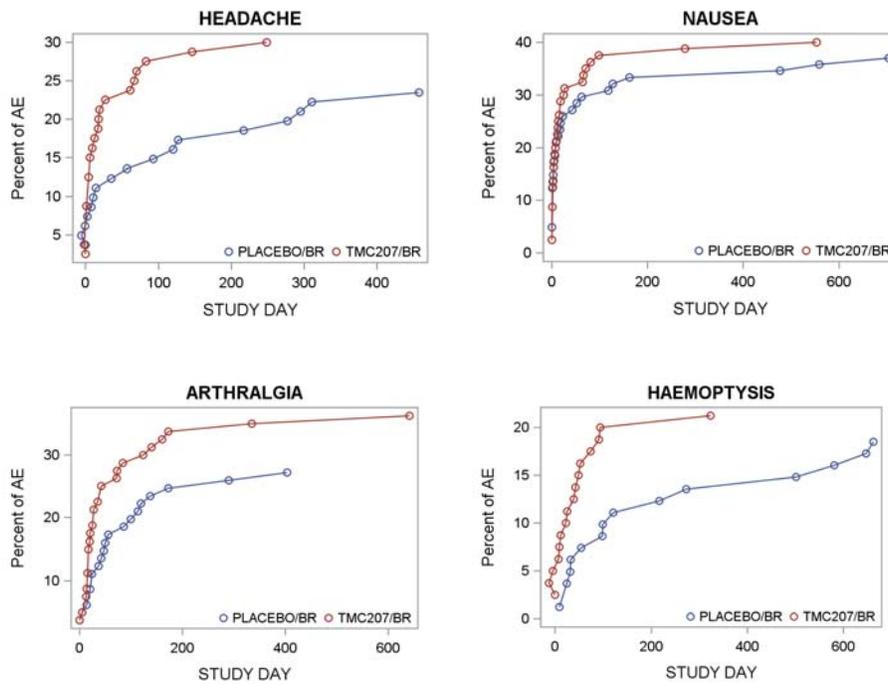
Figure 4: Relationship between AE incidence and AUC$_{24h}$ at Week 2. The blue points are observed quartile mean. The green shaded area is model-estimated 95% CI based on a logistic analysis
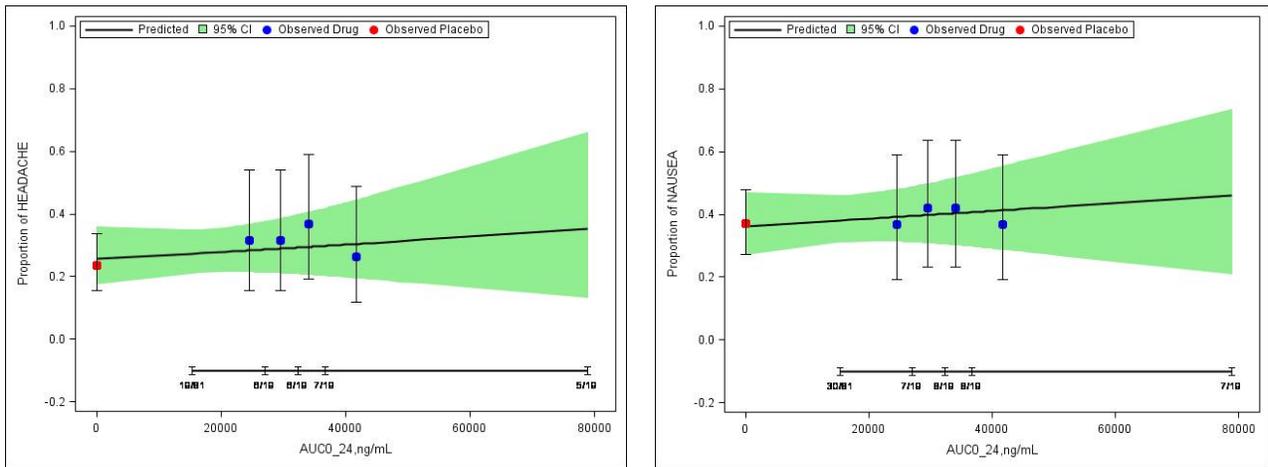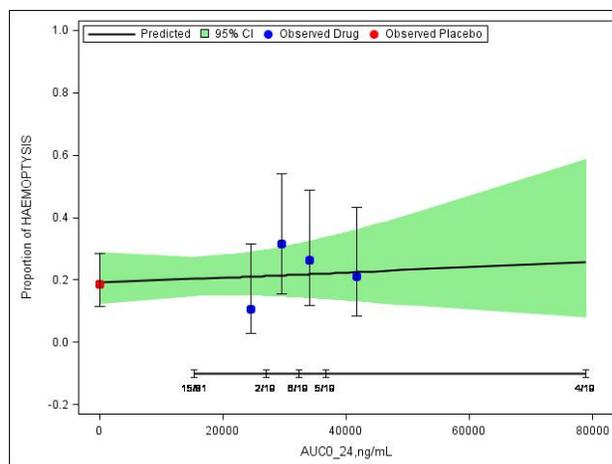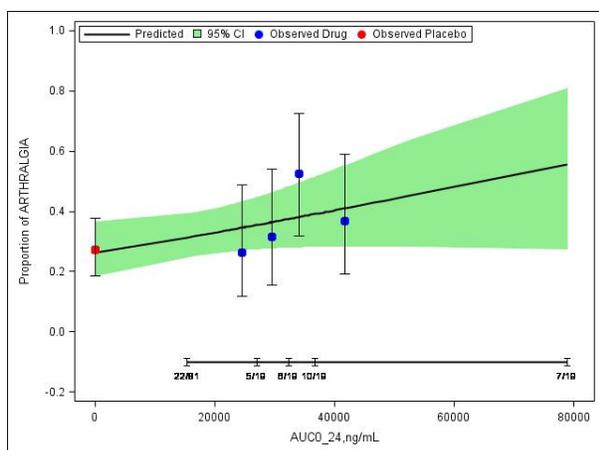
1.1.3. Are there any covariates that significantly affect TMC207 PK parameters?

In a population PK study, patients of black race were found to have a higher clearance. Individual PK parameters were estimated by the sponsor's final population PK model. The relationships between TMC207 oral clearance (CL/F) and selected covariates, including body weight, age, sex, Cr_{CL}, albumin, and race were explored. As demonstrated in Figure 5 below, there are no significant relationships between TMC207 clearance and the covariates of interest, except race, where patients of black race were observed to have clearance that was 52% higher compared to subjects of other race. Addition of black race to the reference population PK model reduced inter-individual variations of apparent clearance (CL/F) by 5%. Using the developed model, the sponsor projected that TMC207 exposure in black patients would be 34.3% lower compared to other races. However, a subgroup analysis did not identify a significant difference in efficacy of bedaquiline among races, suggesting that higher clearance might not be clinically significant. The sponsor did not propose dose-adjustment in African-American patients. There were no significant relationship between central volume of distribution (Vc/F) and the selected covariates (data not shown).

PK Parameter-Covariate Relationships

Figure 5: PK parameter-covariates relationships. The red lines are smoothed lines showing the trend. The box plots and black circles are based on empirical Bayesian individual estimates

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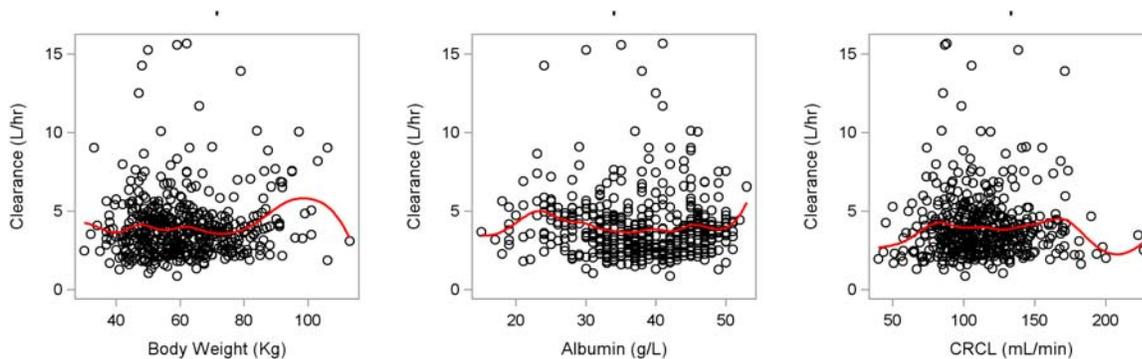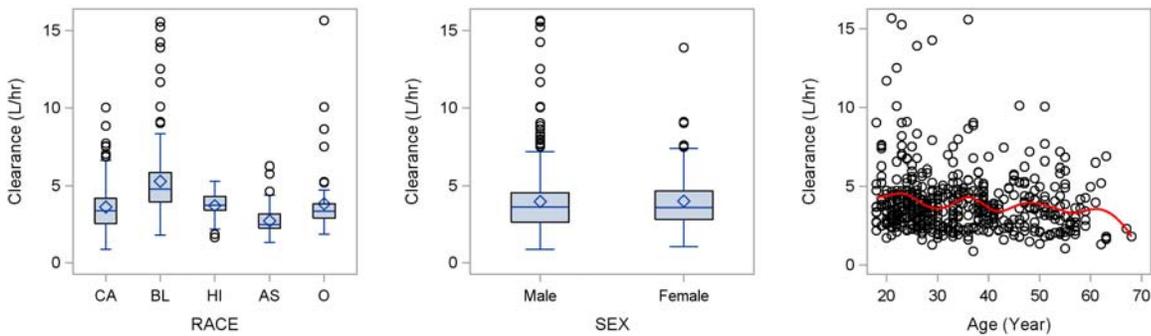
Recommendations

The sponsor's conclusions based on population PK analyses and exposure-response analyses are acceptable.

2. Results of Sponsor's Analysis

2.1. Population PK Analysis

Objectives: The sponsor conducted population PK analysis with major objectives to:
1. Develop a population pharmacokinetic model for TMC207 based upon currently available Phase I and II data.
2. Ensure that the model correctly describes the disposition of TMC207 and adequately captures the apparent terminal elimination half-life.
3. Determine the influence of subject covariates on the pharmacokinetic parameters of TMC207.

Data: Data used to develop the population PK model were obtained from 9 Phase I to Phase II trials in healthy volunteers and patients. The age of subjects ranged from 18 to 68 years with body weight ranging from 30 to 113 kg in a total of 366 male and 165 female subjects. The majority subjects were of Black race (170), with 142 Caucasian, 101 Asian, 44 Hispanic, and 74 of 'Other' races. A total of 480 subjects with 5222 concentrations were included in the final datasets.

Methods: The population PK analysis was conducted using NONMEM (version VII, level 2.0) with Intel Fortran Compiler XE as Fortran compiler. Models were fitted to transformed data using a log transform both sides (LTBS) approach. Parameter estimates were obtained using the FOCE method with the INTERACTION option.

Examined covariates included age, total body weight, race, sex, creatinine clearance, albumin, TB type, HIV status. The final model is a four-compartment model with schema as follows:

Figure 6: Schematic Diagram of a 4-Compartment Disposition Model with Sequential Zero-Order First-Order and Zero-Order Dual Input.

Final Model Schema

Lag time (ALAG1) → Dose (D1 zero-order) ↘ FR1 → Input Compartment → KA → Central Compartment

Lag time (ALAG1 + TLAG) → Dose (D2 zero-order) ↘ (1-FR1) → Central Compartment

Central Compartment ⇄ 1st Peripheral Compartment
Central Compartment ⇄ 2nd Peripheral Compartment
Central Compartment ⇄ 3rd Peripheral Compartment
Central Compartment ↓ Clearance (CL/F)
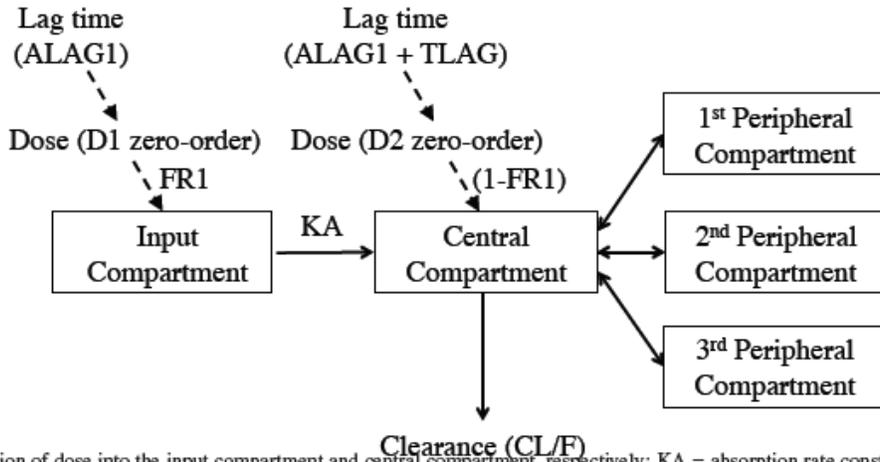
D1 & D2 = duration of dose into the input compartment and central compartment, respectively; KA = absorption rate constant; FR1 = fraction of dose into the input compartment.

Results: The sponsor's final model using FOCE estimation method is summarized in table below:

Table 1: Parameter Estimate for the Final Model

Parameter		Parameter Estimate	Parameter SEE (CV%)	BSV Estimate (CV%)	BSV SEE (CV%)
CL/F (L/hr)	θ_1	2.78	5.1	50.4	12.3
V_c/F (L)	θ_2	164	5.0	39.1	15.6
CL_{p1}/F (L/hr)	θ_3	11.8	7.6		
V_{p1}/F (L)	θ_4	178	8.1		
CL_{p2}/F (L/hr)	θ_5	8.03	4.9		
V_{p2}/F (L)	θ_6	3010	9.0		
CL_{p3}/F (L/hr)	θ_7	3.58	9.0		
V_{p3}/F (L)	θ_8	7350	5.8		
FR1 (%)	$\theta_9/(1+\theta_9)$	58.5	11.1*	113	15.9
D1 (hr)	θ_{10}	2.22	1.0		
TLAG (hr)	θ_{11}	1.48	3.2		
D2 (hr)	θ_{12}	1.48	3.2		
ALAG1 solution (hr)	θ_{13}	0.541	5.7		
ALAG1 tablet (hr)	θ_{14}	0.917	0.6		
Study R207910-CDE102 or TiDP13-C104 on F	θ_{15}	1.51	7.5		
Other Studies on F**	θ_{16}	2.03	4.7		
Increase in CL with Black race (%)	θ_{17}	52.0	21.2		
Decrease in V_c with female sex (%)	θ_{18}	-15.7	42.5		
Increase in CL for healthy volunteers or C202 (%)	θ_{19}	37.5	35.2		
Between-subject variability on F	η_F			39.6	9.3
RUV (CV%)		20.6	3.3		
RUV on TiDP13-C208 or TiDP13-C209 (CV%)		27.7	3.2		
Correlation CL/V_c		0.407			

*On estimate of θ_9 (=1.41)
**Refers to studies TMC207-TiDP13-C109, TMC207-TiDP13-110, TMC207-TiDP13-111, TMC207-TiDP13-202 and TMC207-TBC1003

Source: Table 24 on page 77 of the sponsor's report

Final Model Diagnostics

The sponsor conducted standard diagnostics. The results are demonstrated in Figure 7 below.

Figure 7: Goodness-of-Fit graphs for final PK model
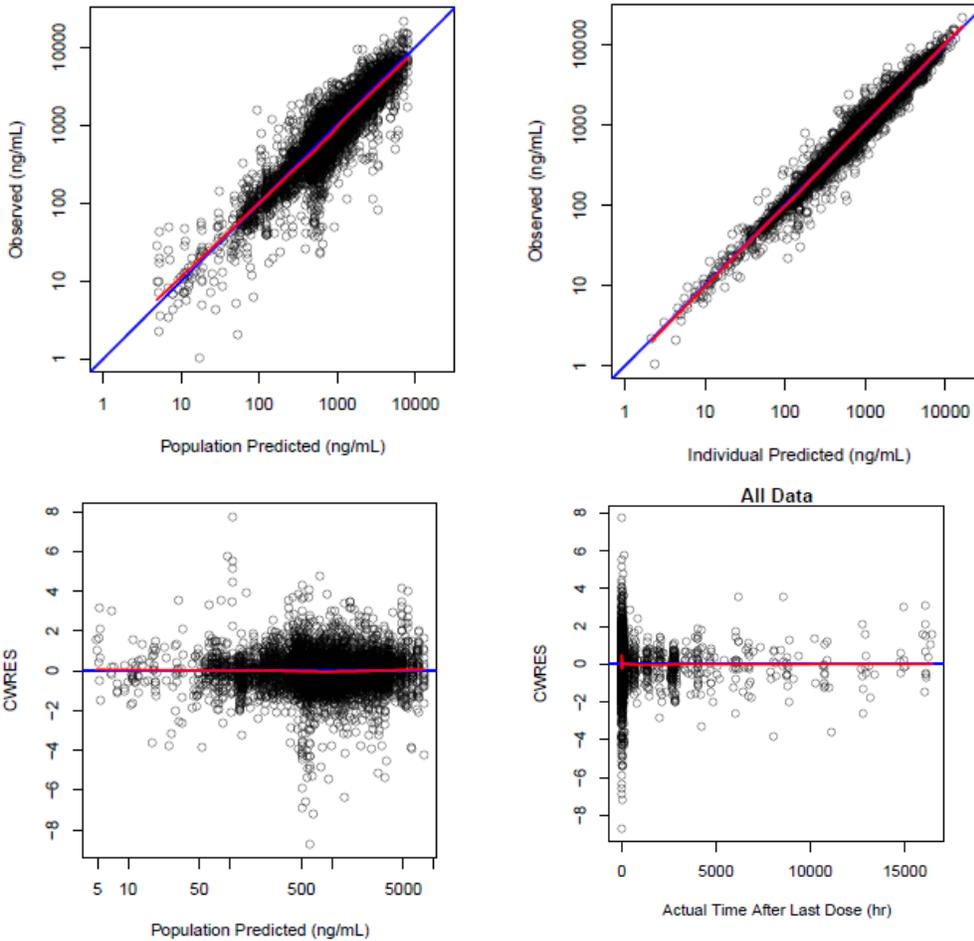
The solid red line shows the trend of the data with the black circles representing the observed data. Darker colouring indicates multiple/overlapping observations.

Source: Figure 41, 42, 44, 45 on Page 79-81 of the sponsor's report

Visual Predictive Check

The sponsor conducted visual predictive check (VPC) to determine if the model's simulation characteristics were adequate. The VPC was performed by simulating 1000 replicates of the dataset from the posterior distribution of the model to compute the 5th, 50th, and 95th prediction intervals. The results of VPC were demonstrated as follows:

Figure 8: Visual Predictive Check: All subjects from 0-16400 hrs Actual Time after Last Dose
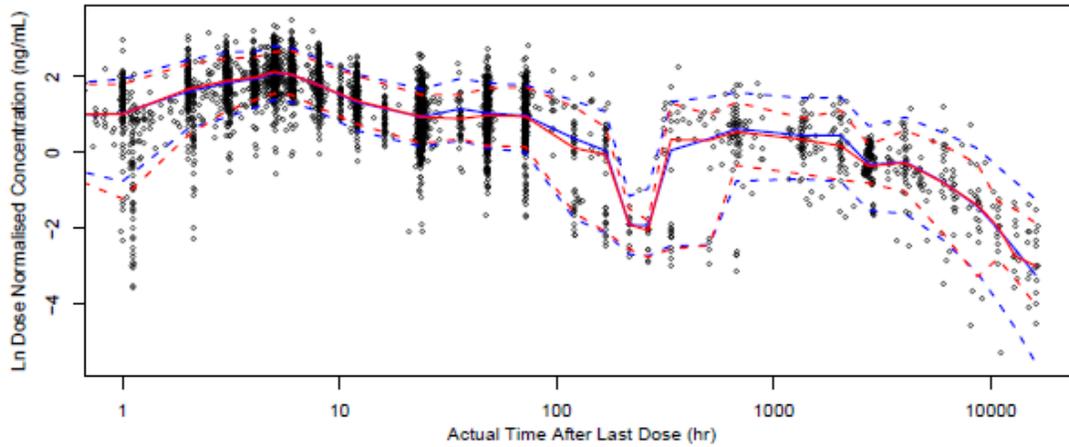
The black circles represent the observed data. The lower and upper red dashed lines represent the 5th and 95th percentiles for the observed data. The red solid line represents the 50th percentile for the observed data. The lower and upper blue dashed lines represent the 5th and 95th percentiles for the simulated data. The blue solid line represents the 50th percentile for the simulated data.

Effect of Covariate on TMC207 Exposure

The impact of the covariate effects in patients was evaluated under the assumption that TMC207 was administered at a dose of 400 mg once a day (QD) for two weeks, followed by 200 mg three times a week (TIW). As demonstrated in Figure 9, Black patients have lower clearance than non-black race. It was estimated based upon a dose of 200 mg TIW, that the AUCss,168h for a typical non-Black subject is expected to be 216000 ng.hr/mL, compared to 142000 ng.hr/mL for a subject of Black race.

Figure 9: Effect of subject race on TMC207 exposure at steady-state
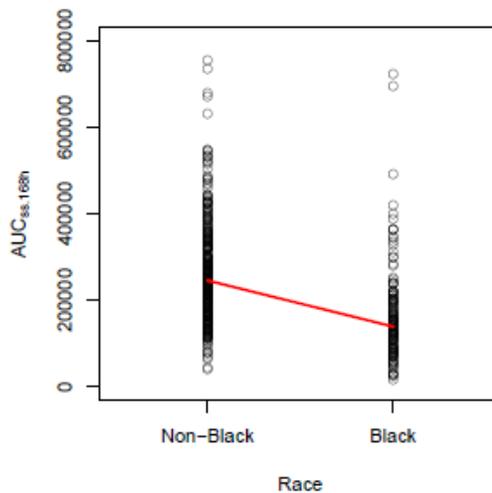
AUCss,168h based upon bioavailability-adjusted CL/F. The solid red line shows the trend of the data with the black circles representing the observed data. Darker colouring indicates multiple/overlapping observations.

Source: Figure 64 on Page 210 of the Sponsor's Report

Conclusion: A population pharmacokinetic model for TMC207 was developed using data from 9 clinical studies that described concentrations to 685 days (16400 hrs) post-dose. Apparent central volume of distribution was lower in females, which may be explained by a difference in body size. The difference in apparent central volume of distribution between females and males was < 20%. Such a difference had minimal impact on exposure and was not considered to be of clinical significance. Apparent clearance was higher in subjects of black race compared to other races, although no difference in effectiveness was observed in the clinical studies. Therefore, the race effect on clearance is not likely to be of clinical significance.

Reviewer's Comments:
The sponsor's final model for the parent drug appears reasonable and acceptable. The model predicted the concentration of the parent drug in human body well. The reviewer conducted independently analysis to verify the sponsor's final model. The results are summarized in section 3 and showed in Figure 5.

2.2.   Exposure-Response Analysis for Efficacy

The sponsor conducted exposure-response analysis for TMC207 efficacy in C208 Stage 2 with PK parameters obtained at Week 2. There was no relationship between the TMC207 plasma AUC24h and the corresponding time to sputum culture conversion (Figure 10).

Figure 10: Time to Culture Conversion (No overruling for Discontinuation Method, 24-week Data selection) versus TMC207 Plasma AUC24h at Week 2 (C208 Stage 2) – mITT)
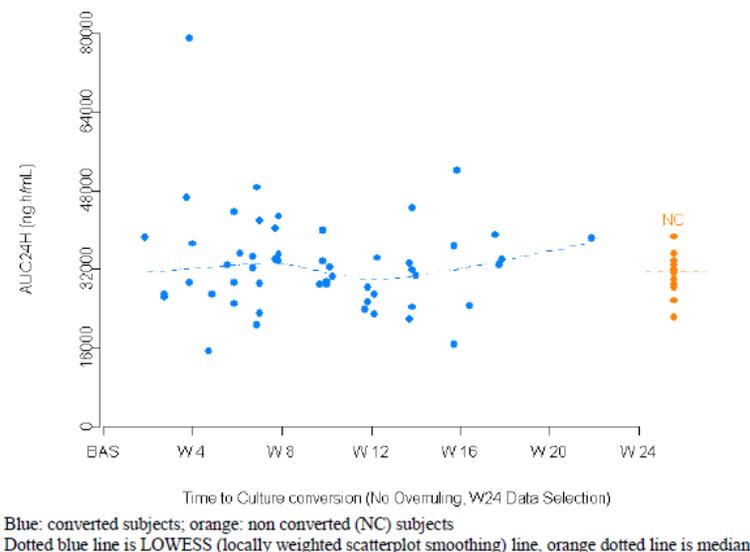
Blue: converted subjects; orange: non converted (NC) subjects
Dotted blue line is LOWESS (locally weighted scatterplot smoothing) line, orange dotted line is median
Source: Figure 22 on page 78 of sponsor's report "Summary of Clinical Efficacy"
There was also no clear relationship (Figure 11) between culture conversion rates (no overruling) at Week 24 and TMC207 plasma AUC24h/MIC (agar) quartiles (at Week 2).

Figure 11: Culture conversion Rates at Week 24 (No Overruling) versus TMC207 AUC24h/MIC quartiles (C208 Stage 2) -mITT
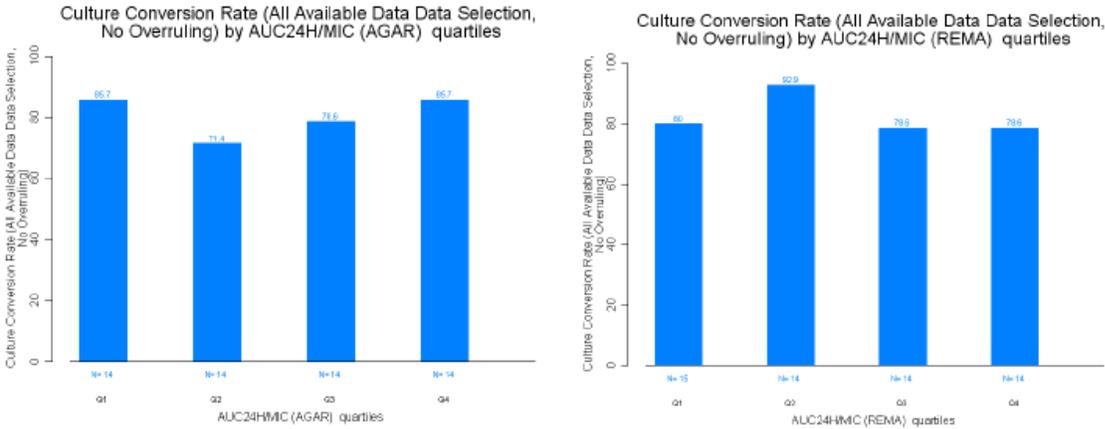
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Culture Conversion Rate (All Available Data Data Selection, No Overruling) by AUC24H/MIC (AGAR) quartiles

Culture Conversion Rate (All Available Data Data Selection, No Overruling) by AUC24H/MIC (REMA) quartiles

Agar: Q1: <= 416.432; Q2:] 416.432; 560.668]; Q3:] 560.668; 1114.016]; Q4: > 1114.016
REMA: Q1: <= 637.802; Q2:] 637.802; 952.886]; Q3:] 952.886; 1577.271]; Q4: > 1577.271

Source: Figure 24 on page 197 of sponsor's report (EudraCT Number: 2007-004462-40)
Reviewer's Comments: It appears higher exposure was not associated with greater efficacy. The reviewer conducted independent analysis of exposure-response analysis; the results are summarized in section 3.

3. Reviewer's Analysis

3.1. Introduction
3.2. Objectives

The reviewer conducted analyses with objectives:
1) to evaluate the adequacy of the sponsor's latest population PK model in characterizing the TMC207 PK data and the effect of covariates of interest on PK parameters.
2) to explore the exposure-response relationship for efficacy and safety to determine whether the proposed dosing regimen is appropriate.

3.3. Methods

3.3.1. Data Sets
Data sets used are summarized in Table 2.

Table 2: Analysis Data Sets

Study Number	Name	Folder
Pop PK	tmc207-all-studies-dose12-obs2-201110241133-csv.xpt	~\datasets\tmc207-201105-poppk\analysis\legacy\datasets\final-covariate
	run99 mod	~\Betaquiline_NDA204384\PPK Analyses\Final Model

3.3.2. Software
NONMEM (Version 7.2) installed on a 48-core Linux cluster was used for the population PK analysis. An R package "popPK" developed by FDA was used for population PK graphing and reporting; SAS for windows 9.3 was used for all graphing and statistical analyses.

3.3.3. Results
The sponsor's final model was tested on the mentioned grid-computing environment using NONMEM 7.2 with gfortran 4.6 as fortran compiler.

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3.3.3.1.   Population PK

3.3.3.1.1.   Population PK Parameter Estimates

The reviewer was able to verity the sponsor's final model, The population PK parameter estimates (showing only CL and V2 in Table 3) for the final PK model were similar to those shown in Table 1.

Table 3: Estimate of TMC207 PK parameters by Reviewer's Final Model

Parameter	Estimate	BSV
CL/F (L/h)	2.754	50.47%
V2 (L)	163	39.01%

Individual empirical Bayes' estimates based on the final model are summarized in table below, black patients have the highest average clearance value while Asian patients have the lowest. Female patients have a central volume of distribution that is 13% lower than male.

Table 4: Summary of individual empirical Bayes' estimates

Parameters		N	Mean	SD	Lower 95%	Upper 95%
CL/F (L/h)	Caucasian	134	3.61	1.54	3.34	3.87
	Black	149	5.28	2.39	4.89	5.67
	Hispanic	41	3.7	0.88	3.42	3.98
	Asian	99	2.73	0.84	2.56	2.89
	Other	57	3.84	2.15	3.26	4.41
V2 (L)	Male	331	167.4	44.58	162.58	172.22
	Female	149	143.57	38.82	137.29	149.86

Effect of covariates on PK parameters was studied. The relationships were demonstrated in Figure 5.

Reviewer's Comments:
The sponsor's model is reasonable and acceptable. The reviewer's analysis is consistent with that of the sponsor. Patients of black race have decreased AUC when compared with patients of other race categories; Age, liver function tests, and creatinine clearance were not found to affect TMC207 clearance and exposure.

3.3.3.2.   Exposure-response relationship for efficacy

Data in Study C208 stage 2 were used to study potential relationships between exposure to TMC207 and clinical efficacy. The primary efficacy endpoint used is time to sputum culture conversions. The reviewer calculated the quartiles of TMC207 exposure (AUC24) at week 2 and stratified the survival plot of TMC207 group by AUC24 quartiles. The distribution of potential risk factors in the quartiles was examined and imbalance was ruled out. As demonstrated below, higher exposure to TMC207 was not found to be associated with shorter conversion time (Figure 12).

Figure 12: C208 Stage 2: Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (24-Week Data selection, Primary Missing=Failure Method-ITT) stratified by quartiles of TMC207 AUC24 or Cmax at Week 2.

AUC24

Conv Time:Median and 95% CI
Placebo:125(98,166)
TMC207 Q1:83(42,97)
TMC207 Q2:72 (69,99)
TMC207 Q3:70 (48, 125)
TMC207 Q4: 70(42,124)

Cmax

Conv Time:Median and 95% CI
Placebo:125(98,168)
TMC207 Q1:83(63,111)
TMC207 Q2:72 (55,125)
TMC207 Q3:84 (50, 98)
TMC207 Q4: 49(40,111)
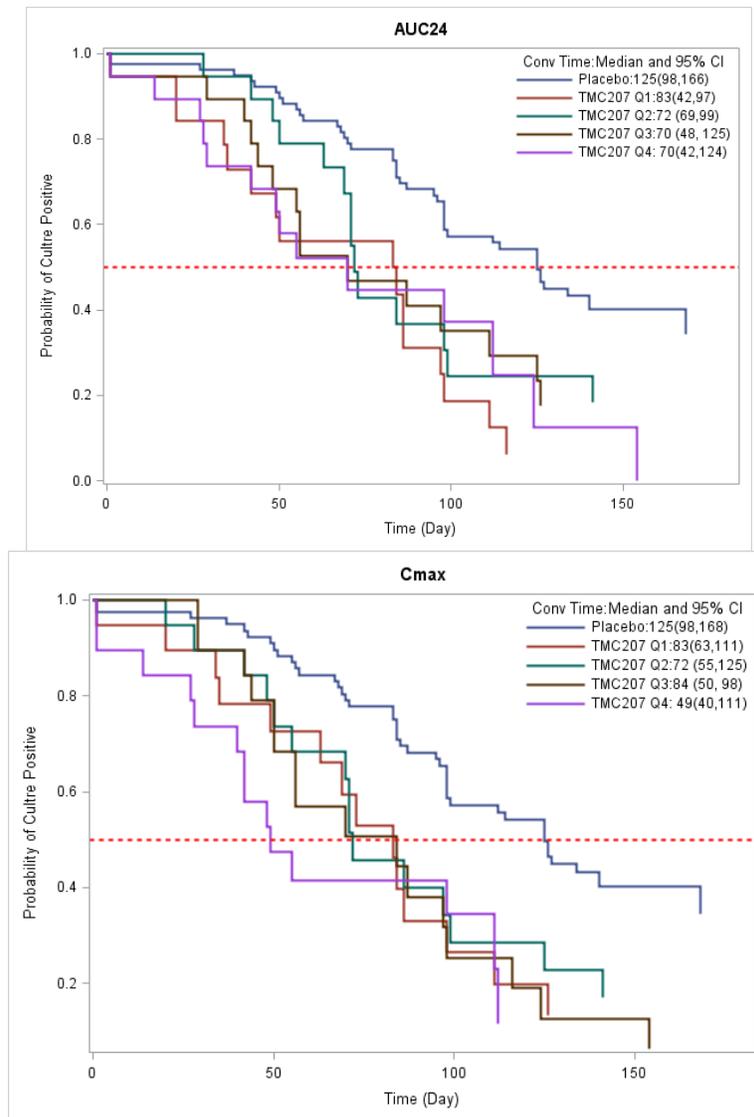
3.3.3.3. Exposure-response relationship for safety

A logistic regression analysis was conducted to assess the association between incidence of most frequently reported AE in study C208 Stage 2 and TMC207 exposure (Cmax, AUC, AUC/MIC) at week 2. Only AEs with incidence rate higher than 15% and consistently greater than that of the Placebo/BR group were included. The AEs that met the criteria included nausea, arthralgia, headache, haemoptysis. no significant association between AE incidence and exposure to TMC207 was identified (Figure 3 and Figure 4).

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/s/

DAKSHINA M CHILUKURI
11/30/2012
Zhixia (Grace) Yan reviewed the in vitro drug metabolism and DDI trials for ketoconazole and rifampin.

SEONG H JANG
11/30/2012

FANG LI
11/30/2012

YANING WANG
11/30/2012

PHILIP M COLANGELO
12/03/2012

BIOPHARMACEUTICS REVIEW **Office of New Drug Quality Assessment**			
Application No.:	NDA 204-384	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	29 June 2012		
Division:	Division of Anti-infective Products	**Team Leader:** Angelica Dorantes, Ph.D. **Acting Supervisor:** Richard Lostritto, Ph.D.	
Sponsor:	Janssen Therapeutics	**Secondary Reviewer:** Angelica Dorantes, Ph.D.	
Trade Name:	TBD (TMC207)	**Date Assigned:**	11 July 2012
		GRMP Date: **Clinical Date:** **PDUFA Date:**	21 Nov 2012 30 Oct 2012 29 Dec 2012
Generic Name:	Bedaquiline	**Date of Review:**	16 Nov 2012
Indication:	Multi-drug resistant tuberculosis	**Type of Submission: Original NDA Review**	
Formulation/strengths	Tablet, 100 mg		
Route of Administration	Oral		

Biopharmaceutics Review Topics:
- Dissolution test method,
- Qualification of commercial product and facility using in vitro dissolution, formulation/process attributes impacting dissolution, and dissolution stability,
- Biowaiver Request

SUBMISSION:

NDA 204-384 seeks accelerated approval for the use of bedaquiline (TMC207) in the treatment of patients with multi-drug resistant tuberculosis (MDR-TB) on the basis of clinical efficacy and safety data through Phase 2b. A confirmatory Phase 3 trial is planned as a post-approval commitment. The active pharmaceutical ingredient, bedaquiline, is a novel diarylquinoline (i.e., new molecular entity) that inhibits the mycobacterial adenosine 5'-triphosphate (ATP) synthase.

The proposed drug product is a tablet formulation comprised of the drug substance (bedaquiline fumarate salt), lactose monohydrate, maize starch, hypromellose 2910, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, anhydrous colloidal silica, and magnesium stearate. One tablet strength of 100 mg bedaquiline is proposed for marketing. The bedaquiline fumarate salt was selected as the drug substance because of its improved physicochemical properties relative to the free base.

A new manufacturing facility, Kemwell, is proposed for the manufacture of Phase 3 and commercial product. The Applicant included a request for a waiver of the requirement to provide data from a bioequivalence (BE) study between the tablets manufactured at the   (b) (4) site and the Phase 2b tablets from   (b) (4)   FDA previously communicated to the Applicant on 7 October 2011 (pre-NDA meeting), under IND 69,600, that given the high variability in the dissolution data between sites, and the lack of f2 similarity, a BE study would be required to support approval of the Kemwell site. In response, the Applicant noted that the dissolution variability was due to variations in the   (b) (4) process and, based on design of experiment (DOE) studies with similarity f2 values as an output, they proposed to implement optimized manufacturing parameters for their product.

BIOPHARMACEUTIC INFORMATION:

This review evaluates the in vitro dissolution test method, dissolution stability data, and the waiver request for bioequivalence studies to support the Kemwell manufacturing facility.   Where drug substance or drug

1

product process controls are critical for dissolution performance, comments for CMC consideration are also noted.

CONCLUSIONS AND RECOMMENDATION:

1. **Dissolution Method**
   The following proposed dissolution method and acceptance criterion are acceptable.

Dissolution Test Method	
Apparatus	USP 1
Paddle Speed	150 rpm
Medium	0.01M HCl, 900 mL
Temperature	$37.0 \pm 0.5°C$
Dissolution Acceptance Criterion	
Q= (b)(4)% at 30 minutes	

2. **Biowaiver request**

   The provided data support the approval of the BE-waiver request for the Kemwell site and it is granted.

3. **Request for alternate approach for similarity f2 testing**

   The alternate proposal for similarity f2 test is rejected. FDA recommends that future in vitro comparability data include the 5 minute sampling time point; however, the 5 minutes dissolution data may be omitted from the similarity f2 test if the RSDs exceed (b)(4)%.

4. **Comments for Applicant**

   The following comment should be conveyed to the Applicant.

   - *FDA recommends that future in vitro dissolution comparability data submitted to the NDA in support of manufacturing changes include the 5 minutes sampling time point to characterize the complete profile. Note that the 5 minutes dissolution data may be omitted from the similarity f2 test, if the RSDs exceed (b)(4)%. Otherwise, FDA considers the 5 minutes dissolution data appropriate for the f2 statistical analysis.*

5. **Overall recommendation**
   From the perspective of Biopharmaceutics, NDA 204-384 for TMC207 (bedaquiline) Tablets is recommended for approval.

APPROVAL SIGNATURES: {see electronic signature page}

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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BIOPHARMACEUTICS REVIEW NOTES

1.0 GENERAL INFORMATION

1.1 Relevant Regulatory History

Original NDA 204-384 was submitted in accordance with the regulations set forth in section 505(b)1 of the FDC act. This NDA seeks accelerated approval for the use of bedaquiline (TMC207), a new molecular entity (NME), in the treatment of patients with multi-drug resistant tuberculosis (MDR-TB) on the basis of clinical efficacy and safety data through Phase 2b.

TMC207 was granted orphan drug status for the treatment of tuberculosis on 10 January 2005. In addition, the drug was granted fast-track designation on 22 April 2011 for the treatment of MDR-TB.

Relevant Biopharmaceutics correspondences under the referenced IND 69,600 were as follows.

- <u>5 November 2009</u>, EOP2 CMC Meeting
  - o Provide during the IND phase of development, justification for the proposed test conditions and acceptance criteria (i.e., demonstrate that the method is discriminating.) specifically, please submit dissolution profiles obtained in different media and at different paddle speeds (i.e., the dissolution method development report).
    - Applicant committed to providing the information to support a biowaiver proposal (new drug product manufacturing site).

- <u>7 October 2011</u>, preNDA Meeting
  - o Regarding the new 1 liter basket dissolution method, FDA commented that the method seemed reasonable. However, the Applicant should include the detailed method development information in the NDA.
  - o Also, regarding qualification of the new site, in vitro bridging studies will be needed to demonstrate similarity in the dissolution profiles from the two manufacturing sites. The proposal to not assess the f2 similarity factor and only consider the acceptability of the profiles by compliance with the acceptance criterion and visual comparison is not acceptable. The high variability observed between batches seem to be because of the difference in the type of ⬚⬚ (b) (4) used in manufacturing the batch given that the within batch variability is low.

    - ⬚ (b) (4)

    - FDA indicated that if the two sites could not be supported using f2 comparison, the approval of the site change must be supported by data generated from an in vivo BE study comparing the drug

products manufactured at the two sites. FDA recommended using the ▮▮▮▮ (b)(4) drug substance (proposed new facility)/Kemwell drug product (proposed new facility) in the BE study.

- 17 May 2012, Preliminary Type A Meeting Comments
    - o FDA agreed that a biowaiver could be granted if the Applicant limits manufacturing at Kemwell to the conditions for which the f2 test would pass ▮▮▮▮ (b)(4)

1.2 Drug Substance Summary

The drug substance TMC207 (aka R403323) is a diarylquinoline that has a unique mechanism of action involving specific inhibition of mycobacterial ATP synthase, an essential enzyme in energy metabolism. This novel mode of action defines a new class of anti-TB compounds, which is thought to minimize cross resistance with existing anti-TB drugs.

The drug substance chemical structure and formula is illustrated below.

$C_{32}H_{31}BrN_2O \cdot C_4H_4O_4$ (671.58 g/mol)
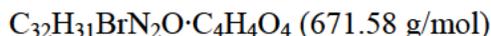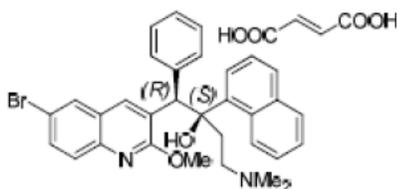
The molecule is a single enantiomer containing two asymmetric carbon atoms.

Some general physico-chemical properties are as follows:

- Practically insoluble in aqueous media and only very slightly soluble in 0.01N HCl.

- The apparent partitioning coefficient (Log R) ranged from 3.7 – 5.0 with increasing pH.

- ▮▮▮▮ (b)(4)

- Not hygroscopic

▮▮▮▮ (b)(4)

The drug substance specification includes tests for appearance, identification, assay, purity, ▮▮▮▮ (b)(4) heavy metals, and particle size.

1.3 Drug Product Summary

The proposed drug product is a tablet formulation comprised of the drug substance, lactose monohydrate, maize starch, hypromellose 2910, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, anhydrous colloidal silica, and

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magnesium stearate. A single strength of 100 mg bedaquiline is proposed for marketing. Additional details on the composition are provided in the following table.

Table 1:   Composition of the Bedaquiline 100-mg Tablet (F001)

Component	Quality Reference	Function	Weight per Tablet	
			(mg)	(%)
Bedaquiline Fumarate	Company specification	Active ingredient	120.89	26.28
Lactose Monohydrate	Ph. Eur./NF	(b) (4)	152.91	33.24
Maize Starch[a]	Ph. Eur./NF		66.00	14.35
Hypromellose 2910 15 mPa.s	Ph. Eur./USP		8.00	1.74
Polysorbate 20	Ph. Eur./NF		1.00	0.22
Purified Water[b]	Ph. Eur./USP		NA	NA
Microcrystalline Cellulose	Ph. Eur./NF		82.20	17.87
Croscarmellose Sodium	Ph. Eur./NF		23.00	5.00
Silica, Colloidal Anhydrous[c]	Ph. Eur./NF		1.40	0.30
Magnesium Stearate	Ph. Eur./NF		4.60	1.00
Total Tablet Weight:			460.00	100.00

[a] Called 'corn starch' in the NF.
[b] Removed during processing.
[c] Called 'colloidal silicon dioxide' in the NF.
NA = Not applicable

Finished tablets are packaged in opaque HDPE bottles with polypropylene child-resistant closures and a foil induction seal.

During the course of development, several drug product formulations were investigated. For the initial clinical studies, two oral solutions of different strengths (F003 and F004) were developed. The two solutions were based on a (b) (4) and differed only in the concentration of TMC207. Subsequently, two prototype immediate-release solid oral dosage forms (capsule F006 and tablet F001) were developed and compared to solution F004 in a relative bioavailability study (Protocol TMC207-C108). The results of the bioavailability study led to the selection of tablet F001 for further clinical studies. A film-coated tablet was also investigated (G001), but the addition of a film-coat resulted in somewhat lower bioavailability compared with F001 (Protocol TMC207-C111). Study C111 also evaluated particle size effects on bioavailability (b) (4) Particle size effects were most noted under (b) (4) (BE not established, see below).

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(b) (4)

Thus, tablet F001 is the proposed commercial formulation and clinical lots were manufactured using the (b) (4) API grade. (*Reviewer's Note: concomitant food intake negates the particle size effects.*)

F001 tablets are manufactured by using a (b) (4)

1.4   Biopharmaceutics Classification System/Pharmacokinetics

A BCS Class II (low solubility, high permeability) is claimed for TMC207. Regardless of the formulation used, drug exposure (Cmax and AUC) is increased when administered with food (~2X). Thus, the Applicant proposed administration with food. Under fed conditions, the mean Cmax and AUC were comparable for the oral solution, the capsule, and the uncoated tablet (study not powered for BE). The median Tmax was 5 hours; however, the estimated terminal elimination half-life was >10 days, depending on dose and study.

In vivo, TMC207 is primarily subjected to oxidative metabolism leading to the formation of *N*-monodesmethyl metabolite (M2). The M2 metabolite is not thought to contribute significantly to clinical efficacy given its lower exposure (about 23% to 31%) in humans and less antimycobacterial activity (4 to 6-fold lower) compared to the parent compound.

1.5   Biopharmaceutics Review Focus

This review evaluates the in vitro dissolution test method, dissolution stability data, and the request for a waiver of the requirement to submit in vivo bioequivalence data supporting the approval of the Kemwell manufacturing facility. Where drug

substance or drug product process controls are critical for dissolution performance, comments for CMC consideration are also noted.

Also, responses to Biopharmaceutics Information Requests submitted during the review (IR letter dated 25 July 2012, responses received in NDA Amendment dated 24 August 2012) are evaluated.

1. The dissolution method development report is incomplete. Provide the complete dissolution profile data (individual values, mean, RSDs, and plots) for all variables tested (i.e., apparatus, media, agitation speed, etc.) to support the selection of the proposed dissolution test method as optimal for your product. FDA was unable to locate the dissolution data using USP Apparatus 2, as referenced in Section 3.2.P.2.2, and summary statistics (i.e., mean and RSDs) were not reported for all other conditions evaluated. In addition, FDA recommends dissolution testing under mild test conditions (i.e., basket method at 100 rpm). To support the faster paddle speed of 150 rpm, provide the dissolution profile data evaluating intermediary paddle speeds (e.g., 110, 125, 140, etc.).

2. Provide the complete dissolution profile data (individuals, mean, RSDs and plots) for all the clinical F001 lots used in the Clinical Phase IIb and Relative Bioavailability studies.

3. Provide the complete dissolution profile data (individuals, means, and RSDs) for the Kemwell DOE test batches and Phase IIb reference batches supporting the f2 similarity values reported in Table 29 of Section 3.2.P.2.3

2.0 BIOPHARMACEUTICS REVIEW TOPICS

2.1 Dissolution Test Method

The proposed dissolution method and acceptance criterion are as follows.

Dissolution Test Method	
Apparatus	USP 1
Paddle Speed	150 rpm
Medium	0.01M HCl, 900 mL
Temperature	$37.0 \pm 0.5°C$
Dissolution Acceptance Criterion	
Q[(b) (4)]% at 30 minutes	

A representative product dissolution profile is illustrated below for clinical lot 10C23.

Mean Drug Release Profile (Lot 10C23/F001), USP 1, 150 rpm, 0.01M HCl, 900 mL

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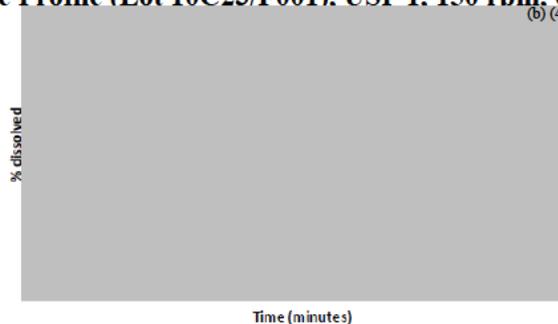
Individual Dissolution Data for Lot 10C23/F001, USP 1, 150 rpm, 0.01M HCl, 900 mL

(b) (4)

2.1.1 Method Development Information

The original NDA submission included a brief dissolution method development summary in Section 2 of 3.2.P.2.2. Supplemental information provided in the NDA Amendment dated 24 August 2012, is also summarized in the appropriate sections.

(b) (4)

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3.0   CONCLUSIONS AND RECOMMENDATIONS

The following dissolution method and acceptance criterion are acceptable.

Dissolution Test Method	
Apparatus	USP 1
Paddle Speed	150 rpm
Medium	0.01M HCl, 900 mL
Temperature	37.0 ± 0.5°C
Dissolution Acceptance Criterion	
Q= (b)(4) % at 30 minutes	

The alternate proposal for the similarity f2 test is rejected. FDA recommends that future in vitro comparability data include the 5 minutes sampling time point; however, the data may be omitted from the similarity f2 test if the RSDs exceed (b)(4) %.

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Reference ID: 3217922

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	NDA 204384	Brand Name	N/A
OCP Division (I, II, III, IV, V)	DCP4	Generic Name	Bedaquiline (TMC207)
Medical Division	DAIP	Drug Class	diarylquinoline
OCP Reviewer	Dakshina M. Chilukuri Zhixia (Grace) Yan Seong Jang	Indication(s)	Treatment of Multi-Drug Resistant TB (MDR-TB)
OCP Team Leader	Kimberly L. Bergman	Dosage Form	Uncoated tablet
Pharmacometrics Reviewer	Fang Li	Dosing Regimen	TMC207 is proposed to be administered at a dose of 400 mg once daily (q.d.) for 2 weeks followed by 200 mg 3 times per week (t.i.w.) for up to 24 weeks, in addition to a background regimen (BR) of anti- TB drugs
Date of Submission	June 29, 2012	Route of Administration	Oral
Estimated Due Date of OCP Review	TBD	Sponsor	Janssen R&D
Medical Division Due Date	TBD	Priority Classification	Yes
PDUFA Due Date	December 29, 2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	16		**Includes assays for TMC207 in plasma and sputum and concomitant medications**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	11		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	2		
P-gp transport studies	X	3		
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-				
single dose:	X	1		**Trial # R207910-CDE-101; Used oral solution (F003 and F004)**
multiple dose:	X	1		**Trial # R207910-CDE-102; Used oral solution (F003 and F004)**

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Patients-				
single dose:				
multiple dose:	**X**			**Proof-of principle trial TMC207-202; Used oral solution (F003 and F004)**
Dose proportionality -				
fasting / non-fasting single dose:	**X**			**Trial # R207910-CDE-101; Used oral solution**
fasting / non-fasting multiple dose:	**X**			**Trial # R207910-CDE-102; Used oral solution**
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**5**		**Trial # R207910BAC1003; used oral solution (F004); Rifampin DDI** **Trial # TMC207-C104; used oral solution (F004); INH and PYR DDI** **Trial # TMC207-C109; used oral solution (F004); Ketoconazole DDI** **Trial # TMC207-C110; used TBM (F001); Kaletra DDI** **Trial # TMC207-C117; used TBM (F001); Nevirapine DDI**
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**X**			**Trial # TMC207-C112; used F001 TBM formulation**
PD -				
Phase 2:	**X**	**2**		**Trial # TMC207-C208; used F001 TBM formulation; conducted in two stages TMC207-C209 (C209); used F001 TBM formulation**
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		**Proof-of principle trial TMC207-202; Used oral solution**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**1**		**2 interim and 1 final models were evaluated. The sponsor has additionally conducted population PK/PD analyses for both efficacy and safety**
Data sparse:	**X**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:		**1**		**TMC207-C108; compared oral solution (F004), tablet (F001) and capsule (F006) formulations;**

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alternate formulation as reference:		1		**TMC207-C111; compared tablet (F001), other formulations (G001, film-coated tablet (b) (4) API) and G001 (film-coated tablet (b) (4) API)**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X			**Food-effect included in trials R207910-CDE-101 and TMC207-C108 and TMC207-C111**
Bio-waiver request based on BCS				
BCS class				**TMC207 is BCS Class II**
Other Studies	X	1		**TMC207-TBC1003; used TBM (F001); TQT trial;**
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				**No genomic based report submitted. However, there appears to be a difference in the PK of TMC207 based on race. A PGx consult will be requested.**
Chronopharmacokinetics				
Pediatric development plan				**Sponsor requested for pediatric waiver under the Orphan Drug Act**
BE Waiver				**Biowaiver request included in Module 3.2.P.2.3.5**
Literature References	X	136		
Total Number of Studies		48		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
**Criteria for Refusal to File (RTF)**					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		Biowaiver request included in Module 3.2.P.2.3.5
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Absolute BA not determined due to unavailability of an IV formulation. Relative BA of formulations used in early and late stage development was evaluated
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow	X			

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	substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Pediatric waiver request submitted under the Orphan Drug Act.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Pediatric waiver request submitted under the Orphan Drug Act.
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		All reports were in English

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_YES_____

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

NA

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

Issues for discussion at Filing Meeting (Not to be sent to the sponsor):
1. A difference in the PK of TMC207 based on race was reported. Clearance in African-American patients was 4.23 L/h compared to non African-American patients (2.78 L/h). No dosage adjustment is being suggested by the sponsor in the absence of clear exposure-response relationship. This needs to be evaluated during the review. Similar differences in exposure were observed between males and females. Again, the sponsor is not seeking a dose-adjustment.
2. The sponsor used the oral solution formulation (F003 and F004) in a few early trials including some DDI trials. However the clinical trial formulation and TBM formulation is a tablet (F001). The sponsor has conducted a relative BA trial comparing the two formulations. The adequacy of the trial is a review issue.

_____

Reviewing Clinical Pharmacologist   Date

_____

Team Leader/Supervisor   Date

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