SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	TMC207 (bedaquiline)

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Status: Approved

Date: 16 June 2017

Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV

Protocol No.: TMC207TBC3001

Title of Study: Early Access of TMC207 in Combination With Other Anti-tuberculosis (TB) Drugs in Subjects With Extensively Drug Resistant (XDR) or Pre-XDR Pulmonary TB

EudraCT Number: 2010-021125-12

NCT No.: NCT01464762

Clinical Registry No.: CR017233

Coordinating Investigator(s): There was no coordinating or overall principal investigator for this study.

Study Center(s): Lithuania (1 site), Russia (3 sites)

Publication (Reference): None

Study Period: 11 January 2012 till 1 December 2016 (last contact in the trial)

Phase of Development: Not applicable; Early Access Program

Objectives:

Primary Objective

The primary objective was to provide early access to bedaquiline (TMC207, also previously known as R207910) for subjects who had pulmonary infection due to strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) with resistance to isoniazid (INH), rifampicin (RMP), and to a fluoroquinolone (FQ) and/or injectable second-line tuberculosis (TB) drug (kanamycin [KAN], amikacin [AMK], or capreomycin [CAP]).

Secondary Objective

The secondary objective was to evaluate the safety and tolerability of bedaquiline. In addition, the results of microbiology assessments which were recommended to be performed during the early access study were to be described.

Hypothesis

The early access study was conducted to make bedaquiline available to subjects with extensively drug resistant (XDR) or pre-XDR TB infection who had limited to no treatment options. Data collection was limited and no statistical hypotheses were tested.

Methodology:

The primary objective of the study was to provide early access of bedaquiline to eligible subjects with pulmonary infection due to strains of *M. tuberculosis* with resistance to INH, RMP, and to a FQ and/or injectable second-line TB drug (KAN, AMK, or CAP) (ie, pre-XDR or XDR) and who were unable/ineligible to participate in bedaquiline clinical trials or the global compassionate use programs (early access programs were done in Russia and Lithuania because these countries did not allow compassionate use at that time). Information on safety and tolerability of bedaquiline in combination with anti-TB drugs was assessed and the results of microbiology assessments which were recommended to be performed during the early access study were collected.

Eligible subjects were provided a 24-week course of bedaquiline which was administered along with their background regimen (BR). Bedaquiline was dosed as follows: 400 mg (given as 100-mg tablets) orally (PO) once daily (qd) for 2 weeks followed by 200 mg PO 3 times weekly for 22 weeks. The selection of the BR was the responsibility of the investigator and had to be constructed with at least 3 anti-TB drugs to which the subject's TB isolate was known to be susceptible from recent drug susceptibility testing results (within the previous 6 months) or likely to be susceptible, based on known treatment history. Acknowledging this text in the protocol differs from the currently approved Prescribing Information in the United States of America and European Union, the intent was to simplify the eligibility criteria in this study.

Once treatment was initiated, subjects were instructed to follow the visit schedule based on routine clinical care.

After their last intake of bedaquiline, all subjects continued to take their BR under the supervision of their treating physician or local health center/hospital in accordance with National Tuberculosis Program (NTP) guidelines and local multidrug resistant TB (MDR-TB) treatment practice (eg, treatment could be extended for reasons of complicated lung disease, etc). Administration of BR drugs was supervised using directly observed treatment therapy (DOT) for MDR-TB. Subjects were followed up for 96 weeks (2 years) after their last dose of bedaquiline to evaluate the microbiological status (measured locally as per local standard of care; eg, smear, culture that was recommended to be performed every 24 weeks). Safety and tolerability of bedaquiline were monitored.

The following adverse events (AEs) were reported and documented in the Case Report Form (CRF):

- All serious AEs (SAEs), regardless of Division of Microbiology and Infectious Diseases (DMID) grade or relatedness to bedaquiline;
- All AEs leading to study discontinuation or interruption of bedaquiline ≥14 days, regardless of DMID grade or relatedness to bedaquiline;
- AEs of specific toxicities, regardless of DMID grade or relatedness to bedaquiline;
- Grade 3 or 4 AEs that were considered to be at least possibly related to bedaquiline by the investigator;
- AEs considered to be medically significant (eg, require medical intervention) that were considered at least possibly related to bedaquiline by the investigator, regardless of DMID grade;
- Any pregnancy in a female subject or female partner of a male subject;
- Special reporting situations: Overdose, suspected abuse/misuse, inadvertent or accidental exposure or medication error of bedaquiline.

Other AEs were collected as per local regulations only.

Laboratory safety data were only routinely captured at screening; at other time points laboratory safety assessments performed at the discretion of the investigator.

Number of Subjects (planned and analyzed):

Since the primary objective was to provide early access of bedaquiline to subjects with XDR or pre-XDR TB infection who had limited-to-no treatment options, no sample size calculation was performed. Subjects could enter the study until bedaquiline was commercially available in the subject's country of residence or could be accessed from another source or until discontinuation of the development program of bedaquiline.

This study included 57 subjects.

Statistical Methods:

No statistical hypotheses were tested and only descriptive statistical analyses were performed. Unless specified otherwise, the intent-to-treat (ITT) population was used for all analyses. Intent-to-treat population includes all subjects who had at least one intake of bedaquiline, regardless of their compliance with the protocol.

RESULTS:

STUDY POPULATION:

A total 61 subjects were screened, of whom 57 were enrolled and treated. Study termination, reasons for study termination, demographic and baseline disease characteristics, and data on the BR are provided in the tables below. The majority (57.9%) of subjects were female.

Forty-three (75.4%) subjects completed the study. Fourteen (24.6%) subjects discontinued the study, of which 5 due to an AE. The 5 subjects who discontinued the study due to an AE included 3 subjects who died (see safety section) and 2 subjects who discontinued bedaquiline due to an AE (nephropathy toxic and depression; see safety section). All subjects who discontinued the study due to an AE had positive baseline mycobacterial growth. Among them, 3 had pre-XDR and 2 had XDR TB infection.

Synopsis Table 1: Study Termination; ITT Population

n (%)	bedaquiline/BR N=57
Completed	43 (75.4)
Discontinued	14 (24.6)
Reasons:	
Adverse event	5 (8.8)[a]
Lost to follow-up	2 (3.5)
Subject non-compliant	1 (1.8)
Withdrawal by subject	2 (3.5)
Other[b]	4 (7.0)

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

[a] These 5 subjects include 3 subjects who died.

[b] These 4 subjects moved their permanent residence to another country or city and did not return to the site.

Synopsis Table 2: Demographic Data; ITT Population

	bedaquiline/BR N=57
Age at screening (years)	
Mean (SD)	31.2 (10.87)
Median (range)	28.0 (18-61)
Weight at screening (kg)	
Mean (SD)	60.37 (9.803)
Median (range)	60.00 (40.0-80.0)
Sex, n (%)	
Female	33 (57.9)
Male	24 (42.1)
Ethnicity, n (%)	
Not Hispanic or Latino	57 (100)
Race, n (%)	
White	57 (100)
Body mass index at screening (kg/m²)	
Mean (SD)	20.44 (2.372)
Median (range)	20.60 (14.0-24.4)
Country, n (%)	
Lithuania	3 (5.3)
Russian Federation	54 (94.7)

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

Synopsis Table 3: Baseline Disease Characteristics; ITT Population

Parameter, n (%)	bedaquiline/BR N=57
HIV status at screening	
Negative	57 (100)
Previous use of second-line drugs [a]	
No	4 (7.0)
Yes	53 (93.0)
Extent of resistance of *M. tuberculosis* strain at screening	
Pre-XDR (FQ-resistant)	14 (24.6)
Pre-XDR (second-line injectable [SLI]-resistant)	13 (22.8)
XDR	30 (52.6)

N=number of subjects with data, n=number of subjects with that observation
[a] Second-line drugs are all anti-TB drugs excluding rifampicin, isoniazid, pyrazinamide, streptomycin, and ethambutol.

Synopsis Table 4: Background Regimen at Baseline; ITT Population

Class Medication, n (%)	bedaquiline/BR N=57
Any use of background TB treatment	57 (100)
Aminoglycosides	**9 (15.8)**
Amikacin sulfate	5 (8.8)
Kanamycin (KAN)	4 (7.0)
Fluoroquinolones	**57 (100)**
Gatifloxacin (GAT)	1 (1.8)
Levofloxacin (LFX)	39 (68.4)
Moxifloxacin (MXF)	15 (26.3)
Ofloxacin (OFX)	2 (3.5)
Miscellaneous anti-TB drugs	**57 (100)**
Augmentin (AUG)	12 (21.1)
Capreomycin (CAP)	44 (77.2)
Cycloserine (CS)	26 (45.6)
Ethambutol (EMB)	17 (29.8)
Linezolid (LZD)	36 (63.2)
Para-aminosalicylic acid (PAS-C)	50 (87.7)
Protionamide (PTH)	19 (33.3)
Pyrazinamide (PZA)	50 (87.7)
Terizidone (TRD)	32 (56.1)

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

Synopsis Table 5: Background Regimen at Baseline: Combinations in >1 Subject; ITT Population

Combination, n (%)	bedaquiline/BR N=57
CAP/ LFX / LZD / PAS-C / PZA / TRD	10 (17.5)
AUG / CAP / LZD / MXF / PAS-C / PZA / TRD	3 (5.3)
CAP / CS / LFX / LZD / PAS-C / PZA	3 (5.3)
CAP / CS / EMB / LFX / PAS-C / PTH / PZA	2 (3.5)
CAP / CS / LFX / PAS-C / PTH / PZA	2 (3.5)
CAP / CS / LZD / MXF / PAS-C / PZA	2 (3.5)

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

Synopsis Table 6: Background Regimen: Tabulation of the Number of TB Drugs in the Background Regimen at Baseline and Post-baseline; ITT Population

	BR			
Total number of TB drugs, n (%)	Baseline N=57	Investigational treatment phase N=57	Overall treatment phase N=57	BR only phase N=55
0	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)[a]
4	1 (1.8)	0 (0.0)	0 (0.0)	5 (9.1)
5	9 (15.8)	6 (10.5)	4 (7.0)	12 (21.8)
6	28 (49.1)	21 (36.8)	15 (26.3)	13 (23.6)
7	17 (29.8)	20 (35.1)	18 (31.6)	12 (21.8)
8	2 (3.5)	8 (14.0)	9 (15.8)	7 (12.7)
9	0 (0.0)	1 (1.8)	8 (14.0)	3 (5.5)
10	0 (0.0)	1 (1.8)	1 (1.8)	0 (0.0)
11	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
12	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
15	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)

N=number of subjects with data, n=number of subjects with that observation
[a] This subject discontinued bedaquiline 1 day before the discontinuation of the BR drugs, and therefore there was no TB treatment during the designated BR only phase.

Synopsis Table 7: Background Regimen: Tabulation of the Number of Newly Added TB Drugs in the Background Regimen Post-baseline; ITT Population

	BR		
Total number of newly added TB drugs compared to baseline, n (%)	Investigational treatment phase N=57	Overall treatment phase N=57	BR only phase N=55
0	36 (63.2)	25 (43.9)	26 (47.3)
1	16 (28.1)	18 (31.6)	16 (29.1)
2	4 (7.0)	4 (7.0)	6 (10.9)
3	1 (1.8)	7 (12.3)	4 (7.3)
4	0 (0.0)	1 (1.8)	1 (1.8)
5	0 (0.0)	1 (1.8)	1 (1.8)
9	0 (0.0)	1 (1.8)	1 (1.8)

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

Synopsis Table 8: Background Regimen: Descriptive Statistics of the Treatment Duration; ITT Population

	BR (Overall treatment phase) N=57		
Standardized medication name, duration (weeks)	n (%)	Mean (SD)	Median (range)
Amikacin sulfate	9 (15.8)	27.7 (31.5)	13.3 (2.1-102.7)
Amoxicillin	1 (1.8)	22.7 (N/A)	N/A
Augmentin	14 (24.6)	48.6 (51.6)	25.6 (1.0-121.3)
Capreomycin	48 (84.2)	53.2 (39.2)	40.0 (3.4-120.9)
Clarithromycin	2 (3.5)	39.8 (21.1)	39.8 (24.9-54.7)
Cycloserine	31 (54.4)	69.2 (39.7)	74.1 (0.9-121.3)
Ethambutol	19 (33.3)	77.9 (45.1)	82.9 (2.1-121.3)
Ethionamide	1 (1.8)	12.0 (N/A)	N/A
Gatifloxacin	1 (1.8)	8.1 (N/A)	N/A
Imipenem[a]	1 (1.8)	32.3 (N/A)	N/A
Isoniazid	2 (3.5)	7.8 (4.7)	7.8 (4.4-11.1)
Kanamycin	4 (7.0)	36.0 (35.0)	22.7 (11.4-87.0)
Levofloxacin	47 (82.5)	70.8 (41.6)	74.1 (2.1-131.1)
Linezolid	38 (66.7)	90.5 (35.0)	103.0 (2.1-121.3)
Lomefloxacin	1 (1.8)	1.0 (N/A)	N/A
Meropenem	1 (1.8)	15.7 (N/A)	N/A
Miscellaneous drugs for treatment of TB	2 (3.5)	45.0 (3.0)	45.0 (42.9-47.1)
Moxifloxacin[b]	33 (57.9)	70.7 (34.1)	68.9 (1.9-120.1)
Ofloxacin	2 (3.5)	22.7 (2.0)	22.7 (21.3-24.1)
PAS-C	51 (89.5)	85.4 (34.7)	87.6 (2.1-131.1)
Primaxin	1 (1.8)	2.4 (N/A)	N/A
Protionamide	21 (36.8)	71.2 (35.7)	72.1 (1.1-125.9)
Pyrazinamide	50 (87.8)	90.8 (34.1)	96.5 (2.1-131.1)
Rifampicin[c]	2 (3.5)	7.8 (4.7)	7.8 (4.4-11.1)
Terizidone	35 (61.4)	82.9 (38.8)	96.3 (0.6-121.3)

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

[a] The data for imipenem include one subject for whom the medication was listed as imipenem and one subject for whom it was listed as primaxin.

[b] Twenty-three subjects received MXF during the administration of bedaquiline. This was not according to the protocol. However, these subjects required addition of MXF, which was the only fluoroquinolone available, in order to construct an adequate regimen with 3 BR drugs.

[c] Note that for the 2 subjects who received RMP, treatment started 15 months and 10 months after bedaquiline treatment, respectively. RMP treatment lasted 4.4 weeks and 11 weeks, respectively.

SAFETY RESULTS:

Three (5.3%) subjects died during the study, all after the end of the investigational treatment phase. Two subjects died during the BR only phase (both due to pulmonary hemorrhage) and 1 subject died during the follow-up phase after completion of the overall treatment phase (due to an acute myocardial infarction). The time interval from last bedaquiline intake to the time of death ranged from 411 to 442 days. All 3 fatal SAEs were assessed as not related to bedaquiline by the investigator. The 2 deaths due to pulmonary hemorrhage were considered TB-related by the investigator and, in both subjects, culture conversion had not occurred as of the last visit.

During the investigational treatment phase, 4 (7.0%) subjects had at least one SAE, which were all considered not related to bedaquiline by the investigator. Two (3.5%) subjects permanently discontinued bedaquiline due to an AE: 1 subject due to depression and 1 subject due to nephropathy toxic; these events were considered not related to bedaquiline by the investigator. Drugs in the BR were permanently discontinued due to depression and temporarily interrupted due to nephropathy toxic. Depression and nephropathy toxic, assessed as non-serious, were considered possibly and very likely related to the BR, respectively, by the investigator. Grade 3 or 4 AEs were reported in 10 (17.5%) subjects (in 4/10 subjects due to elevations in liver transaminases), of which none were considered at least possibly related to bedaquiline by the investigator. Adverse events of grade 1 or 2 were considered at least possibly related to bedaquiline by the investigator in 6 (10.5%) subjects.

At least one AE was reported in 47 (82.5%) subjects during the investigational treatment phase. The most frequently (>15.0% of subjects) reported AEs were aspartate aminotransferase (AST) increased (23 [40.4%] subjects), alanine aminotransferase (ALT) increased (12 [21.1%] subjects), and eosinophilia (10 [17.5%] subjects). Grade 3 ALT increased was reported in 3 (5.3%) subjects and AST increased in 2 (3.5%) subjects. There were no reports of grade 4 AST or ALT increased. In one subject grade 2 ALT increased was associated with a concurrent grade 1 AE blood bilirubin increased, and in another subject grade 2 AST increased was associated with a concurrent grade 2 AE hyperbilirubinemia. Of the 10 subjects with eosinophilia, the AE was grade 1 in severity in 4 subjects and grade 2 in 6 subjects. None of the eosinophilia AEs were considered related to bedaquiline by the investigator or led to discontinuation of bedaquiline.

Of note, 4 (7.0%) subjects had the AE hypokalemia and 4 (7.0%) subjects had the AE hypothyroidism, which could potentially increase the risk of cardiac arrhythmias, during the investigational treatment phase.

During the investigational treatment phase, 5 (8.8%) subjects experienced an event identified by the acute pancreatitis Standardized Medical Dictionary for Regulatory Activities Query (SMQ), 3 (5.3%) subjects experienced an event identified by the Torsade de Pointes/QT prolongation SMQ, and 27 (47.4%) subjects experienced an event identified by the drug-related hepatic disorders - comprehensive search SMQ. No events of ventricular arrhythmia or Torsade de Pointes were reported. All events in these SMQs of interest were grade 1 or 2 in severity, except for a grade 3 acute pancreatitis SMQ event in 1 (1.8%) subject (pancreatitis acute) and grade 3 drug related hepatic disorders - comprehensive search SMQ events in 4 (7.0%) subjects (1 subject with both AST and ALT increased, 2 subjects with ALT increased only and 1 subject with AST increased only). None of the SMQ events were considered serious or led to permanent discontinuation of bedaquiline. No events were identified by the severe cutaneous adverse reactions and rhabdomyolysis/myopathy SMQs.

During the investigational treatment phase, 31 (54.4%) subjects experienced an adverse drug reaction (ADR) listed for bedaquiline. The most frequently (>10.0% of subjects) observed ADRs were AST increased (23 [40.4%] subjects), ALT increased (12 [21.1%] subjects), and nausea (8 [14.0%] subjects). No formal analyses to identify cases meeting laboratory criteria for Hy's Law were performed as laboratory data were only routinely captured at screening (at other time points it was performed at the

discretion of the investigator), and the DMID grading scale for bilirubin does not allow comprehensive identification of all Hy's Law cases.

During the investigational treatment phase, an increase from baseline in QT interval corrected for heart rate according to Fridericia (QTcF) >60 ms was observed in 4 (8.2%) subjects and increases from baseline between 30 and 60 ms in QTcF in 2 (4.1%) subjects. Based on medical review, 1 subject who had a QTcF increase by >60 ms was receiving MXF at 400 mg PO qd in addition to bedaquiline as part of the BR at the time this QTcF increase event of interest was recorded. The other 5 subjects were receiving LFX as part of the BR at the time this QTcF increase event of interest was recorded. For 1 subject who had a QTcF increase by >60 ms, a concurrent grade 1 AE hypokalemia was reported. None of the subjects were receiving clofazimine. No QTcF >450 ms based on actual values was observed.

The AE data and AEs of clinical interest identified by SMQs are summarized in the tables below.

Synopsis Table 9: Adverse Events Summary; ITT Population

	bedaquiline/BR N=57	
n (%) of subjects with	**Investigational treatment phase**	**Overall treatment phase**
Any AE	47 (82.5)	50 (87.7)
Any grade 3 or 4 AE	10 (17.5)	15 (26.3)
Any grade 3 or 4 AE that is at least possibly related to bedaquiline	0 (0.0)	0 (0.0)
Any AE at least possibly related to bedaquiline	6 (10.5)	6 (10.5)
Any death	0 (0.0)	2 (3.5)[b]
Any SAE[a]	4 (7.0)	8 (14.0)
Any SAE[a] at least possibly related to bedaquiline	0 (0.0)	0 (0.0)
Any AE leading to permanent discontinuation of bedaquiline	2 (3.5)	2 (3.5)
Any AE leading to permanent discontinuation of bedaquiline that is at least possibly related to bedaquiline	0 (0.0)	0 (0.0)
Any grade 3 or 4 AE OR AE leading to permanent discontinuation of any study medication OR any SAE[a]	16 (28.1)	23 (40.4)

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

[a] Serious AEs include deaths.

[b] A third subject died during the FU phase.

Synopsis Table 10: Adverse Events of Clinical Interest Identified by SMQs; ITT Population

Standard MedDRA Query Preferred term, n (%)	bedaquiline/BR N=57 Investigational treatment phase	 Overall treatment phase
Any SMQ	29 (50.9)	37 (64.9)
Drug Related Hepatic Disorders - Comprehensive Search (SMQ)	**27 (47.4)**	**34 (59.6)**
AST increased [a]	23 (40.4)	28 (49.1)
ALT increased [a]	12 (21.1)	15 (26.3)
Blood bilirubin increased	2 (3.5)	2 (3.5)
Bilirubin conjugated increased	1 (1.8)	2 (3.5)
Hepatotoxicity	1 (1.8)	3 (5.3)
Hyperbilirubinemia	1 (1.8)	2 (3.5)
Acute Pancreatitis (SMQ)	**5 (8.8)**	**8 (14.0)**
Blood bilirubin increased	2 (3.5)	2 (3.5)
Blood amylase increased [a]	1 (1.8)	3 (5.3)
Hyperbilirubinemia	1 (1.8)	2 (3.5)
Pancreatitis acute	1 (1.8)	1 (1.8)
Torsade de Pointes/QT Prolongation (SMQ)	**3 (5.3)**	**3 (5.3)**
ECG QT prolonged	2 (3.5)	2 (3.5)
ECG repolarization abnormality	1 (1.8)	1 (1.8)
Rhabdomyolysis/Myopathy (SMQ)	**0 (0.0)**	**0 (0.0)**
Severe Cutaneous Adverse Reactions (SMQ)	**0 (0.0)**	**0 (0.0)**

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

[a] Upon query, the investigator clarified that for 1 subject, the increases in ALT, AST and amylase that were reported as AE during the BR only phase were due to alcohol consumption. Alcohol abuse itself was not required to be reported as AE per the protocol.

EFFECTIVENESS RESULTS:

As “efficacy” reflects a controlled clinical study while “effectiveness” reflects the real-world use as in this Early Access Program, the term “effectiveness” will be used in this study report.

Out of the 56 subjects with baseline microbiology results, 52 (92.9%) had a positive mycobacterial culture. For subjects who had mycobacterial growth at baseline and with post baseline results available, no growth was observed at Week 24 in the majority of subjects (31/36 [86.1%] subjects). Of the 25 subjects with negative mycobacterial growth at Week 24 who had growth results available at later time points, only one subject had at least 1 positive result afterwards.

Per the protocol, all 57 (100%) subjects were infected with strains of *M. tuberculosis* that showed resistance to INH and RMP. The majority of bacterial strains were also resistant at baseline to aminoglycoside antibiotics, FQs, and other antibiotics including PZA, EMB, ethionamide, and CAP. Culture conversion occurred regardless of the extent of resistance of the TB infection at baseline.

After 24 weeks of treatment, the percentage of subjects with positive mycobacterial growth decreased ~90%. Five (12.5%) subjects showed positive mycobacterial growth at Week 24: 1 out of 19 subjects with XDR TB infection, 3 out of 11 subjects with pre-XDR (FQ resistant) TB infection, and 1 out of 10 subjects with pre-XDR (SLI-resistant) TB infection.

STUDY LIMITATIONS:

No control arm was included in this study and only subjects with pre-XDR or XDR TB were allowed to participate. Enrollment was predominantly in Russia. There was no central laboratory, or central ECG collection, or central laboratory confirmation of microbiological status. Only targeted AEs were collected. Culture methods were not standardized and varied (solid or liquid or both were performed) according to the local standard of care.

CONCLUSION(S):

Of the 57 subjects who started treatment with bedaquiline in combination with a BR of anti-TB drugs (ITT population), 43 (75.4%) subjects completed the study and 14 (24.6%) subjects discontinued the study.

The results of this final analysis show that bedaquiline treatment in combination with a BR of anti-TB drugs for 24 weeks was generally safe and well tolerated. A trend towards higher incidence of reported AEs related to ALT/AST increase (which have already been identified as ADRs) and eosinophilia was observed as compared to the incidence of these AEs described previously in the Phase 2b bedaquiline studies (ie, TMC207-C208 and TMC207-C209). None of the eosinophilia AEs were considered related to bedaquiline by the investigator or led to discontinuation of bedaquiline. No QTcF >450 ms based on actual values was observed. In this early access study, culture conversion was observed in the majority of subjects with XDR and pre-XDR pulmonary TB after bedaquiline treatment in combination with a BR of anti-TB drugs for 24 weeks. The risk-benefit remains positive for the population studied.

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