19 December 2013
EMA/CHMP/329898/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

SIRTURO

International non-proprietary name: bedaquiline

Procedure No. EMEA/H/C/002614/0000

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Product information

Name of the medicinal product:	SIRTURO
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse BELGIUM
Active substance:	bedaquiline fumarate
International Non-proprietary Name:	Bedaquiline
Pharmaco-therapeutic group (ATC Code):	Drugs for treatment of tuberculosis (J04A)
Therapeutic indication:	SIRTURO is indicated for use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. See sections 4.2, 4.4 and 5.1. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Pharmaceutical form:	Tablet
Strength:	100 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	188 tablets

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List of abbreviations

TB definitions and their abbreviations:

MDR TB: Multidrug resistant tuberculosis is the clinical definition for all tuberculosis that is resistant to at least rifampicin (R) and isoniazid (H).

The terms below specifically state the degree of resistance for the TB isolate:

$MDR_{H\&R}$-TB: Multidrug resistant tuberculosis, resistance to isoniazid (H) and rifampicin (R), but susceptible to both second line injectables and flouroquinolones.

Pre-XDR-TB: Pre-extensively resistant tuberculosis, resistance to isoniazid (H) and rifampicin (R), but still susceptible to *either* (but not both) second line injectables *or* fluoroquinolones.

XDR-TB: Extensively drug resistant tuberculosis, resistance to isoniazid (H) and rifampicin (R), second line injectables and fluoroquinolones.

ADR	Adverse drug reaction
AE	Adverse event
AFB	Acid fast bacillus
AG	Aminoglycoside
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMK	Amikacin
AR	Assessment report
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATP	adenosine 5'-triphosphate
AUC	Area under the plasma concentration-time curve
b.i.d.	Bis in die; twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BR	Background regimen
BSA	Bovine serum albumin
BUN	Blood urea nitrogen
Caco-2 cells	Colon carcinoma-derived cells
CAD	Cationic amphiphilic drug
CAP	Capreomycin
CFU	Colony forming unit
CI	Confidence interval
Cl	Clearance
CK	Creatine kinase
Cmax	Maximum concentration
Css	Steady state concentration
CPK	Creatine phosphokinase
CPK-MB	Creatine phosphokinase - muscle-brain isoenzyme
CrCl	Creatinine clearance
CRP	C-reactive protein
CS	Cycloserine
cTnI	Cardiac troponin I
CU	Compassionate use
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DOT	Directly observed therapy

DR	Drug-resistant
DS	Drug-susceptible
DST	Drug susceptibility testing
EAP	Early Access Program
EBA	Early bactericidal activity
ECG	Electrocardiogram
eEBA	Extended early bactericidal activity
EFV	Efavirenz
EMB	Ethambutol
ESR	Erythrocyte sedimentation rate
ETH	Ethionamide
F	Absolute bioavailability
FDA	Food and Drug Administration
Fpen	Penetration factor
FQ	Fluoroquinolone
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
H	Isoniazid
hERG	Human ether-à-go-go-related gene
HIV-1(2)	Human immunodeficiency virus – type 1 (type 2)
HP-β-CD	Hydroxypropyl-beta-cyclodextrin
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
IKr	Delayed rectifier potassium current
I_{Ks}	Slowly activating rectifying potassium current
INH	Isoniazid
INN	International nonproprietary name
ITT	Intent-to-treat
IV	Intravenous(ly)
KAN	Kanamycin
LCMS/MS	Liquid chromatography coupled to tandem mass spectrometry
LDH	Lactate dehydrogenase
LFT	Liver function test
LJ agar	Lowenstein-Jensen agar
LVX	Levofloxacin
M. tuberculosis	*Mycobacterium tuberculosis*
M2	*N*- monodesmethyl metabolite of bedaquiline
M3	N-didesmethyl-bedaquiline
MAA	Marketing Authorization Application
MBC	Minimum bactericidal concentration
MDR	Multidrug resistant
$MDR_{H\&R}$-TB	Multidrug resistant tuberculosis, i.e., resistant to isoniazid (H) and rifampicin (R), excluding pre-XDR and XDR (see TB definitions above)
MDR-TB	Multidrug resistant tuberculosis including pre-XDR and XDR (see TB definitions above)
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	Mycobacteria growth indicator tube, refers to MGIT™ from Becton, Dickinson and Company (BD) incubated using the BACTEC™ MGIT™ 960 system
MIC	Minimum inhibitory concentration
MIRU-VNTR	Mycobacterial interspersed repetitive units – variable number tandem repeats
mITT	Modified intent-to-treat
MPS	Mononuclear phagocytic system
N(t)RTI	Nucleoside (nucleotide) reverse transcriptase inhibitors
N/A	Not applicable
NDA	New Drug Application
NIH	National Institute of Health
NOAEL	No observed adverse effect level
NOEC	No Observed Effect Concentration

NTP	National TB Program
NVP	Nevirapine
OECD	Organisation for Economic Co-operation and Development
OFL	Ofloxacin
P.O.	Oral(ly)
PD	Pharmacodynamic
PEC	Predicted Environmental Concentration
P-gp	P-glycoprotein
PK	Pharmacokinetic
PNEC	Predicted No Effect Concentration
Pop-PK	Population PK modelling
PP	Per protocol
pre-XDR-TB	Pre-extensively drug resistant tuberculosis (see TB definitions above)
PT	Prothrombin time
PZA	Pyrazinamide
q.d.	Quaque die; once daily
QT	Interval between the start of the Q wave and the end of the T wave on ECG
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
R or RIF	Rifampicin (rifampin)
RBC	Red blood cell
REMA	Resazurin microtiter assay
RFLP	Restriction fragment length polymorphism
RMP	Risk Management Plan
SAE	Serious adverse event
SCC	Sputum culture conversion
SD	Standard deviation
SM	Streptomycin
SMQ	Standardized MedDRA Query
SOC	System Organ Class
$t_{1/2}$	Half-life
t.i.w.	3 times weekly
TB	Tuberculosis
t_{max}	Time to maximum concentration
TLI	Trypsin-like immunoreactivity
TQT	thorough QT
TRD	Terizidone
ULN	Upper limit of normal
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis (see TB definitions above)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 28 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for SIRTURO, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2011.

SIRTURO was designated as an orphan medicinal product EU/3/05/314 on 26 August 2005. SIRTURO was designated as an orphan medicinal product in the following indication: treatment of tuberculosis.

The applicant applied for the following indication: SIRTURO is indicated in adults (≥ 18 years) as part of combination therapy of pulmonary tuberculosis due to multi-drug resistant *Mycobacterium tuberculosis*.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that bedaquiline fumarate was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/55/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/55/2011 not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claim(s):

- SIRTURO falls within the category of "medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000

- SIRTURO also falls within Article 2(1) of EC No 507/2006 "medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases"

New active Substance status

The applicant requested the active substance bedaquiline fumarate contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on March 2009 and June 2011. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

SIRTURO has been given a Marketing Authorisation in the United States of America on 28 December 2012.

1.2. Manufacturers

Manufacturer responsible for batch release

Janssen Pharmaceutica
Turnhoutseweg, 30
B-2340 Beerse
Belgium

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

- The application was received by the EMA on 28 August 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012.
- During the meeting on 10 January 2013, the PRAC agreed RMP Advice and assessment overview.
- During the meeting on 17 January 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 January 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 May 2013.
- During the meeting on 13 June 2013, the PRAC agreed RMP Advice and assessment overview.
- During the CHMP meeting on 27 June 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 13 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 6 September 2013.
- During the meeting on 5 September 2013, PRAC endorsed PRAC Rapporteur assessment report on the RMP.
- During the CHMP meeting on 19 September 2013, it was planned to have outstanding issues addressed by the applicant during an oral explanation before the CHMP. In view of a new proposal made by the Applicant, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- During the meeting on 24 October 2013, the CHMP agreed to one month Clock stop extension request dated 14 October 2013.
- The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on 18 November 2013
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second list of outstanding issues to all CHMP members on 27 November 2013.
- During the meeting on 5 December 2013, PRAC endorsed PRAC Rapporteur assessment report on the RMP.

- During the meeting on 19 December 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to SIRTURO.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease to be treated

About a third of the global population, more than 2 billion people, is infected with *M. tuberculosis*, of which the majority is latent.

The life time risk to fall ill in overt TB is around 10% in general, but many times higher (around 10% annual risk) in untreated HIV-positive individuals. Tuberculosis is the leading cause of death in the latter population. It was estimated that a total of 8.8 million new TB cases occurred in 2010, including 1.1 million people co infected with HIV, and that about 1.45 million people died due to TB.

During more recent years the burden of TB resistant to first line therapy has increased rapidly. Such multidrug resistant tuberculosis (defined later in this assessment report) has been reported in all regions of the world. Presently around 500.000 of new MDR cases are estimated to emerge every year, which is close to 5% of all new TB cases. China and India carried nearly 50% of the total burden of incident MDR-TB cases in 2008, followed by the Russian Federation (9%). The incidence of MDR-TB in US and EU was reported to be 1.1% and 2.4%, respectively. Within the EU, the incidence is much higher in certain Eastern European countries, with the largest burden in Romania, Latvia and Lithuania.

MDR TB is an orphan disease in the EU, US and in Japan.

Current TB therapy and definitions

Treatment of pulmonary drug susceptible TB typically takes 6 months resulting in cure rates in well over 90% of cases with good treatment adherence. The two most important drugs in this treatment are isoniazid (INH) and rifampicin (RIF).

TB with resistance to at least both INH and RIF is called multidrug resistant (MDR) TB. The two most important “classes” of second-line TB drugs to be used in such cases are injectable drugs (the aminoglycosides amikacin and kanamycin, and the related agent capreomycin) and fluoroquinolones. Apart from these agents a number of miscellaneous drugs are used in addition, as part of combination therapy. The effectiveness of these latter miscellaneous drugs is generally lower, the tolerability is problematic and established breakpoints for resistance determination are lacking.

The term pre-XDR (pre-extensively drug resistant) TB is used when resistance is present also to one of the two main second-line class agents (injectables or any of the fluoroquinolones), and XDR-TB when resistance is present to INH+RIF + injectables + fluoroquinolones.

The WHO standard treatment for MDR-TB is commonly divided into 2 phases:

- a 4 to 6-month intensive treatment phase in which an injectable drug plus 3-4 other drugs, including a fluoroquinolone,
- a continuation phase without the injectable drug and often without pyrazinamide (PZA) for a total duration of 18-24 months.

Using this approach, cure rates in MDR-TB are much lower than those seen in DS-TB (ranging from less than 50% to around 75%), despite the higher number of agents and longer treatment duration. Hence, MDR TB is associated with a high mortality and is considered an important major threat to public health.

More recent approaches to evaluate various MDR TB regimens have yielded somewhat more optimistic outcomes, despite shorter treatment durations. In these non-randomised studies (with low number of patients) cure rates in the range of 90% were achieved by including a fourth generation fluoroquinolone and by increasing the number of agents even further, to include up to 7 agents in the intensive phase, and still 4-5 agents in a second phase.

2.1.2. About the product

SIRTURO (bedaquiline, formerly known as TMC 207) is a new agent of a unique class, specific for mycobacteria, and seemingly without cross-resistance to available TB agents. A large number of pre-clinical studies showed promising results for bedaquiline. For example, in animal models bedaquiline + pyrazinamide cured TB at a higher rate than the traditional first line combination, even when therapy was shortened for the former combination.

The clinical program for bedaquiline has been aimed at treating MDR-TB, and data is now available from phase 2b studies of moderate size, both placebo-controlled and non-controlled studies. The treatments given in these studies were similar to those recommended by the WHO, although the number of agents used was slightly higher (five agents in the preferred background regimens). Bedaquiline (versus placebo in the controlled study) was added during the first (intensive) treatment phase, while the background regimens were generally unchanged throughout the complete course of therapy (18-24 months).

On the basis of these studies, the applicant submitted an application for a conditional approval for bedaquiline, with the proposed indication: treatment of adult patients infected with pulmonary tuberculosis due to MDR *M. tuberculosis*, as part of combination therapy.

In line with the approach in the phase 2 studies, Sirturo is only to be used during the first 6 months of therapy.

However the planned pivotal study (as a specific obligation) will test for 40 weeks of bedaquiline treatment.

2.2. Quality aspects

2.2.1. Introduction

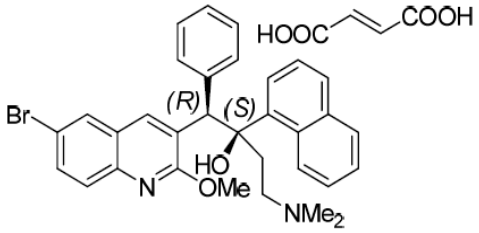
SIRTURO is presented as tablets containing 100 mg of bedaquiline, in the form of fumarate salt, as the active substance. The tablets are uncoated, white to almost white round and biconvex, 11 mm in diameter, with debossing of "T" over "207" on one side and "100" on the other side.

Excipients used in the preparation of SIRTURO tablets include lactose monohydrate, maize starch, hypromellose, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, anhydrous colloidal silica and magnesium stearate.

The tablets are packed in high density polyethylene (HDPE) bottles fitted with child resistant polypropylene (PP) closure with aluminium seal liner.

2.2.2. Active Substance

Bedaquiline (INN) is chemically designated as (1R,2S)-1-(6-bromo-2-methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol with fumaric acid (1:1), and has the following structure:



Bedaquiline fumarate is a white to almost white powder. It contains two asymmetric carbon atoms, C-1 (R), C-2 (S) and exhibits ability to rotate the orientation of linearly polarized light (optical rotation). The substance is non-hygroscopic. It is practically insoluble in aqueous media over a wide pH range and very slightly soluble in 0.01 N HCl. The substance is soluble in a variety of organic solvents. Due to the low solubility Log KD (log P) could not be determined experimentally.

In Biopharmaceutics Classification System (BCS) bedaquiline is classified as a Class 2 compound (expressing low solubility and high permeability).

Bedaquiline exists in only one non-solvated crystalline form: Form A. In addition 2 pseudopoly-morphs were found: Form B and Form C. The substance can also be made amorphous. Sufficient evidence was provided to demonstrate that Form A is obtained by the employed manufacturing process of the active substance.

Particle size was considered a critical quality attribute of the active substance as bedaquiline is not dissolved in the dosage form. Therefore an appropriate test on particle size determination was included in the active substance specification. The acceptance criteria are based upon the capabilities of the milling process, batch and stability data, and the known impact of the particle size on manufacturability, *in-vitro* release, and *in-vivo* performance.

Manufacture

During development, the critical quality attributes (CQAs) of the active substance were established based on the potential to impact the performance and manufacturability of the finished product and these include impurities (organic, inorganic and stereoisomeric impurities, residual solvents) and particle size. Process development efforts have focused on the identification and control of active substance CQAs and the Critical Process Parameters (CPPs) that impact them. The CQAs of the active substance requiring investigation have been determined and an appropriate control strategy for the manufacturing process has been employed.

The synthesis of bedaquiline involves four steps which consist of one synthetic coupling step resulting in a mixture of stereoisomers followed by purification by a controlled crystallization using enantiomeric organophosphate and formation of the fumaric salt. Subsequently the substance is milled. The manufacturing process has been suitably described in flow charts and a narrative description. The length of the synthesis was justified in terms of control of purity profile of the starting materials. Only single synthetic coupling step is involved in the synthesis and the applicant has provided extensive evidence supporting the use of the proposed starting materials. The proposed starting materials constitute major structural fragments of the final active substance and the synthetic steps to form the starting materials are non-critical and non-complex organic reactions. The proposed process is robust enough to control the stereochemistry of the active substance. Furthermore the introduction of stereochemistry is part of the GMP-controlled process. The synthetic path has high purifying capacity and the analytical methods employed are capable of detecting impurities even with structures very similar to the intermediate or final active substance. The purifying capacity has also been demonstrated by extensive spiking experiments. Steps in which genotoxic impurities may be formed are included in the GMP-controlled process. The potential genotoxicity has been evaluated *in-silico* for impurities originating from up streams of the proposed starting materials and no structural alerts were identified.

Potential impurities have been well discussed in relation to their origin (raw material, manufacturing process and degradation products) and potential carry-over into the final active substance. The fate of the impurities was studied by spiking the intermediates with known amounts of the impurities and performing the standard processes to obtain the non-milled drug substance. Impurities derived from starting materials as well as process impurities formed in the manufacturing process have been demonstrated to be sufficiently controlled by the applied analytical methods, the specifications, and the manufacturing process.

The possibility of genotoxic impurities was also addressed during the development. All impurities were assessed regarding their genotoxic potential, in addition to all intermediates, solvents and reagents used in the synthesis. None of the structures assessed resulted in a positive. No potential genotoxic impurities were found.

In general, sufficient information regarding the manufacturing process, starting materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described.

Confirmation of the chemical structure of bedaquiline was provided by elemental analysis (confirmation of the determined elementary composition), spectroscopic methods as UV, IR, ^{1}H-NMR, ^{13}C-NMR as well as by mass spectral (MS) analysis.

An extensive polymorphism screening study has been performed in order to identify all polymorphic forms of the active substance. A series of crystallization experiments were conducted using various solvents covering a broad range of solvent properties such as polarity, hydrogen bond donor and acceptor propensity, dielectric constant, and other parameters. Different crystallization approaches were applied. The main approaches were crystallization experiments, evaporation tests, precipitation with anti-solvent, and slurry experiments. It was found that the bedaquiline exists in only one non-solvated crystalline form: Form A. This form was obtained in most of the experiments of the polymorph screening. All manufactured batches produced only Form A. No evidence for the presence of the other crystalline form or amorphous form was found. The synthesis process consistently produces Form A. The stability of Form A has been demonstrated by monitoring it during stability studies.

Specification

The active substance specification includes tests for appearance, identification (IR), assay (HPLC), chromatographic purity (HPLC), residual solvents (GC), residue on ignition, heavy metals and particle size (laser diffraction).

The manufacturing process has been shown to consistently produce polymorphic Form A (17 batches tested) and no changes in the polymorphic form have been observed in the stability study. A test for the polymorphic form was therefore excluded from the active substance specification.

A detailed description for all analytical methods was provided. Complete method validation data was provided for the non compendial (*in-house*) analytical methods.

In general specification limits and analytical methods proposed are suitable to control the quality of the active substance.

Batch analysis results for bedaquiline have been presented. All batches were manufactured by the proposed commercial manufacturers according to the proposed process. Batches were used in clinical studies, stability studies and process validation. In total 17 batches of bedaquiline have been manufactured and tested during the development phase. All batches showed comparable impurity profile. In addition, batch results were presented for batches manufactured using different synthesis methods used in earlier steps of the development. It can be concluded that the batch analysis results indicate that the manufacturing process is reproducible and under control.

Stability

Stability studies according to ICH guidelines have been initiated on commercial scale batches of the active substance stored in the commercial packaging. Long-term (30°C/65% RH), accelerated (40°C/75% RH), and stress stability studies are being conducted on the 3 primary stability batches and 5 process validation batches manufactured at by the final synthesis method. The stability study for batches already put on stability is planned for 60 months for the three process validation batches and 36 months for the other batches.

Stability testing for bedaquiline included also forced degradation study. The forced degradation study included testing the effects of thermal oxidation, thermal acidic, neutral and alkaline conditions, photolysis and solvolysis. The study revealed that the substance is extremely unstable under basic conditions and prone to significant breakdown under neutral and acidic conditions and

in ethanol. The substance is also prone to significant degradation under H_2O_2 conditions. Bedaquiline is only slightly sensitive to photolysis.

All results reported are within proposed specifications. No trends are seen in the primary and supportive studies. The post-approval stability protocol is acceptable and a sufficient number of batches from the supply chains will be added to the program.

Based on the available stability data, bedaquiline showed to be a stable when packaged in the proposed container closure system.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to obtain a solid, oral dosage form that would deliver the required dose of the active substance.

Several variants of the active substance have been investigated with respect to solubility and stability: salt form, polymorphism and particle size. The fumarate salt was selected for further development, taking into account its solubility, toxicity and manufacturability.

Several finished product formulations were investigated in the early development phase. For the initial clinical studies 2 aqueous oral solutions of different strength were developed. Subsequently, 2 prototype immediate release oral solid dosage forms (capsule and tablet) were developed and compared to solution in a relative bioavailability study. This led to the selection of the tablet for further clinical investigation and for commercialisation.

The development of the tablet formulation followed a classic development approach and adopted elements of QbD methodology. An in-depth understanding of the effects of formula components, process intermediates and process parameters was obtained from design of experiment studies (DoEs) and scale-up studies. Based on these studies, appropriate control strategy has been implemented to mitigate the risks identified initially and to ensure that the characteristics specified in the Quality Target Product Profile (QTPP) will be met consistently.

The manufacturing process development has been well documented. The applicant also followed an enhanced approach to development of the manufacturing process. Laboratory scale process was optimised for commercial production by the manufacturing of 2 characterization batches and a full factorial design of experiments (DoE) study at full scale. A criticality analysis (CA) was performed to assess the manufacturing process. This included the identification of the critical quality attributes (CQAs), determination of critical process parameters (CPPs) and the design of an effective control strategy. Process steps and parameters, including assessment of in-process controls (IPCs) that affect the CQAs of the finished product were identified. Furthermore experience gained from the manufacture of these batches was used to set appropriate process parameters. Based on the results obtained proven acceptable ranges (PARs) have been proposed for several critical process parameters (CPPs), but no target values. The PARs are wider than what is normally acceptable in strictly traditional process descriptions, based on a traditional approach to pharmaceutical development. However, no design space has been claimed. Consequently, the manufacturing process of the finished product is expected to run within the approved ranges and with traditional control strategy (including in-process controls.

The DoE study was conducted to investigate the criticality of granulation, blending, and compression. From the granulation study it was evident that the granulation conditions influence the granule particle size distribution. However, conclusions regarding the suitability of the granulation parameters, and the resulting chemical and physical characteristics of the granules could only be made after blending and tablet compression. In the blending study the parameters selected for the study resulted in acceptable content uniformity for the final blends. Tablets from all final blends were compressed at different compression forces and different table speeds and the effect on tablet weight, hardness, thickness, disintegration time, friability, and dissolution was investigated. The choice of the process was considered justified and the critical process parameters and process equipment were generally satisfactorily identified. It has been shown that the manufacturing process was robust.

It can be concluded that the formulation development of the product was satisfactorily described. The key critical parameters were identified and successfully evaluated.

Adventitious agents

It has been certified by the supplier that lactose is produced in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products". Lactose is produced from milk obtained from healthy cattle under the same conditions as milk intended for human consumption.

Magnesium stearate is of vegetal origin and relevant certificates from manufacturers of this excipient have been provided.

Manufacture of the product

Standard process is employed for the manufacture of SIRTURO tablets. The manufacturing process comprises a conventional wet granulation followed by compression. No intermediates are isolated during the process.

Overall, description of the manufacturing process was adequate. Critical steps have been identified and properly evaluated at the commercial scale. The reproducibility of the process has been suitably demonstrated during the development.

Formal validation will be performed post-approval on the first three consecutive commercial batches, prior to launching the product. An acceptable validation plan has been provided. Since the process has been extensively evaluated and the critical process parameters for the process have been identified and characterised at full scale it was considered sufficient to provide a validation plan and perform the validation post-approval.

Product specification

The finished product is controlled by testing attributes relevant for this dosage form. The finished product specification includes tests for appearance, identity of the active (IR and HPLC), assay (HPLC), degradation products (HPLC), uniformity of dosage units, dissolution and microbial purity.

The proposed specifications were justified based on the batch and stability results and are generally adequate for assuring the product quality and therefore were accepted.

A detailed description for all analytical methods was provided. Full method validation data was provided for the non compendial (*in-house*) analytical methods.

Batch results are provided for 4 production scale batches and 15 pilot scale batches used in clinical studies, process development studies and primary stability studies. Batch analysis results demonstrated compliance with the proposed specifications and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed specifications.

Stability of the product

Stability studies have been initiated according to ICH guidelines on 3 pilot scale and 4 production scale batches of the finished product packaged in its commercial packaging. Data were provided from six months of accelerated conditions (40°C/75% RH), six months of intermediate conditions (30°C/75% RH) and 12 months of long term conditions (25°C/60% RH). No significant changes or trends in any of the parameters monitored have been seen and all data are within proposed specifications.

In addition force degradation studies have been included in the stability programme. The forced degradation study included testing the effects of thermal oxidation, thermal acidic, neutral and alkaline conditions and photolysis on the finished product.

The results of the forced degradation study show that in acidic medium, a similar extent of degradation is obtained for both active substance and finished product. Under neutral and in particular under basic conditions, however, the extent of degradation for the finished product is much lower than for the active substance. The same is observed under oxidative conditions (H_2O_2) where the product was found much less sensitive for oxidation than the substance. Under light conditions a photolytic degradation is observed but there is no significant difference in sensitivity between the finished product and the active substance. No additional forced degradation products were observed for the finished product in comparison with the active substance.

The overall stability data showed that SIRTURO tablets were stable under all tested conditions. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided about the active substance, bedaquiline, was of acceptable quality. In general sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described.

Specification limits and analytical methods are suitable to control the quality of the active substance.

A retest period was supported by satisfactory stability studies which show that the active substance is stable.

The finished product is an immediate release uncoated tablets containing 100 mg of bedaquiline. The development pharmaceutics has been satisfactorily described. The excipients are well

established and used in acceptable quantities. Their function has been satisfactorily described. The formulation is considered satisfactorily justified.

The method of manufacture is considered standard and has been satisfactorily described, including in-process tests. The data shows consistent manufacture and is considered sufficient for this manufacturing process. A satisfactory validation protocol has been provided.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance (bedaquiline) and the finished product (tablets 100 mg) have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that bedaquiline as well as the tablets can be reproducibly manufactured. Therefore the product should have a satisfactory and uniform performance.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamic studies

The applicant has conducted studies of bactericidal and sterilizing activity of bedaquiline in murine and guinea pig models of tuberculosis infection. In these animal models, bedaquiline showed bactericidal and sterilizing activity in TB infected mice and guinea pigs, alone and in combination with several DS and MDR-TB regimens. Bedaquiline showed selectivity towards ATP synthase in mycobacteria compared to ATP synthase from a human cancer cell line. In isolated human mitochondria, nano-molar concentrations of bedaquiline had no effect on ATP synthesis, while concentrations of 100 µM bedaquiline lead to approximately 30 % inhibition. The in vitro potency of the major metabolites M2 and M3 were about 5- and 187-fold less than that of bedaquiline, respectively.

Secondary pharmacodynamic studies

In a secondary pharmacodynamics study bedaquiline showed interaction with histamine-2 receptors (87%), sodium channel (71%) and dopamine transporters (54%) whereas low interaction potential was observed with any of the other receptors or transporter binding sites tested (including, but not limited to, adenosine, adrenergic, angiotensin, cholecystokinin, dopamine, endothelin, muscarinic, neurokinin, opioid, serotonin, vasopressin receptors or calcium, potassium, chloride channels or norepinephrine transporters). The potential clinical impact of the observed interaction with histamine2 receptors, sodium channels and dopamine transporters was discussed by CHMP. It was agreed that taken together studies both *in vitro* and *in vivo* indicated that bedaquiline had a potential to adversely affect the cardiovascular system both at the electrophysiological and the histological level and that any interference by bedaquiline with dopamine transporters appears unlikely to have any clinical relevance. At therapeutic doses, electrophysiological effects of sodium channel blockade and the interaction potential with histamine2 receptors, are expected to be limited with no functional consequences.

Safety pharmacology programme

The standard battery of cardiovascular safety studies showed a concentration- dependent inhibition of bedaquiline and M2 on the rapidly activating rectifying potassium current (IKr) from 0.03 µM to 3 µM with a 50% inhibitory concentration (IC50) of 0.37 µM (0.2 µg/mL) for bedaquiline and 0.45 µM (0.24 µg/mL) for M2. Inhibition of the slowly activating rectifying potassium current (IKs) was observed up to 32% for bedaquiline starting from 0.003 µM (0.002 µg/mL), and up to 37% for M2 starting from 0.3 µM (0.17 µg/mL). In these *in vitro* studies, analyses of the solutions revealed a low to very low recovery (51-0.5%) of locally applied bedaquiline concentrations. In conclusion, bedaquiline and M2 showed inhibitory effects on cardiac potassium currents in the hERG assay at low concentrations. The actual inhibitory concentrations could not be determined from these studies.

There were no relevant effects on the duration of the PQ and QRS interval of the ECG or on the ECG morphology in anesthetized guinea pigs, but the heart rate was increased and the duration of QT and QTc was decreased.

Bedaquiline had no effects on cardiovascular parameters at a single oral dose of 20 mg/kg (plasma conc. 1757 ng/ml) in a preliminary non-GLP study in telemetered dogs. In the pivotal study, at single oral doses up to 160 mg/kg, bedaquiline had no effects on blood pressure and heart rate. The electrocardiogram was unchanged at 10 mg/kg, but at 40 and 160 mg/kg a marginal shortening of the P-Q interval and a slight increase in P-wave duration was observed. Plasma levels at 6h were 0.8, 1.8 and 4.9 µg/ml, respectively. However, the results from these single dose studies may not be predictive for the potential cardiovascular effects in the clinical situation since the concentrations of bedaquiline and its metabolites build up over time after repeated administration due to the very long elimination half-lives. Cardiovascular parameters were also monitored in the repeated dose toxicity studies as well as in the clinical studies. The possible “multi-ion channel” blocking properties of bedaquiline and its metabolite M2 as indicated by the studies in isolated hearts and by the *in vivo* studies performed in guinea pigs and dogs have been discussed and while a proarrhythmic potential cannot be excluded at therapeutic doses, the agreed Sirturo Summary of the Product Characteristics (SmPC) provides adequate guidance to the prescribers on the issue.

Cardiovascular effects in combination with moxifloxacin (with known cardiovascular effects) were investigated in telemetered dogs. Following 6 days of bedaquiline administration, a slightly higher increase in QT and QTc intervals was observed following the combination administration of bedaquiline with moxifloxacin than in animals administered moxifloxacin alone. This could potentially indicate a cardiovascular effect of bedaquiline in combination with moxifloxacin.

Bedaquiline tested up to a maximum plasma concentration of 4.9 µg/mL in telemetered dogs showed no potential to affect the measured respiratory parameters and did not influence the locomotor activity.

Bedaquiline had no CNS effects in a modified Irving test in rats at doses up to 200 mg/kg (Cmax 3.3 µg/ml, AUC was 132 µg.h/mL). Dosing at 800 mg/kg led to slight behavioral effects as evidenced by an increased locomotor activity and aberrant motor-affective and sensori-motor responses. Overall, bedaquiline has a low potential for pulmonary or nervous system effects.

All in vitro safety pharmacology studies with bedaquiline and M2, and two of the in vivo studies were not conducted according to GLP standards. The applicant has adequately justified the lack of GLP compliance in the pivotal safety pharmacology studies. Furthermore, the actual concentrations of bedaquiline and M2 in several of the in vitro studies were significantly lower than intended. However, in most cases in vivo data are available that corroborate the in vitro results.

Pharmacodynamic drug interactions

In vitro interactions of bedaquiline with other anti-TB drugs have not been studied. Instead, a series of animal experiments were conducted where bedaquiline was administered with various combinations of anti-TB drugs.

In the murine model of established TB infection (treatment starts approximately 2 weeks after TB infection), bedaquiline (25 mg/kg) as monotherapy was at least as bactericidal as the first-line triple combination therapy (i.e., R + INH + PZA) and more active than R alone.

Furthermore, when added to the first-line triple combination therapy (R + INH + PZA) for DS-TB, bedaquiline at 25 mg/kg resulted in a greater decrease in bacterial load in the lungs (relative to the standard R + INH + PZA treatment regimen) by 2 log units after 1 month of therapy and by a further 1 log unit after 2 months of therapy ($p < 0.0018$ in both cases). When substituting one of the first-line drugs of the R + INH + PZA combination with bedaquiline (25 mg/kg), the activity of each regimen was significantly better than that of R + INH + PZA, particularly after 1 month of treatment ($p < 0.0018$).

Sterilizing activity of bedaquiline in combination with first-line anti-TB drugs

Swiss mice intravenously inoculated with *M. tuberculosis* strain H37Rv (established infection model), were treated with bedaquiline-containing regimens, and followed for 3 more months without treatment to determine relapse rates.

Quantitative lung and spleen CFU counts at the end of therapy and relapse rates 3 months after the end of therapy were compared for various regimens.

Table 1 *Positive* Culture status (Lung / Spleen) at the End of Treatment and 3 after, Swiss mice.

	At the End of Treatment	3 Months After the End of Treatment[a]

Regimen	Month 2	Month 3	Month 4	Month 6	Month 2 (+ 3)	Month 3 (+ 3)	Month 4 (+ 3)	Month 6 (+ 3)
2 (RHZ) + 4 (RH)	ND	ND	ND	0/10	ND	ND	ND	5/30 [b]
2 (RMZ) + 2 (RM)	ND	5/9	0/8	NA	ND	16/19	8/19	NA
2 (JR) + 2 (JR)	1/6	1/7	0/7	NA	10/18	5/18	2/15	NA
2 (JHZ) + 2 (JH)	0/9	0/9	0/8	NA	13/19	13/18	5/17	NA
2 (JRHZ) + 2 (JRH)	0/9	0/9	0/9	NA	12/18	7/20	1/17	NA

J = bedaquiline; M = MXF; R = rifampicin Z = PZA
ND = not done, NA = not applicable

Most mice became culture negative after just 2 or 3 months of treatment with bedaquiline containing regimens. The relapse rate was lower after 4 months of R + INH + PZA + bedaquiline compared to 4 months with a regimen that was so far described to be the most active in mice (R + MXF + PZA).

Bactericidal activity of bedaquiline in combination with second-line anti-TB drugs

Mice were infected drug sensitive H37Rv strain of *M. tuberculosis* (established infection model) and treated 5 times per week with bedaquiline alone or with bedaquiline combined with first-line anti-TB drugs (R-INH-PZA) or with various combinations of second-line anti-TB drugs. Bedaquiline accelerated the bactericidal activity of the drug regimens.

Table 2: Bactericidal activity of bedaquiline + second-line drugs in murine TB model

	Mean Log CFU Counts ± SD (mice with negative cultures/total)			
Regimens[a]	**Spleen 1 Month**	**Spleen 2 Months**	**Lungs 1 Month**	**Lungs 2 Months(**
Untreated	6.5 ± 0.2	-	5.9 ± 0.5	-
J	2.6 ± 1.3	1.2 ± 0.5 (0/8)	2.9 ± 0.9	0.2 ± 0.3 (6/8)
RHZ	4.5 ± 0.3	1.9 ± 0.5 (1/10)	3.7 ± 0.4	1.0 ± 0.5 (0/10)
RHZJ	1.9 ± 0.31	0.1 ± 0.2 (4/10)	1.8 ± 0.4	0 ± 0 (10/10)
AEMZ	3.2 ± 0.5	1.6 ± 0.4 (1/10)	2.9 ± 0.2	0.1 ± 0.1 (5/10)
AEZ	4.0 ± 0.3	2.8 ± 0.3 (0/10)	3.7 ± 0.2	1.2 ± 0.3 (0/10)
AMZ	3.6 ± 0.2	1.9 ± 0.5 (0/10)	3.4 ± 0.3	0.8 ± 0.6 (0/10)
AEZJ	1.2 ± 0.2	0.1 ± 0.1 (7/9)	0.2 ± 0.3	0 ± 0 (9/9)
AMZJ	1.2 ± 0.2	0 ± 0 (8/8)	0.2 ± 0.3	0 ± 0 (8/8)
AEMZJ	1.2 ± 0.3	0 ± 0 (8/8)	0.5 ± 0.4	0 ± 0 (8/8)

J = bedaquiline;[R=rifampicin; Z=PZA]=first line; [A=AMK; E=ETH; M=MXF]=second line

These observations in mice may suggest that bedaquiline-containing MDR-TB regimens could have the potential to significantly shorten treatment duration, similar to what was seen when bedaquiline was added to the first-line regimen R + INH + PZA.

Mice were given 12.5 and 25 mg/kg in these studies.

When comparing steady state exposures in mice dosed 20 mg/kg, and the exposure in patients dosed bedaquiline 200 mg t.i.w. (end of C208 stage 1), the mice/human ratios for bedaquiline AUC and Cmax were 0.3. Same ratios for M2 were around 4. MICs for M2 are around 4-6 times higher than for the parent compound.

In vivo synergy of bedaquiline with pyrazinamide

Further studies in mice indicate a synergistic effect with PZA:

Mice were infected and treated 2 weeks later with a daily treatment (5 days per week) for 2 months. R + INH + PZA did not lead to clearance of the lung. Bedaquiline monotherapy was able to convert 22% of the mouse cultures. When PZA was combined with bedaquiline, all mice were culture negative after 2 months of treatment, table next page.

In each treatment group, 10 mice were sacrificed after 1 month of treatment, and 10 were sacrificed after 2 months of treatment.

Table 3: Bacterial counts and proportion of mice with negative cultures in the lungs after treatment

Group[a]	Bacterial Count (Log_{10} CFU) (Mean ± SD)			Mice Culture Negative at 2 Months
	Day 0	1 Month	2 Months	
Untreated	7.2 ± 0.5			
bedaquiline		4.1 ± 1.8	2.3 ± 0.7	20%
PZA		6.2 ± 0.3	6.4 ± 0.9	0
bedaquiline + PZA		1.6 ± 1.6	0	100%
R + INH + PZA		3.9 ± 0.7	2.2 ± 0.6	0

Bedaquiline 25 mg/kg; R 10 mg/kg; INH 25 mg/kg; PZA 150 mg/kg

2.3.2. Pharmacokinetics

Bedaquiline is a poorly soluble drug substance that has low apparent permeability across Caco-2 cell monolayers but can be considered as a moderate to high permeability compound since it is well absorbed in preclinical species.

After single IV administration, bedaquiline displayed slow kinetics. In dogs, it was slowly eliminated from plasma with a clearance about 19-fold lower than the hepatic blood flow, and it was

extensively distributed to tissues with a volume of distribution about 60-fold higher than the total body water.

After a single PO administration in mice, rats, dogs and monkeys, maximum concentrations were observed between 0.5 h and 8 h after dosing with low doses, while absorption was slower at higher doses. The plasma concentration-time profiles of bedaquiline showed a multi-phasic decline with a long terminal elimination t1/2 ranging from 2 to 3 days in mice, 3 to 5 days in male rats, 6 to 9 days in female rats and monkeys and up to 50 days in dogs. In dogs, there was evidence that steady-state was reached at Week 13 in most cases. The exposure to bedaquiline and M2 (Cmax and AUC0-24h) increased dose proportionally or less than dose proportionally in mice, rats and dogs.

The bioavailability after a single bedaquiline dose was 36%, 40% and 79% in the dog, monkey and rat, respectively. After a single dose the mean AUC0-24h of the major metabolite M2 was 2 to 7-fold higher than AUC0-24h of bedaquiline in mice and was generally similar to 2-fold lower in rats and dogs.

The total radioactivity was widely distributed to the tissues in pigmented rats and monkeys after single PO administration of 14C-bedaquiline. High tissue concentrations (AUC-T/B or AUC-T/P ratios generally between 20 and 100) were associated with the adrenal gland, lung, spleen and liver. The decline of the concentrations of TR in most tissues and plasma was parallel, indicating that there was no undue retention. Brain tissue uptake was low compared to other tissues, with AUC-T/B or AUC-T/P ratios generally below or close to 1. In pregnant rats, distribution to the placenta and the foetus was moderate to low, AUC values for the placenta and the foetus being 3-fold and 0.4-fold the AUC value for the maternal blood, respectively. Following repeated PO administration of bedaquiline to mice, rats and dogs, the bedaquiline trough concentration T/P ratios were above 30 in lung, spleen, lymph nodes and thymus. The tissue concentrations of M2 were generally higher than those of bedaquiline.

Bedaquiline and M2 were extensively bound to plasma proteins (99.9%) in mice, rats, dogs, monkeys, rabbits and humans. Distribution of the two compounds to blood cells appeared to be limited.

No chiral conversion of bedaquiline occurred in vivo after administration of bedaquiline to mice, rats, dogs, monkeys and humans. In hepatocytes and subcellular fractions from preclinical species and humans, the in vitro metabolism of ^{14}C-bedaquiline was via Phase I reactions and the most important pathway was N-demethylation to M2, which was followed by a second N-demethylation to M3, oxidation and epoxidation. M2 was the major circulating metabolite in all preclinical species as determined by radioactivity profiling and LC-MS/MS in the animals. No mass balance study with radiolabelled bedaquiline has been conducted in humans. It can therefore not be excluded that additional undetected metabolites may be formed in humans that are not formed in the animal species. M2-AUC_{0-24h} plasma levels were generally comparable to 2-fold lower than those of bedaquiline in rats and dogs upon repeated administration of bedaquiline, and 3.5- to 4.5-fold lower in human subjects with MDR-TB. In addition to M2 and M3, a hydroxylated derivative of M2 (M20) and a dihydrodiol derivative of M2 (M11), were detected in human plasma. These two metabolites were also found in rats and dogs at similar relative concentrations.

In all preclinical species, the drug related material was slowly excreted, predominantly in faeces.

The milk concentrations of bedaquiline and M2 were 4 to 12-fold higher than the corresponding plasma concentrations in milk samples collected from lactating dams in a pre- and post-natal development study in Sprague-Dawley rats.

In conclusion, the absorption, distribution, metabolism and excretion of bedaquiline in animals have been adequately investigated. The relevance of the animal species for safety testing is limited by the lack of adequate data on mass balance in humans.

2.3.3. Toxicology

The toxicological profile of bedaquiline was characterised in studies in mouse, rat and dog. In pivotal studies, rats were treated for 26 weeks and dog for 39 weeks followed by a 12-13 week treatment-free period to evaluate reversibility of the effects. Mice were generally a less appropriate species to use, due to their low tolerance to bedaquiline and to the high formation of M2. Maximum doses used were around 25 mg/kg in rat and 40/20 mg/kg in dog. Studies included exposure determinations of parent compound as well as major metabolites M2 and M3. In addition specific studies were conducted to address local tolerance, mechanistic aspects, metabolite toxicity, impurities and immunotoxicity. Overall the non-clinical characterisation of toxicological aspects of bedaquiline and metabolites is considered adequate and in line with relevant guidelines and where appropriate conducted in accordance with GLP principles, but some uncertainties as to the species used in the toxicological evaluations in terms of the level of predictivity persist in the absence of human mass balance data.

Single dose toxicity

In mouse and rat, single oral doses of 800 mg/kg produced lethality preceded by signs of general toxicity. Mortalities in mouse and dog after single and repeated doses were principally attributed to skeletal muscle/myocardial degeneration and/or pancreatitis.

Repeat dose toxicity

Bedaquiline and the M2 metabolite are cationic amphiphilic substances (CADs) and induce phospholipidosis. The cells of the monocytic phagocytic system (MPS) are affected in all species. Data from in vitro studies using human monocyte cell-line indicated that the phospholipidogenic potential was highest for the M2 metabolite followed by M3 and the parent compound. Several mechanisms for phospholipidosis have been suggested and different inducing agents may interact with different putative phospholipidosis-relevant targets. Although frequently described as an adaptive response tissue damage has been observed in association with phospholipidosis and the clinical significance of such findings are still largely unknown.

Safety pharmacology studies *in vitro* showed that bedaquiline had the potential to inhibit Ikr and Iks and while no ECG abnormalities or prominent QT effects were recorded in short term dog studies QT prolongation was evident in a 2/6 month toxicity study in dog at 40/20mg/kg, but not in the 39 week study at a dose of 18 mg/kg. Monitoring in clinical trials has also showed that QT effects may occur with treatment with bedaquiline and sections of the SmPC provide information and recommendations on these aspects.

In addition findings of myocardial degeneration/necrosis/fibrosis were reported in toxicity studies in dog. The possibility that this may relate to the primary pharmacological mode of action (inhibition of ATP synthase) would also be consistent with reports of pancreatitis in dog. Taken together the available data, including electron micrographs of various tissues do not, however, indicate any relevant potential for mitochondrial toxicity of bedaquiline.

In *in vivo* repeat dose toxicity studies phospholipidosis or phospholipidosis-like changes (e.g. microvacuolation, foamy macrophages, histiocytosis, swollen macrophages, histiocytic infiltrates) were reported in liver (rat, dog), skeletal muscle (rat), lung (mouse, rat, dog), spleen (dog), kidney (mouse), pancreas (mouse) and thymus (dog). In general the doses at which phospholipidosis was evident corresponded to exposure ratios from <1, x2-x5 to x2-x9 (dog) the expected clinical value. Partial recovery was evident although changes were still present after up to a 12 week treatment free period. Considering phospholipidosis like changes in skeletal/striated muscle and changes in serum chemistry parameters such as increases in CK and ALP this could be interpreted as indicative of a possible relation between induction of phospholipidosis and functional impairment. The mechanism behind myopathy is, though, proposed to be related to interference with membrane function and not per se to phospholipidosis.

The principal organs affected in most mouse studies were liver and skeletal muscle at exposure ratios to clinical levels of <1 for bedaquiline and x8 (males)-x5 (females) for the M2 metabolite. No relevant NOAELs in mouse studies were evident. The main target organs in rat were liver, skeletal muscle, lung, thyroid and kidney in longer term studies. Doses coupled to these changes provided exposure ratios relative to expected human of approx. <1 (males)-approx. x2 (females) for bedaquiline and x3-6 for the M2 metabolite. In dog, organs/tissues with findings included lung, heart, stomach, and pancreas at doses of 40/20 mg/kg corresponding to exposure ratios of x3-5 for bedaquiline and x6-10 for the M2 metabolite. At the NOAEL AUC ratios to expected clinical levels were <x1 for bedaquiline and approx. x2 for the M2 metabolite.

In most repeated dose toxicity studies body weight and/or body weight gains were decreased with treatment with bedaquiline.

Overall a range of organs/tissues showed various histopathological alterations after treatment with bedaquiline:

- Liver: mouse, rat, dog-phospholipidosis, hypertrophy, necrosis, degeneration bile duct epithelium (dog). Hypertrophy showed reversibility after a 3 month treatment free period. The lowest doses associated with liver changes corresponded to exposure multiples lower or approx. 1 compared with expected human values, except in dog were ratios of 5 to 6 were calculated. Occasionally liver changes were coupled to increases in liver enzymes such as AST and ALP.
- Pancreas: mouse, dog-phospholipidosis, necrotic cells, inflammation. In mouse, but not in dog, minor effects on amylase and lipase were recorded. The lowest doses associated with pancreatic changes corresponded to exposure multiples lower than 1 in mouse and <1 to 3 in dog compared with expected human values. Recovery during a 13 week treatment free period appeared incomplete.
- Stomach: mouse, dog. Degenerative changes (fundic glands), necrosis. At high doses in dogs, inflammatory infiltrates and signs of phospholipidosis were evident. Stomach lesions

showed incomplete reversibility after a treatment free period. The lowest doses associated with stomach lesions corresponded to exposure multiples lower than 1 in mouse and 1 to 5 in dog compared with expected human values.

- Striated muscle: mouse, rat, dog. Tongue: degenerative, necrotic changes, muscle fibre degeneration, histiocytosis (mouse, rat, dog); quadriceps, psoas muscle; myopathy, muscle cell degeneration, fibriohistiocytic infiltrates (rat, dog). Heart: degeneration of cardiomyocytes, fibrosis, necrosis (dog). In the 2/6 month dog study where doses were lowered from 40 to 20 mg/kg after 2 months QT/QTc interval, total CK, cTnI and myoglobin were increased in relation to sings of cardiac degeneration/necrosis. Doses corresponded to multiples of 5-6 the expected human exposure. Following treatment free periods there were signs of recovery.
- Thyroid: rat-hypertrophy follicular epithelium. Full recovery of this change was observed. In separate studies it was shown that thyroxine uridine diphosphate glucuronyltransferase (UDP-GT) was induced by bedaquiline and the change was considered to result from liver enzyme induction ultimately leading to stimulation of the thyroid. The clinical relevance of the findings seems low taking into account that changes were only noted in rat, a species that is more responsive to hormonal imbalances than human. In addition reversibility was evident.
- Genital tract: mouse, dog-granulocytic infiltrates, necrosis of corpora lutea. In addition tubular atrophy was noted in testes in dog at doses starting from 10 mg/kg, corresponding to exposure multiples of 2 to 3 compared with human exposure.
- Spleen: mouse-red pulp hyperplasia (mouse)
- Eye: dog-conjunctivitis, corneal opacities, intolerance to bright light at high doses. Tissue distribution studies in rat showed high distribution of radioactivity to the uveal tract.
- Kidney: rat-basophilia/nephropathy. Changes in calcium (increases) and phosphate (decreases) levels appeared related to this finding that was only seen in rat and may have reflected an exacerbation of existing susceptibility to kidney effects.

Haematology data showed decreases in haemoglobin, haematocrit and increases in reticulocytes primarily in mouse and rat. Clinical chemistry indicated increases in creatinine kinase and AST in mouse, increases in cholesterol, BUN, glucose, CK and decreases in lymphocytes and inorganic phosphate in rat. In dog ALT, AST, ALT, thrombocytes and fibrinogen as well as cTnI and myoglobin were increased.

There were no major differences in target organ toxicity between juvenile and adult rats and no additional toxicity was identified in the juvenile rat. However, in the juvenile rat an observation of males with small flaccid testes/small epididymides was recorded but likely was not treatment related.

Genotoxicity

Bedaquiline tested negative for genotoxic potential in standard *in vitro* and *in vivo* tests including *Salmonella typhimurium*, mouse lymphoma and mouse micronucleus test.

Carcinogenicity

Long term carcinogenicity studies in Sprague-Dawley rats are ongoing. It was clarified that the report writing of the carcinogenicity study in the rat (bedaquiline-NC112) is ongoing and will be submitted when completed. Due to poor tolerability of bedaquiline in mouse, likely reflecting high formation of the more cytotoxic M2 metabolite and resulting in low exposure levels to parent compound relative to expected humans, a carcinogenicity study in mouse is not being conducted. CHMP concurred with this approach.

Reproduction Toxicity

The potential for reproduction toxicity was investigated in rat and rabbit in studies covering all stages of the reproductive process. Bedaquiline had no effect on fertility in females up to the highest dose tested, 24 mg/kg. Male fertility appeared to be decreased with a NOAEL of 5 mg/kg. Relevant information is included in the Sirturo SmPC section 5.3.

In addition in a 6-week dog study phospholipidosis like changes in testes were recorded, but the relevance of this finding for fertility seems to be of minor significance. The testicular Sertoli cells which are part of the MPS are known to be susceptible to phospholipidosis.

In embryofoetal toxicity studies conducted in rat and rabbit bedaquiline appeared to have no adverse effects on the embryonal development and the incidence of variations and malformations in foetuses in bedaquiline groups were within normal ranges. Exposure to bedaquiline and the M2 metabolite in rat at the high dose was considerable (up to 6-7 times higher compared with expected human exposure), while in rabbit a maximum exposure ratio of 2 were achieved. However, in rabbit the high dose of 100 mg/kg caused deaths, one abortion and increases in pre and postimplantation losses.

A pre and postnatal development study in rat was conducted with treatment from gestation day 6 through lactation day 6. Pups of F1 generation were exposed via maternal milk and exhibited higher exposures to bedaquiline than dams while exposure to the M2 metabolite was slightly lower. Pups from treated females had lower body weights and lower body weight gains and this was ascertained to relate to exposure via maternal milk. Assessment of functional and behaviour capabilities, sexual maturity and reproductive capacity indicated no adverse effects of pre postnatal exposure to bedaquiline and its metabolites.

Toxicokinetic data

Local Tolerance

Other toxicity studies

Bedaquiline tested positive for phototoxicity in an *in vitro* 3T3 neutral red uptake test. However, after single doses up to 100 mg/kg (AUC approx. x3 expected clinical) in pigmented rat no skin or ocular reactions were recorded that could be coupled to phototoxicity. Considering the pharmacokinetics of bedaquiline it was discussed whether a negative result in a single dose study in

rat was sufficient to conclude on a negative phototoxic potential, as in addition the actual concentrations of bedaquiline and M2 in several other in vitro studies were much lower than intended confounding interpretation of data. Clinical data do however, not indicate any phototoxicity to date.

Bedaquiline did not appear to have any ocular irritant effects and was a non-sensitiser in a mouse study. Several rat studies specifically addressed aspects of immunotoxicity and while neither lymphocyte subsets nor T-cell dependent antibody response were affected by up to 4 weeks treatment with 60 mg/kg the substance seemed to mediate a higher susceptibility for infection in a host resistance assay with *Listeria monocytogenes*. The potential immunomodulatory effect of bedaquiline has been discussed and the data overall do not indicate an adverse impact on the functionality of macrophages resulting in immune suppression at clinically relevant exposures.

A dedicated M2 short term toxicity study in mouse was consistent with that the metabolite had a higher potential for toxicity than the parent compound. Furthermore, *in vitro* cytotoxicity studies in primary hepatocytes showed a higher cytotoxicity of bedaquiline in mouse and rat compared with dog and human and the M2 metabolite was more toxic in hepatocytes from all species. This pattern also corresponded to a higher *in vitro* phospholipidogenic potential of M2.

While overall no clear effect of frequency of dosing on toxicological responses was recorded in rat studies a dose of 100 mg/kg per week tended to cause less severe effects than the same dose administered twice a week in divided doses. Considering specifically liver changes, effects appeared related to total dose over one week rather than frequency of dosing. In dog twice weekly doses of 140 mg/kg seemed better tolerated than a daily dose of 40/20 mg/kg.

2.3.4. Ecotoxicity / environmental risk assessment

Table 4: Summary of main study results

Substance (INN / Invented Name): Bedaquiline / SIRTURO (bedaquiline, R403323)			
CAS-number (if available): 845533-86-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential bedaquiline-TIDP13-NC218 GLP	OECD107	log D_{ow} 2.93 at pH=3	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default Fpen = 0.01 Refined F_{pen} based on sales forecast 2018 (MDR TB patient pool) = 6.4 x 10^{-7}	2 0.00013	µg/L µg/L	> 0.01 threshold: Yes > 0.01 threshold: No
Other concerns (e.g. chemical class)	Antimicrobial effect		Yes
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 with deviations due to low solubility of the test substance in 0.01M	$K_{oc,ads}$ =40428-370745	Soils I: 60709 II: 40428

bedaquiline-TiDP13-NC210 GLP	$CaCl_2$. Obtained values were considered as distribution parameters. Soil/sludge:solution=1/100 14C-bedaquiline 0.15 ng/ml 3 types of soils, 2 types of sludge				III; 370745 Sludge I: 75244 II: 81448 Based on $K_{oc, ads}$ values, **high adsorption to sludge and soil expected.**
Ready Biodegradability Test bedaquiline-TiDP13-NC219 GLP	OECD 301F	Test concentration: 101 mg/L bedaquiline was not biodegradable under the 28 day test conditions.			**Not readily biodegradable. Together with results from OECD106 this triggers terrestrial risk assessment.**
Aerobic and Anaerobic Transformation in Aquatic Sediment systems bedaquiline-TiDP13-NC211 GLP	OECD 308 Two water-sediment system over a period of 100 days	14C-bedaquiline **$DT_{50, water}$** =2.3-2.7 days **$DT_{50, sediment}$**: 64.3-75.1% in sediments at 100 days **$DT_{50, whole\ system}$** =163-257 days % shifting to sediment = 75.3-91.7%			Only minor amounts of metabolites detected in water and sediment. Levels of radioactivity in water <1% after 100 days. bedaquiline rapidly dissipated from the water phase into sediment. Once in the sediment it was slowly degraded and formation of bound residues was observed. **This triggers a sediment toxicity test.**
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata* bedaquiline-TiDP13-NC214	OECD 201	NOEC	≥ 0.77	µg/L	72 h static test Nominal test concentrations: Up to 10 µg/L. Highest nominal bedaquiline concentration tested resulted in precipitation and actual conc. was measured to 0.77 µg/L
Daphnia sp. Reproduction Test/ *Daphnia magna* bedaquiline-TiDP13-NC215 GLP status unknown	OECD 211	NOEC	≥ 4.7	µg/L	21 days Nominal test concentrations: Up to 10 µg/L. The highest test conc. was above the solubility of the test item and corresponded to an actual conc. of 4.7 µg/L
Fish, Early Life	OECD 210	NOEC	≥ 4.1	µg/L	Nominal test

Stage Toxicity Test/*Brachydanio rerio (Zebra fish)* bedaquiline-TiDP13-NC216 GLP			Egg development, Time to hatch/ develop. rate, survival, length, weight.		concentrations: Up to 10 µg/L. The highest test conc. was above the solubility of the test item and corresponded to an actual conc. of 4.1 µg/L
Activated Sludge, Respiration Inhibition Test bedaquiline-TiDP13-NC213 GLP	OECD 209	EC_{10} EC_{50}	≥ 1000 Could not be calculated, but > 1000 mg/L	mg/L	Test concentration: up to 1000 mg/L. At 1000 mg/L test item was not completely dissolved in the test medium. Actual conc. not determined. 3 h test period
Phase IIb Studies					
Bioaccumulation *Onchorhynchus Mykiss* bedaquiline-TiDP13-NC217 GLP	OECD 305	BCF	**0.17 µg/L** BCF_{fitted}=2717 DT_{50}:7.23 d **0.59 µg/L** BCF_{fitted}=3885 DT_{50}: 6.14 d BCF_{lipid}: 8850-19147	L/kg	28 days exposure (steady state not reached), 28 days depuration Since steady state was not reached, calculation and data fitting from measured values was performed. For both dose levels, mainly unchanged bedaquiline was detected in all samples. TGD B criterion: BCF > 2000 **bedaquiline bioaccumulates in rainbow trout**
Aerobic transformation in soil bedaquiline-TiDP13-NC224 GLP	OECD 307	DT50 $\%CO_2$	Soil I: > 1 year Soil II: > 1 year Soil III: 344 days Soil I: 1.0 Soil II: 1.2 Soil III: 2.8		3 soils 0.7 mg bedaquiline/kg dry soil, incubated up to 120 days. Complete recovery in all 3 soils. Several metabolites detected in soil samples.
Soil Micro organisms: Nitrogen Transformation Test bedaquiline-TiDP13-NC220 GLP	OECD 216		After 28 days nitrate formation in treated soil deviated by < 10% from the control.		28 day exposure. Test concentration: Up to 100 mg bedaquiline /kg dry soil.
Terrestrial Plants,	OECD 208	NOAEC	1000	mg/kg	Each plant species

Growth Test/ Cabbage, mung bean, sugar beet, tomato, ryegrass, wheat. bedaquiline-TiDP13-NC221 GLP		Germination, survival, height, dry weight measured. No obvious adverse effects.			was sown into treated soil and monitored for 15-16 days, following a minimum of 50% germination in the control. 1000 mg bedaquiline/kg dry soil
Earthworm, Acute Toxicity Tests/ *Eisenia fetida* bedaquiline-TiDP13-NC222 GLP	OECD 207	NOEC	≥ 1000	mg/kg	14 day test 1000 mg bedaquiline/kg dry soil.
Collembola, Reproduction Test bedaquiline-TiDP13-NC223 GLP	ISO 11267	NOEC LOEC	250 500	mg/kg	4 weeks Test concentration: up to 1000 mg/kg dry soil.
Sediment dwelling organism	Not performed	NOEC		mg/kg	**Significant shift to sediment and slow degradation shown in a test according to OECD 308.**

Based on the data available the substance was considered as persistent, bioaccumulative and toxic.

Table 5 : PBT-assessment of BDQ

	PBT-criteria	**Results for BDQ**
Persistence	Half-life in freshwater: DT50 > 40 days Half-life in sediment: DT50 > 120 days	DT50,river = 2.7 days DT50,system = 257 days
Bioaccumulation	BCF > 2000	BCF = 1433 (low dose) and 2049 (high dose)
Toxicity	Chronic NOEC < 10 µg/L	NOECalgae = 0.77 µg/L NOECfish = 4.1 µg/L

As the substance meets the PBT criteria as specified in the REACH regulation no safe level can be established and therefore no standard risk assessment based on comparison of PEC/PNEC is applicable. Adequate wording was included in the SIRTURO SmPC.

2.3.5. Discussion on non-clinical aspects

The conducted studies provide a comprehensive characterisation of the potential for toxic manifestations of bedaquiline and its major metabolite M2. However, in the absence of human mass balance data there are uncertainties as to the species used in toxicological evaluations in terms of

their level of predictivity. Both are medium to strong inducers of phospholipidosis in preclinical species at exposure levels not much in excess of expected clinical. The relation of phospholipidosis, toxicity and impairment of organ function is not clear, but data in preclinical species are consistent with bedaquiline being involved in all three events at the cellular level. The apparent very high potential to accumulate in tissues/organs may also be a confounding factor when considering long term effects. Since the M2 metabolite appears more potent, both in terms of toxicity and phospholipidosis, but is formed to a lesser extent in humans it may be that clinical concern is also lower, however, the toxicity of bedaquiline is to be considered in the overall assessment of benefit/risk. Many of the potential toxic effects identified in non-clinical studies are also possible to monitor clinically.

Assessment of paediatric data on non-clinical aspects

As there were no major differences in target organ toxicity between juvenile and adult rats and no additional toxicity was identified in the juvenile rat study, the CHMP considered that these results do not point towards specific risks in the paediatric population.

2.3.6. Conclusion on the non-clinical aspects

Overall the results from the non-clinical studies that deal with the general toxicity including mechanistic aspects, as well as toxicity to reproduction, genotoxicity, phototoxicity, toxicity of impurities are adequate and sufficient in scope and extent to support a positive benefit risk profile.

2.4. Clinical aspects

2.4.1. GCP

The CHMP has asked for a routine inspection to be carried out of the conduct of the clinical study bedaquiline-C208 on 3 study sites (2 in Peru and 1 in South Africa), in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and article 15 of Directive 2001/20/EC. Based on the quality identified during these three clinical sites inspections, it is likely that the deviations and findings identified during the inspections did not in any major sense influence or change the results as they were presented in the study report. It was therefore recommended that the study report can be used for evaluation and assessment of the application.

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 6: Tabular overview of clinical studies

Study ID	Belgium	Brazil	China	Estonia	Germany	India	Latvia	Lithuania	Peru	Philippines	Russia	South Africa	South Korea	Thailand	The Netherlands	Turkey	UK	Ukraine	USA
CDE101																	x		
CDE102																	x		
BAC1003																	x		
C104																	x		
C108															x				
C109	x																		
C110																			x
C111																			x
C112					x														
C117												x							
TBC1003																			x
C202												x							
C208 stage I												x							
C208 stage II		x				x	x		x	x	x	x		x					
C209			x	x			x		x	x	x	x	x	x		x		x	
TBC3001								x			x								

2.4.2. Pharmacokinetics

Absorption

The solubility of bedaquiline is low at physiological pH and according to the pKa, the molecule is positively charged. The solubility is increased, but still low, at acidic pHs.

The partitioning between 1-octanol and aqueous buffered solutions at different pH showed high lipophilicity. Bedaquiline had a low permeability in Caco-2 cells. In contrast, the bioavailability was 73%, 79%, 36% and 40% in mouse, rat, dog and monkey. The bioavailability of bedaquiline in man is unknown. The absorption is quite slow with a median tmax of 4 to 6 hours. At clinically relevant doses the absorption of bedaquiline appears linear following administration of an oral solution. However the solution contains solubility enhancers. In several clinical trials, a second peak is observed in the plasma concentration-time profile of bedaquiline either due to bile salts aiding solubility and thereby absorption, or due to enterohepatic recirculation.

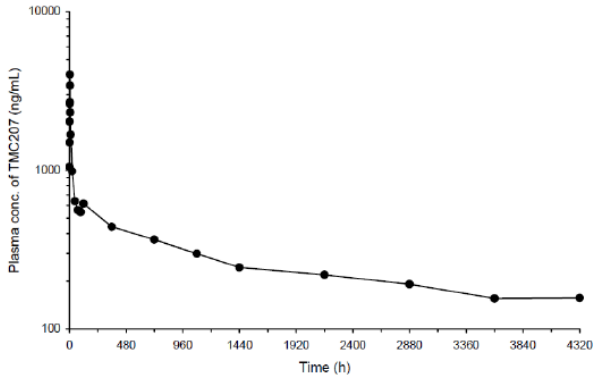
In vitro Caco-2 cell data indicate no Pgp involvement in the intestine. The concentrations were too high for “systemic” Pgp involvement to be excluded (risk of saturation).

The intended marketing formulation was used in the pivotal phase III studies. However, an oral solution has also been used in interaction studies. The exposure obtained with a 100 mg dose as solution and as the marketing formulation is similar during fed conditions. Administration of 100 mg bedaquiline as the marketing formulation under fed conditions (a breakfast but not the standardised high-fat breakfast) resulted in a higher mean Cmax and AUClast with LS mean ratios (fed/fasted) of 2.6 and 1.9, respectively. Surprisingly, metabolite M2, which has been associated to safety findings in preclinical species, had only a negligible increase in exposure. In another food interaction study with the same type of breakfast, the LS mean ratios of bedaquiline were 3.8 and 2.4, respectively. The effect of food on the absorption from an oral solution was much less pronounced (AUC increased 27%). This may be due to the additions of solubility enhancers in the solution but also to a different breakfast being served in this study. The effect of a high-fat breakfast has not been studied. However bedaquiline has been taken with food in the clinical phase II studies and although a high-fat study would have been valuable to estimate the worst-case food effect, this is not considered necessary. The phase II food intake is probably very variable and the impact of a single meal low with the quite long half-life. Bedaquiline is intended to be taken together with food.

Distribution and protein binding

The disposition of bedaquiline has 4 phases. Bedaquiline and an active metabolite M2 have a long terminal half-life, ~5.5 months in patients. The long terminal half-life corresponds to distribution from a deep department (tissues).

Figure 1 Mean plasma concentration-time profile for bedaquiline after last dose of a 400 mg qd regimen for 15 days



The long half-life can be explained by the cationic amphiphilic characteristics of the compounds causing accumulation in various tissues. Bedaquiline is 99.9% protein bound and M2 also showed a similar binding in a separate study. The blood-to-plasma ratio of M2 was on average 1.0. No ratio

has been found for bedaquiline. M2 has low permeability and may be a Pgp substrate. The efflux ratio in Caco-2 cells was up to 3.

- Peripheral blood monocytes

The kinetics in monocytes followed that in plasma. Slightly higher accumulation was observed in monocytes (1.88 - 3.28, vs. plasma, 1.90 - 2.44) but despite this difference in accumulation the half-life was similar.

- Sputum

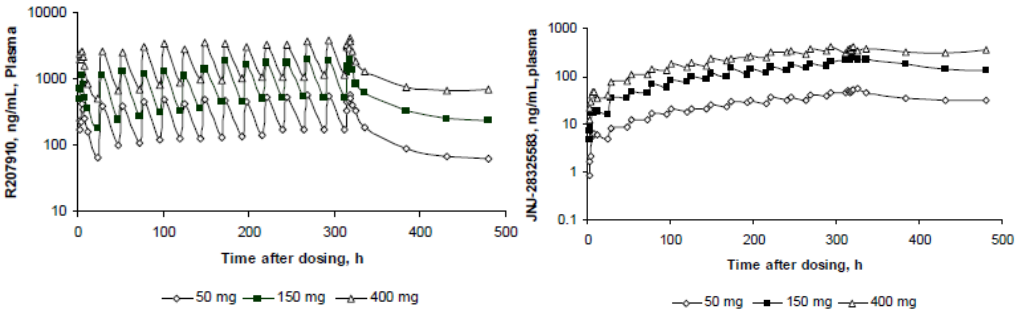
After 7 days of bedaquiline treatment, the mean sputum-to-plasma concentration (Css,avg) ratios of bedaquiline varied between 0.64 and 1.22 for the different doses investigated (25 mg, 100 mg, 400 mg). For M2 the corresponding Css,avg ratios varied between 2.13 and 3.03. The mean bedaquiline-to-M2 ratio in sputum, after administration of the 400 mg dose was 0.58. In one study, the mean sputum concentration of M2 was approximately 2-3 fold higher than that of bedaquiline during the first two weeks of bedaquiline treatment. This difference in concentration between parent and metabolite concentration seems to level out upon continued administration of bedaquiline.

Taken together, it may be concluded that the metabolite-to-parent ratio in plasma differs from the one estimated for sputum. This could suggest that plasma is not reflecting the metabolite pattern of bedaquiline in target tissue. However, based on plasma exposure M2 is unlikely to contribute significantly to efficacy. M2 has been associated with safety issues in the preclinical species. The applicant needs to clarify elimination of M2 post authorisation through further in vitro studies as outlined further below.

Elimination

Based upon plasma concentration measurements taken during a 2-year washout period after the last dose of bedaquiline in trial C208, the mean terminal t1/2 was 5.5 months for bedaquiline and 5.3 months for M2. In healthy volunteers, a half-life of ca 30 hours was detected after a 400 mg single-dose. The effective half-life of bedaquiline is much shorter based on the accumulation ratio at 14 days of dosing and also time to steady state. Steady state of bedaquiline was reasonably reached already after 1 week. In contrast, M2 reaches steady state after ca. 14 days. The accumulation ratio of bedaquiline and M2 is 1.9 and 10.4, respectively, indicating a longer effective half-life of M2 than of bedaquiline.

Figure 2: Mean plasma concentration-time profiles of bedaquiline (left) and M2 (right) with once daily dosing of bedaquiline for 14 days.



No mass-balance study has been performed with bedaquiline. The applicant argues that due to the long half-life, performing a mass-balance study is unethical. Mass-balance studies have been performed in preclinical species including monkey. The elimination in man has been poorly characterised. There are some data obtained with cold (unlabelled) drug but little data supporting main elimination pathways is provided. The *in vitro* metabolism studies were not investigating metabolite formation and thus, the data may not be coupled to the *in vivo* data available. Due to the lack of radiolabelled mass-balance data, the evaluation of whether the species have been exposed to "major metabolites" in plasma may not be performed. Furthermore, and importantly, the major elimination pathways of elimination as well as M2 formation and elimination are difficult to characterise. Safety is unknown at increased exposure and DDIs giving rise to increased exposure may not be predicted.

Bedaquiline may be eliminated through metabolism and may also be subject to biliary excretion. Renal clearance appeared to be an insignificant route of elimination.

Metabolite profiling of faeces extracts was performed in patients after 400 mg qd bedaquiline for one week. Faeces were collected for 24 h post-dose and could thus contain material from several previous doses. A longer collection of faeces post-dosing would have been valuable as well as a single dose design. Bedaquiline represented 75%-85% of drug related material found in faeces. A large part of this may be unabsorbed drug. However, major biliary excretion may not be excluded and was observed in preclinical animals. Metabolites, including M2, were excreted in small amounts. The metabolism of bedaquiline has been studied *in vitro* but without mass-balance data, the *in vivo* relevance of the *in vitro* enzyme contribution cannot be assessed. CYP3A4 seem to catalyse M2 formation. The CYP3A4 involvement is supported by in vivo DDI data but the contribution may not be quantified in these studies. There seems to be no data on M2 elimination, besides some contribution of biliary excretion. Pgp, BCRP or other transporters may be involved in such an excretion. The applicant is also proposing M2 elimination through metabolism. Involved enzyme is unknown.

The lack of data supporting model of elimination, in combination with the limited safety data on supra-therapeutic exposures is included in the risk-benefit analysis.

No inter-conversion of bedaquiline into either the RR or the SS enantiomer was observed *in vivo*.

Available data on metabolite exposure: There is no complete information on metabolite exposure as there is no mass-balance data. Thus, it may not be excluded based on human exposure that there are metabolites that should have been characterised preclinically. Plasma samples obtained after 400 mg bedaquiline qd for 10 days were analysed for metabolites. Samples collected at 0-12 h were

pooled per individual. Four metabolites were identified: an N-desmethyl metabolite (M2), an N-didesmethyl metabolite (M3), an oxidated N-desmethyl metabolite and a dihydrodiol of the N-desmethyl metabolite. The latter two metabolites were only detected in minor amounts in three out of six individuals.

Dose proportionality and time dependencies

The exposure of bedaquiline as single dose conditions after administration of the oral solution (10-700 mg) is dose proportional and thus the elimination appears independent of dose. The data on metabolite M2 is more difficult to interpret. The Cmax of metabolite M2 seems dose proportional but the data does not allow any conclusions regarding AUC. The data available does not allow an evaluation on whether there is any time dependency in the pharmacokinetics of bedaquiline. The accumulation ratio of bedaquiline and M2 is 2 and 11, respectively. Steady state (or almost steady state concentrations) of bedaquiline is reached in ca 1 week. This would mean that the effective half-life is ca. 2 days in contrast to the terminal half-life which is ca. 5 months. The effective half-life is 24 hours based on the accumulation ratio (2).

Variability

The inter-individual variability was low to moderate. In DS-TB infected patients, CV of Cmin, Cmax, and AUC24h ranged from 30% to 49%. The inter-individual variability of M2 was approximately in the same range. In the population pharmacokinetic analysis, inter-individual variability was estimated to similar values.

Target and Special populations

- Target population:

A population PK (PPK) analysis was conducted by the use of nonlinear mixed effects modelling in NONMEM. The analysis included data from trials in healthy subjects (C102, C104, C109, C110, C111, TBC1003) as well as trials in DS-TB (C202) and in MDR-TB infected subjects (C208 (Stages 1 and 2, C209). A total of 480 (5222 observations) patients (369) or healthy subjects (111) were included.

The final base model included a dual zero order input and a 4-compartment disposition model. Relative bioavailability (F) was dependent on study. A higher F (2.03) was estimated in the studies with healthy volunteers compared with the studies conducted in MRD-TB patients. Exploratory analyses did not demonstrate any changes in bioavailability over time. The final covariate model included Black race and subject status (patients vs. healthy volunteer) as covariates on CL/F and sex on V_c/F. Healthy subjects and DS-TB infected subjects had a 37.5% higher CL/F than MDR-TB patients. Taking into account the higher F, the CL/F for healthy subjects and DS-TB infected subjects was 68% (1.375/2.03) of the CL/F for the MDR-TB infected subjects. Similarly, black subjects had a CL/F that was 52.0% higher than non-Black subjects, equating to a 34% lower exposure in Black subjects. Females were identified to have a Vc/F that was 15.7% lower than males. The small effect of gender was considered as not being clinical relevant. Also the effect of Black race was considered as not being clinical relevant given the demonstrated efficacy in Black subjects.

- Renal impairment

No conventional study has been performed investigating the effect of renal impairment. Renal elimination of unchanged drug is negligible. The effect of impaired renal function was explored in the population PK analysis using creatinine clearance as a surrogate. Within the limited range of CRCL values (39.8-227 ml/min) in the included population no statistical significant relationship between CRCL and CL/F was found. Only a few individuals with moderate impairment were included in the analysis. However, based on the assumed limited renal excretion it is not expected that mild or moderate renal impairment will have a clinically relevant effect on the exposure to bedaquiline. In subjects with severe renal impairment or end-stage renal disease, concentrations may be increased due to alteration of drug absorption, distribution, and metabolism secondary to renal dysfunction. There may be pharmacologically active metabolites eliminated through renal excretion. This is not indicated by the data but the lack of mass-balance data precludes firm conclusions to be drawn.

- Hepatic impairment

The effect of hepatic impairment on total (bound plus unbound) exposure was quite limited. AUC_{last} of bedaquiline and of metabolite M2 were both reduced by 19% in moderate hepatic impairment. The degree of protein binding was not measured in the study and as an effect of unbound fraction (fu) is likely, as indicated both by the high protein binding in healthy volunteers and by the decrease instead of increase in exposure, the results of the study are of little value. As no information on fu is currently available, the labelling recommendations needs to be based on predicted effects.

- Gender, weight, race and age:

The effect of gender, BMI and race on the pharmacokinetics of bedaquiline was evaluated in the population pharmacokinetic analysis. The population consisted of 149 Black, 134 Caucasian, 99 Asian, 41 Hispanic and 57 subjects with race classified as "other**",** 331 males and 149 females and included a BMI range of a 13.1 to 36.8 kg/m2**.** Apparent V_c/F was lower in females (138 L) than males (164 L), a difference not considered clinically relevant. Differences in weight/BMI were also found to have a non-significant effect on the PK. Black subjects were found to have a decreased exposure (34%) due to an increased CL/F. The predicted decrease is however not considered being clinically relevant based on the demonstrated equally good efficacy in Black subjects. As the reason for the lower exposure in Black subjects compared to other ethnicities is unknown it is encouraged that the effect of Black race and potential clinical consequences of the lower exposure is re-evaluated in the planned phase III study. Limited data is available on the use of bedaquiline in elderly. Patients older than 65 years were excluded from the clinical studies

Pharmacokinetic interaction studies

- Effects on enzymes

In vitro experiments showed that the potential for bedaquiline and M2 to inhibit CYP isoenzymes may be considered to be low. The reported IC_{50} values were high in comparison to the Cmax, unbound values obtained in clinical trials. However, clarification from the applicant is needed to exclude the potential for bedaquiline to inhibit intestinal CYP3A4 (to be evaluated in a phase 3 study

post authorization)..The potential for bedaquiline to inhibit CYP2C9 and CYP2C8 needs to be investigated separately post authorisation with a sensitive marker reaction as outlined further below.

The in vitro induction studies are difficult to interpret due to different shortcomings. There are in vivo indications of induction from both the DDI study with ketoconazole and with lopinavir/ritonavir. In order to estimate the potency of bedaquiline as an inducer, the applicant should perform an interaction study with midazolam. In *in vitro* enzyme inhibition assays, bedaquiline did not inhibit any of the tested CYPs at *in vivo* relevant concentrations (50*$Cmax_u$). The metabolite M2 had higher inhibition potency but the inhibition was not significant at relevant concentration.

- Effects on transporters:

Bedaquiline and M2 inhibited efflux transport of paclitaxel in Caco-2 cells, while bedaquiline did not inhibit taxol transport in another Caco-2 cell assay. The applicant should perform *in vitro* studies investigating the effect on the transporters listed in the revised DDI guideline: BCRP, OATP1B1 (SLCO1B1), OATP1B3 (SLCO1B3), OCT2 (SLC22A2), OAT1 (SLC22A6) and OAT3 (SLC22A8), preferably also OCT-1, MATE1 (SLC47A1) and MATE2 (SLC47A). These data may be of importance for DDI predictions with HIV drugs but could be submitted post-approval.

- *In vivo* DDI studies

The effect of rifampicin 600 mg qd for 7 days on bedaquiline and M2 after a 300 mg bedaquiline single-dose before and on the 7th treatment day was investigated. Rifampicin induced the metabolism of bedaquiline and reduced the AUC0-t of bedaquiline by 52% and the AUC of M2 by 25%. The effect if probably markedly underestimated as rifampicin treatment did not cover a major part of the bedaquiline AUC. In the SmPC 4.5, it is concluded that co-administration of bedaquiline and rifamycins or other potent CYP3A4 inducers used systemically should be avoided.

The interaction with isoniazid/ pyrazinamide was investigated. The pharmacokinetics of isoniazid/pyrazinamide qd for 5 days, alone or on the 11th (to 15th) day of bedaquiline 400 mg qd treatment was investigated. Full pharmacokinetic profiles of bedaquiline and metabolite M2 were determined on day 10 and day 15 of the bedaquiline treatment. Isoniazid/pyrazinamide reduced the AUC24h of bedaquiline 13% while the AUC of M2 was increased by 30%. The effect may have been underestimated. Bedaquiline increased the C0h, Cmax and AUC24h of isoniazid with 20%, 20% and 7%, respectively. Cmin was not included in the statistical analysis of isoniazid as more than half of the individual values on day 5 after treatment of isoniazid/pyrazinamide alone were below the LLOQ. The mean terminal t½ of isoniazid following co-treatment with bedaquiline was 3.8 h (±1.7 h).

The effect of nevirapine on the pharmacokinetics of bedaquiline was investigated in HIV patients. Bedaquiline was administered as a 400 mg dingle dose before and after start treatment with nevirapine in combination with 2 NRTIs at the recommended dosing regimen (200 mg qd for two weeks followed by 200 mg bid). There was a 2-4 week washout between the bedaquiline dose and the nevirapine/NRTI combination. After 4 weeks of nevirapine at a dose of 200 mg bid, a second single dose of bedaquiline 400 mg was co-administered. The HIV treatment was continued after the bedaquiline dose. Nevirapine did not affect bedaquiline exposure. This is surprising as the drug is a CYP3A4 inducer *in vivo*. The Cmax of M2 was 25% reduced by the HIV treatment but here there was

a substantial carryover and the effect could have been more marked. However, M2 AUC was unchanged.

The effect of efavirenz was investigated in a published paper. The single-dose pharmacokinetics of bedaquiline was investigated before and after 14 days of treatment with efavirenz 600 mg qd (without food). Efavirenz was continuously administered throughout the bedaquiline sampling period (336 h). Efavirenz reduced bedaquiline AUC_{336h} by 18%, whereas Cmax was unaffected. M2 Cmax was 89% increased, but M2 AUC_{336h} was unchanged.

The DDI between ketoconazole and bedaquiline was investigated but the design of the study was not optimal. Ketoconazole 400 mg qd for 3 days alone after the three last days of a bedaquiline 400 mg qd 2-week regimen. Bedaquiline was administered as the 400 mg qd regimen alone and to investigate the effect of ketoconazole, Bedaquiline PK was studied on the 11th day of bedaquiline 400 mg qd and on the 14th day (after 3 days of ketoconazole co-treatment). Ketoconazole increased the bedaquiline AUC24h by 22%. The Cmax and AUC24h of the metabolite M2 were unaffected by ketoconazole. Bedaquiline slightly reduced the exposure of ketoconazole possibly due to enzyme induction.

The effect of lopinavir/ritonavir was also investigated. The exposure of bedaquiline was determined when a 400 mg dose was administered alone as well as on the 11th day of a lopinavir/ritonavir 400/100 mg bid treatment for 24 days. The bedaquiline doses were administered 4 weeks apart. Lopinavir/ritonavir increased the AUC_t of bedaquiline by 22%, whereas Cmax of the compound was unaffected. A significant period effect was observed and the patients treated with bedaquiline alone first, followed by the PIs had a 40% increase in AUC while there was no effect if the order of treatment was the opposite. Lopinavir/ritonavir reduced AUC_t of M2 by 39%. M2 AUC_t decreased by 62% if the combination was administered first sequence.

The effect of bedaquiline 400 mg qd on the exposure to co-administered anti-tuberculosis drugs in the background regimen was evaluated at week 2 of study C208 comparing the pharmacokinetics of these drugs in the bedaquiline and placebo groups (i.e. parallel study design). The results did not indicate any significant effect on ofloxacin, cycloserine/ terizidone, ethambutol, kanamycin or pyrazinamide.

- *Planned phase III study*

In the phase III study planned by the applicant, protease inhibitors will be allowed. Preferably, a well performed PK DDI study with results possible to extrapolate to the therapeutic situation should be performed to allow prospective dose adjustment unless safety is. Regardless which route is taken, effort should be made to extract as much information as possible from the study. This is recommended:

- Sparse sampling and population PK analysis with effort made to obtain very accurate information on concomitant medication, time point of last dose, dose and dose intervals, duration, etc. This is essential for the possibility of documenting the interactions with commonly used drugs.
- Blood sampling for genotyping intended to clarify enzyme and transporter involvement as well as to document exposure in subgroups: including genotyping for CYP2C19 and other potential enzyme candidates as well as of genes coding for polymorphic transporters potentially involved in biliary excretion (OATP1B1, OCT-1, BCRP etc.).

➢ *PK/PD*

The relationship between bedaquiline exposure and short- or long-term anti-mycobacterial activity was evaluated in study C202, C208 and C209 by the use of graphical exploratory plots, Cox-proportional hazard and logistic regression models. In study C202, a trend towards greater decreases in $\log_{10}$ sputum CFU count with greater exposure at Day 7was found. In trial C208 (stage 2), no clear relationship between AUC24h and time to sputum culture conversion was evident. Neither was a clear relationship between AUC24h stratified on quartiles and culture conversion rates identified. In C209 was no clear relationship observed between Cavg values and times to culture conversion. Culture conversion rates analyzed by quartile ranges of pharmacokinetic parameters at Week 24 showed a somewhat higher conversion rates in higher Cavg quartiles compared to lower Cavg quartiles in Q4 (Cavg > 1447 ng/mL), 91.3% of subjects were responders, while in Q1 (Cavg < 796.9 ng/mL), 83.0% of subjects were responders.

Pharmacokinetics using human biomaterials

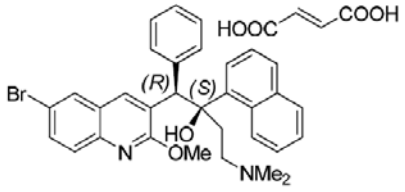
2.4.3. Pharmacodynamics

Adequate microbiological methods were used for documentation of bedaquiline in the clinical studies and assessments of MIC were carefully and properly described.

Mechanism of action

Bedaquiline is the first diarylquinoline reported to exhibit anti-TB activity that is being developed for the treatment of patients with pulmonary MDR-TB. Findings indicate that bedaquiline inhibited the proton pump of M. tuberculosis ATP synthase. It was also clarified that the M2 metabolite does have the same mechanism, since the same point mutations in the atpE-gene that are involved in resistance to the mother compound induced cross resistance to M2.

Although selection experiments indicate that certain point mutations in the atpE gene are involved in resistance to bedaquiline, these mutations were only found in a smaller proportion of isolates in these in vitro studies, and in none of the resistant clinical isolates obtained studies C208/C209. During the procedure it was clarified that functional assays using efflux inhibitors (verapamil, resperpine) imply the involvement of an efflux-based mechanism. This is certainly an area for further studies.



Molecular formula: $C_{32}H_{31}BrN_2O_2 \cdot C_4H_4O_4$

Molecular weight: 671.58 (555.50 + 116.07)

Primary and Secondary pharmacology

In vitro activity against M. tuberculosis isolates

The in vitro susceptibility tested for a wide variety of strains, both those susceptible to first line agents (DS-TB) and MDR-strains. MIC ranged from ≤ 0.008 to 0.12 µg/mL without obvious differences by resistance to other agents, and subtype. This wide difference in MICs may be related to methodological difficulties in these low ranges of MICs. When looking at clinical outcomes, no relation was found between baseline MICs, for bedaquiline, and effects.

MICs were generally < 0.1 µg/mL also for other mycobacterial species, including species naturally resistant to many other anti-TB agents and involved in opportunistic infections, such as M. avium complex.

The MIC for M2, the main metabolite, was 3-6 times higher than that of the parent compound.

Bactericidal activity

In various in vitro experiments bedaquiline has been shown to be bactericidal properties, including for dormant bacilli as shown in the table 7 below.

Table7 : Comparative Killing Activity of TB Compounds (Rifampicin("R"), Isoniazid ("INH") and BDQ) for Actively Replicating ("MBC") and Dormant ("WCC") *M. tuberculosis*

Compound	MBC (µg/mL)	WCC (µg/mL)	WCC/MBC
RMP	0.03	0.5	17
INH	0.25	>64	>256
BDQ	2	1	0.5

The WCC/MBC ratio reflects the comparative killing efficiency. It should be noted that bedaquiline is slightly more potent toward dormant bacteria with a low WCC/MBC ratio compared to rifampicin and isoniazid. Isoniazid has no detectable activity on dormant bacteria and rifampicin is significantly less active on dormant as compared to actively replicating bacilli.

In vitro, the killing effect is time- rather than concentration-dependent, which is in line with data obtained with short course monotherapy in TB patients.

In vitro, presumably a post-antibiotic effect was shown in vitro (9 hrs, compared to 15 hours for isoniazid used as control).

Specific activity for Mycobacteria species

The activity of bedaquiline was tested against a panel of other bacteria, all showing very high MICs for bedaquiline (*Corynebacterium, Helicobacter, Nocardia, E--coli, Haemophilus influenza, Streptococcus pneumonia, Staphylococcus aureus)*.During the review process it was also clarified that, from a mechanistic point of view, non-mycobacterial species are considered intrinsically resistant to bedaquiline, which also means that there should be no risk for enrichment or maintenance of resistance within the gut flora.

Monotherapy in murine models

Bedaquiline has been investigated at various doses in a considerable number of animal studies, mice models and a Guinea Pig model, in monotherapy, as well as in combination with other TB agents.

In monotherapy (mice) one important finding was that the efficacy of intermittent dosing seemed comparable to that obtained with daily dosing. Bedaquiline alone was at least as bactericidal as the first-line triple combination therapy (i.e., R + INH + PZA) and more active than R alone.

Guinea Pigs infected by aerosol show lung lesions with similarities to natural infections in humans, including lung cavitations etc. In this respect, this model might be of particular interest. Here bedaquiline, still as monotherapy, was highly effective, with almost complete eradication after 6 weeks therapy, and showed higher efficacy than conventional therapy of R + INH + PZA.

Pharmacodynamic interactions with other TB agents

In vitro interactions of bedaquiline with other anti-TB drugs have not been studied. Instead, a series of animal experiments were conducted where bedaquiline was administered with various combinations of anti-TB drugs.

Increased effect was seen when bedaquiline was added to a first-line triple combination therapy (R + INH + PZA) for DS-TB in mice. When substituting one of these first-line drugs with bedaquiline, the activity of each regimen was significantly better than that of R + INH + PZA, particularly after 1 month of treatment.

When following mice for longer, to study relapse rates after various regimens with and without bedaquiline (added or substituted for) of 3 months or longer, end of treatment responses were similar for tested regimens, but relapse rates were considerably lower in regimens that included bedaquiline.

These studies also looked at combinations of bedaquiline with some second-line agents (amikacin, ethionamide, moxifloxacin) with the same promising results.

Table 8: Bactericidal activity of bedaquiline + second-line drugs in murine TB model

	Mean Log CFU Counts ± SD (mice with negative cultures/total)			
Regimens[a]	**Spleen 1 Month**	**Spleen 2 Months**	**Lungs 1 Month**	**Lungs 2 Months(**
Untreated	6.5 ± 0.2	-	5.9 ± 0.5	-
J	2.6 ± 1.3	1.2 ± 0.5 (0/8)	2.9 ± 0.9	0.2 ± 0.3 (6/8)
RHZ	4.5 ± 0.3	1.9 ± 0.5 (1/10)	3.7 ± 0.4	1.0 ± 0.5 (0/10)
RHZJ	1.9 ± 0.31	0.1 ± 0.2 (4/10)	1.8 ± 0.4	0 ± 0 (10/10)

AEMZ	3.2 ± 0.5	1.6 ± 0.4 (1/10)	2.9 ± 0.2	0.1 ± 0.1	(5/10)
AEZ	4.0 ± 0.3	2.8 ± 0.3 (0/10)	3.7 ± 0.2	1.2 ± 0.3	(0/10)
AMZ	3.6 ± 0.2	1.9 ± 0.5 (0/10)	3.4 ± 0.3	0.8 ± 0.6	(0/10)
AEZJ	1.2 ± 0.2	0.1 ± 0.1 (7/9)	0.2 ± 0.3	0 ± 0	(9/9)
AMZJ	1.2 ± 0.2	0 ± 0 (8/8)	0.2 ± 0.3	0 ± 0	(8/8)
AEMZJ	1.2 ± 0.3	0 ± 0 (8/8)	0.5 ± 0.4	0 ± 0	(8/8)

J = bedaquiline; [R = rifampicin Z = PZA]=first line; [A = AMK; E = ETH; M = MXF]=second line

The study above is, according to the company, the first study in which a regimen without INH and R was able to reach lung and spleen culture conversion within 2 months of therapy in mice. These observations in mice may suggest that bedaquiline-containing MDR-TB regimens could have the potential to significantly shorten treatment duration, similar to what was seen when bedaquiline was added to the first-line regimen R + INH + PZA.

In two other studies (mouse model) pharmacodynamic data was also generated for the combination of bedaquiline, clofazimine (CFZ) and PZA. Here it was shown that when combining bedaquiline + PZA, the best 3rd drug was CFZ, as compared to adding rifampicin, rifapentine or moxifloxacin (*killing effect*; decrease in Lung log CFU count over 1 month). In the second study, again the same combination yielded a seemingly high *sterilizing activity* also with a short course, table below, Hence, CFZ may be an important agent to be used as part of the background regimen to bedaquiline.

Table 9. Relapse rates (spleen) 3 months after treatment completion, in a mouse model.

	Proportion (%) relapsing after treatment for:			
Drug regimen	**4 weeks**	**6 weeks**	**8 weeks**	**10 weeks**
BDQ + PZA	ND[a]	14/15 (93)	10/15 (67)	8/15 (53)
BDQ + PZA + RPT	ND	5/15 (33)	0/15 (0)	ND
BDQ + PZA + CFZ	ND	1/15 (7)	0/15 (0)	ND
BDQ + PZA + PNU	ND	8/15 (53)	6/15 (40)	ND
BDQ + PZA + RPT + CFZ	4/15 (27)	0/15 (0)	ND	ND

[a] ND, not done (Adapted from: Williams et al., Antimicrob Agents Chemother 2012)

With regards to sterilizing activity, the issue how bedaquiline could work on dormant bacilli was raised during the review, taking the mechanism of action into account. It was clarified that the *de novo* ATP synthesis is essential for the viability of hypoxic non-replicating mycobacteria. As the intracellular concentration of ATP is lower in during such conditions (by a factor 5 or so), this makes non-replicative bacteria exquisitely sensitive to further depletion. Hence, the effect on dormant bacilli is much higher for bedaquiline than for INH and RIF as outlined in the section on bactericidal activity above.

The exposures of bedaquiline and M2, major metabolite with MIC values being around 5 times higher- achieved in the animal studies was discussed during the review procedure. When looking at the steady state, the combined exposure of active moieties seen in mice was slightly lower than the combined exposure seen in patients treated with bedaquiline 200 g thrice weekly (i.e. end of study C208, stage 1). Hence, the exposures in the animal studies seem relevant to human conditions.

The mean time to positive signals in the MGIT (liquid) culture system (a secondary end point in study C208) was longer in the bedaquiline-treated patients. In stage 2 of study C208 this also seems to be the case at time points way past week 24 (when bedaquiline had been stopped). In addition, it was clarified that by the methods used (including the lysis of cells as part of the procedure) there would be no risk for bedaquiline concentrations high enough to cause an effect on growths of the bacteria/resistance development in vitro.

Bedaquiline showed a high in vitro activity against *M. tuberculosis,* without any relevant difference in strains, and regardless of resistance to first line agents. Also non-tuberculosis strains, such as MAC, are sensitive in vitro. Hence, also for these infections (rather common in advanced HIV disease) might be a future target for TMC 207.

Animal models highly support that bedaquiline is active in vivo; that synergism with other agents is likely, and that bedaquiline have sterilizing effects. This might mean that therapy could be shortened when this agent is used.

There is no suggestion for negative pharmacodynamic interactions, thus far studied for first line agents, as well as for amikacin (injectable), moxifloxacin (fluoroquinolone) and ethionamide.

The achieved plasma concentrations and the demonstrated MICs for the two major metabolites of bedaquiline, M2 and M3, indicate that they do not contribute to the overall anti-mycobacterial activity during clinical use of bedaquiline. In contrast, in the murine models M2 has a more relevant part of activity (levels much higher than in humans). The exposures of active moieties (bedaquiline + M2) that were seen in the models were relevant for human conditions.

2.4.4. Discussion on clinical pharmacology

The main clinical pharmacology issues in this application are the lack of information regarding potential routes of elimination for bedaquiline other than CYP3A4, and how the active/toxic metabolite M2 is eliminated. These shortcomings render interaction potential as well as effects of pharmacogenetics difficult to predict. Given the relatively narrow range of exposures observed in clinical studies, potential safety issues resulting from increased exposures are also difficult to predict. The lack of elimination data is an important risk the needs to be addressed post approval, as specified in the RMP.

- *PK/PD*

Based on the provided data no clear exposure response relationship was established. A trend towards higher conversion rates in patients with higher exposures was seen in study C209. The lack of established PK/PD relationship may be due to the limited range of doses included in the exposure response analysis.

2.4.5. Conclusions on clinical pharmacology

A number of issues have been identified particularly pertaining to the lack of information regarding the elimination of bedaquiline and M2. The lack of elimination data is an important risk identified in the RMP and considered in the benefit-risk assessment. In the absence of this information a combination of restrictive labelling as well as studies to be performed post-approval are proposed.

The CHMP considers the following additional measures necessary to address the issues related to pharmacology:

- Identification how M2 is eliminated and which transporters are involved.
- In vitro studies of bedaquiline as a substrate of canalicular efflux transporters (in accordance with the Guideline on the Investigation of Drug Interactions, CPMP/EWP/560/95/Rev. 1 Corr).
- An in vitro study on CYP2C8 and CTP2C9 enzyme inhibition.
- An in vitro study to assess the potential of BDQ and M2 to inhibit the transporters: OATP1B1, OATP1B3, BCRP, OAT1, OAT3 and preferably also OCT1, OCT2, MATE1 and MATE.
- Exploration of mechanisms of resistance other than that known to date.

These measures are also reflected in the Risk Management Plan as further detailed below.

2.5. Clinical efficacy

The proposed indication for bedaquiline is treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* as part of combination therapy in adults (≥18 years). The applicant has used the following definition for MDR-TB: Tuberculosis due to infection with a strain of *M. tuberculosis* that is resistant to at least isoniazid (INH or H) and rifampicin (R), the 2 most important first-line drugs used to treat DS-TB. Furthermore, $MDR_{H\&R}$-TB was used to refer to *M.tuberculosis* resistant to INH and R, excluding pre-XDR (resistance to isoniazid (H) and rifampicin (R), but still susceptible to either, but not both second line injectables or fluoroquinolones) and XDR (resistance to isoniazid and rifampicin, second line injectables and fluoroquinolones).

Clinical documentation to support this application includes four Phase II trials.

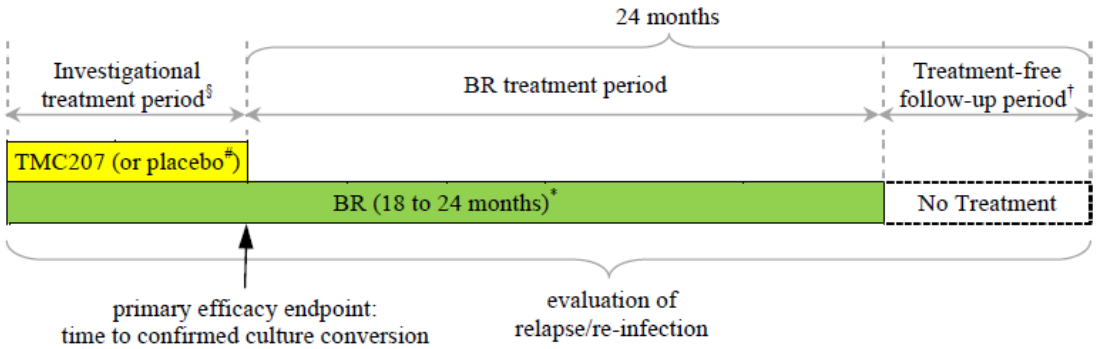
Table 10: Overview of trials providing clinical efficacy data

Trial (Status)	Design	Population	Treatment	Dose	TMC207 Treatment Duration	Primary Efficacy Endpoint	N
TMC207-C202 (completed)	Randomized, open-label, active-controlled	DS-TB	TMC207 or RMP or INH followed by standard TB therapy	TMC207 25 mg q.d. TMC207 100 mg q.d. TMC207 400 mg q.d. RMP 600 mg q.d. INH 300 mg q.d.	7 days	Degree of reduction in the sputum viable count over a 7-day period (eEBA)	75 (TMC207 25/100/400 mg: 15/16/14; RMP: 15; INH: 15)
TMC207-C208 Stage 1 (completed)	Randomized, double-blind, placebo-controlled	newly diagnosed $MDR_{H\&R}$-TB/ pre-XDR-TB	TMC207 or placebo + preferred BR composed of: KAN, OFL, ETH, PZA, and CS/TRD	Week 1-2: TMC207 400 mg q.d Week 3-8: TMC207 200 mg t.i.w. BR drugs: standard dose	8 weeks	Time to culture conversion in MGIT during the 8-week investigational treatment period	47 (TMC207: 23; placebo: 24)
Stage 2 (investigational treatment completed)	Randomized, double-blind, placebo-controlled	newly diagnosed $MDR_{H\&R}$-TB/ pre-XDR-TB	TMC207 or placebo + preferred BR composed of: KAN, OFL, ETH, PZA, and CS/TRD	Week 1-2: TMC207 400 mg q.d Week 3-24: TMC207 200 mg t.i.w. BR drugs: standard dose	24 weeks	Time to culture conversion in MGIT during the 24-week investigational treatment period	160 (TMC207: 79; placebo: 81)
TMC207-C209 (investigational treatment completed)	Open-label, uncontrolled	newly diagnosed or previously treated $MDR_{H\&R}$-TB/ pre-XDR-TB/ XDR-TB	TMC207 + individually optimized BR	Week 1-2: TMC207 400 mg q.d Week 3-24: TMC207 200 mg t.i.w. BR drugs: standard dose	24 weeks	Time to culture conversion in MGIT during the 24-week investigational treatment period	233

N = number of subjects treated; RMP = rifampin; INH = isoniazid; KAN = kanamycin; OFL = ofloxacin; ETH = ethionamide; PZA = pyrazinamide; CS = cycloserine; TRD = terizidone

Overview of trial designs and treatment periods is shown below:

Figure 3: Overview of trial design and treatment periods in Phase IIb trials



§ 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.

Based on the above mentioned studies, the applicant applies for a conditional approval for bedaquiline.

2.5.1. Dose-response studies

C202 - a short term exploratory study on early bactericidal activity (Single centre, South Africa)

This study examined the reduction of viable count of M. *Tuberculosis* in daily sputum samples in 75 treatment naïve, smear positive, patients treated (1:1:1:1:1, i.e. around 15 patients per arm) for 7 days with

- Bedaquiline dosed 25 mg, 100 mg or 400 mg qd, or
- Rifampicin 600 mg qd, or
- Isoniazid 300 mg qd

Early bactericidal activity (EBA) was found to be higher in the rifampicin and isoniazid groups, compared to the bedaquiline groups. The lower doses (25 mg and 100 mg) did not show statistically relevant changes during the 7 days of treatment, and the highest dose, 400 mg qd, showed a modest effect of 1 $\log_{10}$ reduction, with a delayed onset. Corresponding effect with INH was 2 $\log_{10}$ reduction. During the review of data the applicant was asked to expand on the fact that while the pharmacodynamic studies in animals (discussed previously) and the phase 2b studies indicated an favourable effect after 1 month and longer, the results of the EBA-study in contrast showed less impressive effects. It was shown that in further studies in mice, this pattern could be verified; during the first week the killing effect of bedaquiline was much lower than during weeks 2-4. The same delayed effect was also shown for bedaquiline in vitro. The applicant concludes that the likely reason is that mycobacteria would carry a pool of ATP reserve, and stated that ATP levels need to drop by some 90% before killing starts (unpublished data).

It was noted that study C202 included patients with a high level of disease and one actually died shortly after the investigational treatment (massive bleeding from cavernous TB).

2.5.2. Main studies

Study C208: A phase II, placebo-controlled, double-blind, randomised trial to evaluate antibacterial activity, safety, and tolerability of bedaquiline in subjects with sputum smear-positive pulmonary infection with multi-drug resistant *Mycobacterium tuberculosis*.

Methods

Study C208 is considered the main basis for this application for a conditional approval. The study consists of two stages, which rather could be considered to be two separate studies. However, both stages share the same methods, end points and background regimens.

The difference between stage 1 and 2 is the duration of bedaquiline (versus placebo) treatment which was 8 weeks in stage 1 (total 47 patients) and 24 weeks in stage 2 (total 160 patients).

Study Participants

The major inclusion and exclusion criteria for C208 trial are given below.

Main inclusion criteria

- Male or female subjects, aged 18-65 years, and with a BMI between 15 and 28 kg/m^2.
- Subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection, with confirmed resistance to at least both R and INH by previous screening from a TB treatment facility. Resistance could be shown by proportion method and/or rapid screen tests, i.e., fast plaque and Genotype MTBDR plus line probe (if resistance to R or INH was based on rapid screen tests, these tests had to be repeated at the screening visit).
  Subjects with newly diagnosed MDR-TB were defined as a) subjects with MDR-TB who had never been treated for TB before, or b) subjects with MDR-TB who had previously been treated with only first-line TB drugs (INH, R, EMB, PZA, or SM).
- Positive for AFB on direct smear examination of expectorated sputum specimen [≥1+].
- Subjects had to consent to HIV-testing.
- Subjects had to discontinue all TB drugs to allow 7 days washout before baseline assessments.

Main exclusion criteria

- Subjects previously treated for MDR-TB, defined as subjects having received any second-line TB drug, including any AG except SM, any FQ, protionamide or ETH, and CS.
- Subjects having a current or past history of alcohol and/or drug use that, in the investigator's opinion, could compromise the subject's safety or compliance.
- Subjects having a clinically significant active medical condition.
- Subjects having a significant cardiac arrhythmia that required medication.
- HIV-infected subjects, a) having a CD4+ count < 300 cells/µL or b) having received antiretroviral therapy (ART) and/or oral or IV antifungal medication within the last 90 days. Also subjects, who might need to start ART during the 24-week treatment period of Stage 2.
- Subjects with complicated or severe extrapulmonary or neurological manifestations of TB.
- Subjects having any concomitant severe illness or rapidly deteriorating health condition, including immune deficiency, or gastrointestinal disease that could interfere with the absorption of bedaquiline.
- Subjects having had DST performed prior to screening and their isolates being not susceptible to at least 3 of the 5 classes of TB drugs used to treat MDR-TB.
- Subjects with the following QT/QTc characteristics at screening: (a) A marked prolongation of QT/QTc interval, e.g., QTcF > 450 ms, (b) A history of additional risk factors for Torsade de Pointes, and (c) The use of concomitant medications that may prolong the QT/QTc interval.

Rollover criteria

Upon availability of the C208 Stage 1 results, a rollover arm was added to Stage 2 per protocol Amendment IV to offer open-label treatment with bedaquiline to subjects from Stage 2 who received placebo and were not adequately responding to their BR regimen after 24 weeks of treatment (including subjects who developed XDR-TB during this period). Subjects with pre-XDR-TB in the placebo group when second-line susceptibility results became available after randomisation had also the option to rollover to this arm.

Treatments

Following screening tests (Week –1), eligible subjects were hospitalized as per standard of care. The treatment regimens administered in Stage 1 and 2 are shown in table 11 below.

Table 11: Treatment regimens

Screening period (Week -1) No treatment administration **Treatment period** (8 weeks at Stage 1, 24 weeks at Stage 2*): Weeks 1 and 2: 400 mg bedaquiline or placebo q.d. (1:1) administered as 4 tablets, and BR** Week 3 to 8(stage 1); Weeks 3-24 (stage 2): 200 mg bedaquiline or placebo t.i.w. (at least one day apart) administered as 2 tablets, and BR **Follow-up period** (96 weeks at both Stage 1 and 2): MDR-TB treatment (i.e. BR only) for 18-24 months, at least 12 months after the first documented negative culture

* Rollover group subjects received the same treatment regimen as the Stage 2 subjects
** The BR is selected according to national guidelines for the treatment of MDR-TB.

Bedaquiline was supplied as 100 mg tablets. There were matching placebo tablets.

Study medication was administered orally with water within 10 minutes following breakfast. Background medication had to be taken before breakfast. Treatment throughout investigational treatment period and the follow-up period was administered by directly observed treatment (DOT). All medication intakes were supervised.

Background regimen

A preferred background regimen consisting of the 5 agents was given for 18-24 months (at least 12 months after the first documented negative culture): KAN, OFL, ETH, PZA and cycloserine/terizidone. An overview of BR treatment is given in table 12 below.

Table 12: Drugs used in the BR for the Treatment of MDR-TB in the C208 Trial

BR drugs	Formulation[a]	Daily dosage[a] (mg)		Phase (intensive/continuation)
		Minimum	Maximum	
Aminoglycosides				
- Kanamycin[b]	Vial, 1g	750	1000	Intensive
- Amikacin[b]	Vial, 1g	750	1000	Intensive
Thioamides				
- Ethionamide[c, d]	Tablet, 250 mg	500	750	Intensive/continuation
- Protionamide[c]	Tablet, 250 mg	500	1000	Intensive/continuation
Pyrazinamide	Tablet, 400 or 500 mg	1200	1600	Intensive
Fluoroquinolones				
- Ofloxacin[e,f]	Tablet, 200 mg	600	800	Intensive/continuation
- Ciprofloxacin[e]	Tablet, 250 mg	1000	1500	Intensive/continuation
Ethambutol[g]	Tablet, 400 mg	1000	1200	Intensive/continuation
Terizidone/Cycloserine[g,h]	Capsule, 250 mg	500	750	Intensive/continuation

[a] The formulations and daily dosage ranges mentioned are recommended formulations and doses (i.e., were to be used as guidance only)
[b] in case of unavailability of kanamycin due to drug supply issues, amikacin could be used.
[c] in case of unavailability of ethionamide due to drug supply issues, protionamide could be used.
[d] for reasons of intolerability (nausea), the dose could be split into 2 parts administered 10-12 hours apart, or the daily dose could be taken in the evening or could be taken with orange juice or milk or other liquid.
[e] in case of unavailability of ofloxacin due to drug supply issues, ciprofloxacin could be used.
[f] for reasons of intolerability, the dose could be reduced during the continuation phase.
[g] in case of intolerance to terizidone/cycloserine and if there was no resistance to ethambutol as determined by drug susceptibility testing, ethambutol could be substituted for cycloserine/terizidone.
[h] to reduce central nervous system effects, 150 mg/day of pyridoxine could be administered.

The BR for each subject was provided through the national TB program. Some predetermined changes were allowed, in case of supply shortage or intolerance. If changes in the BR were made for reasons of toxicity or safety, this had to be reported as an AE. Changes (pre-determined agents) could also be made for reasons of resistance (cultures obtained with time).

Treatment administration was using DOT throughout the study, with time (i.e. when the patient was discharged from the hospital) a procedure supervised by family members/community members. Randomization was scheduled one week after screening, using a central randomization system. A minimization technique was used to ensure balance across the treatment groups in each stratum.

The treatments included in the preferred BR, and the duration, is in line with the WHO recommendations for MDR-TB therapy (at least at the time of these studies). Normally aminoglycosides would be used only during the first 4-6 months, and during the review it was clarified that in these studies the injectable was kept for longer in many cases; in particular in those allocated to placebo. For example in study C208 (stage 2) at week 36 injectables were still used by some 30% in the bedaquiline arm, 50% in the placebo arm, and at week 48: 16% vs 22%. Hence, this would be one drawback accounted for by the placebo-controlled design.

The individual BR regimens did change over time (mainly during the BR treatment period) with addition of some of these other drugs (in particular PAS-C and capreomycin). Such changes were more common in the placebo-arm than in the bedaquiline-arm.

Disallowed medications included those with large effects on CYP3A activity (e.g., rifampicin) and those associated with QT-prolongation.

Objectives

Stage 1: The objective of Stage 1 was to evaluate the PK, antibacterial activity, safety, and tolerability of bedaquiline compared to placebo when added to an MDR-TB BR for 8 weeks in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.

Stage 2: The primary objective of Stage 2 was to demonstrate superiority in the antibacterial activity of bedaquiline compared to placebo when added to a BR for 24 weeks in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint was time to sputum culture conversion (SCC) during treatment with bedaquiline or placebo. This parameter was based on the qualitative assessment of culture growth in MGIT using spot sputum samples.

Sputum culture conversion was defined as two negative cultures at consecutive visits within the 8 week investigational phase in stage 1. In stage 2, the same definition applied, but the negative cultures needed to be at least 25 days apart.

Sputum culture conversion was overruled when followed by a confirmed positive culture result (2 consecutive visits with positive sputum results), defined as relapse (during treatment, or after stopping treatment).

For subjects who discontinued before the end of the analysed time period, the following methods were applied to calculate the time to SCC:

- Primary missing = failure analysis: They were considered treatment failures and their time to SCC was censored at their last assessment with sputum culture.
- End-censored missing = failure analysis: They were considered treatment failures and were carried forward as not converting through the considered time period. The subjects' time to SCC was censored on the last day of the analysed time period.
- No overruling for discontinuation analysis: The discontinuation information was not taken into account.

Secondary efficacy endpoints

Culture Conversion Rates was calculated to determine the proportion of subjects with MGIT SCC, the following definitions were used:

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

subject discontinued during the considered time frame regardless of the status at the last assessment.

A second method was also performed as sensitivity analysis to calculate culture conversion rates, using the no overruling (i.e. discontinuation information was not taken into account) analysis. Subcategories for non-responders were: Failure to culture convert, relapse, re-infection and discontinued with microbiological status 'converted'.

Genotyping of *M. tuberculosis* isolates was to be done when a confirmed positive sputum culture was observed (or a single positive culture after the subject discontinued or completed the trial) in subjects whose microbiological status was “converted” previously. If genotyping information was missing, the subject was considered as relapser.

Other secondary end points included among others time to positive signal in MGIT, changes in CFU counts and changes in chest X-Ray and weight.

The applicant considered all of the above parameters as **interim status indicators** for MDR-TB subjects due to the long duration of MDR-TB therapy. The following treatment outcomes as defined by an international expert group (Laserson *et al* 2005) and slightly adapted for practical use were thus also included in the protocol as secondary endpoints:

Cure: An MDR-TB patient who completed treatment according to protocol and was consistently culture-negative (with at least five results) for the final 12 months of treatment. If only one positive culture is reported during that time, a patient would still be considered cured, provided that this was followed by a minimum of three consecutive negative cultures over a period of at least 56 days.

Treatment failure: Treatment would be considered “failure” if ≥2 of the 5 cultures recorded in the final 12 months were positive, or if any one of the final three cultures was positive. Treatment would also be considered “failure” if treatment was terminated early due to poor response or AEs.

At the final analysis, the number of subjects with a relapse and the time-to-relapse was also to be evaluated, in addition to the above treatment outcomes. Relapse was defined as a positive sputum culture after a subject was defined converted.

Sample size

It was planned to enrol 50 subjects in Stage 1, however, less than 50 subjects could be randomised if the Sponsor considered the sample size sufficient to meet the primary objectives of this stage.

The objective of Stage 2 is to demonstrate superiority of 24-week bedaquiline treatment compared to placebo. According to the protocol, a sample size of 75 subjects per group was considered sufficient to achieve 80% power which could detect a difference of 22% in the 24- week conversion rates between the placebo group (50%) and the bedaquiline group (72%) at a 5% level of significance (2-sided). These proportions corresponded with a median time to conversion of 168 days when treated with placebo and of 92 days when treated with bedaquiline.

Randomisation

Following screening tests (Week –1), eligible subjects were hospitalised as per standard of care. Subjects were randomised in a 1:1 ratio to the two treatment groups. Randomisation of subjects was stratified for both trial site and extent of lung cavitation as determined by chest X-ray at screening. However a detailed description of the procedure has not been presented. Since a minimization technique was used it is unclear whether a random component was included or a strict deterministic method was used. With a deterministic method the randomization could have been predictable by the investigator since one of the stratification factors was the centre. However, if this was the case it would most probably have favoured the placebo arm and is therefore not considered an issue.

Blinding (masking)

During treatment with bedaquiline or placebo, the investigator, the sponsor and subject had to remain blinded regarding the treatment group the subject was randomised. The code could only be broken in case of an emergency regarding the need for further treatment.

Statistical methods

Study populations

Three subject populations were defined:

1. **Intent-to-treat population (ITT):** all randomised subjects, who had at least 1 intake of double-blind study medication (bedaquiline/placebo).
2. **Modified intent-to-treat population (mITT):** the subset of the ITT population excluding:

- Subjects whose MGIT results did not allow for primary efficacy evaluation (i.e. no evidence of culture positivity prior to first intake or no results during the first 8 weeks after first intake).
- Subjects infected with a DS or XDR *M. tuberculosis* strain or subjects for whom the MDR-TB status could not be confirmed based on DST results obtained prior to randomisation.

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

The primary analysis population was the mITT population. For the main trial C208 Stage 2 the following analyses were performed:

Primary efficacy analysis was performed once all subjects had finished 24-weeks of treatment with bedaquiline or placebo (or discontinued earlier).

Interim analysis was performed on data up to the cut-off date of 10 May 2011, at which time all subjects had completed the Week 72 visit or discontinued earlier.

Final analysis was performed when all subjects had completed the trial (except for the rollover arm) or had discontinued earlier, including the completed 24-week investigational treatment period and completed 96-week follow-up period.

Drug Susceptibility Testing

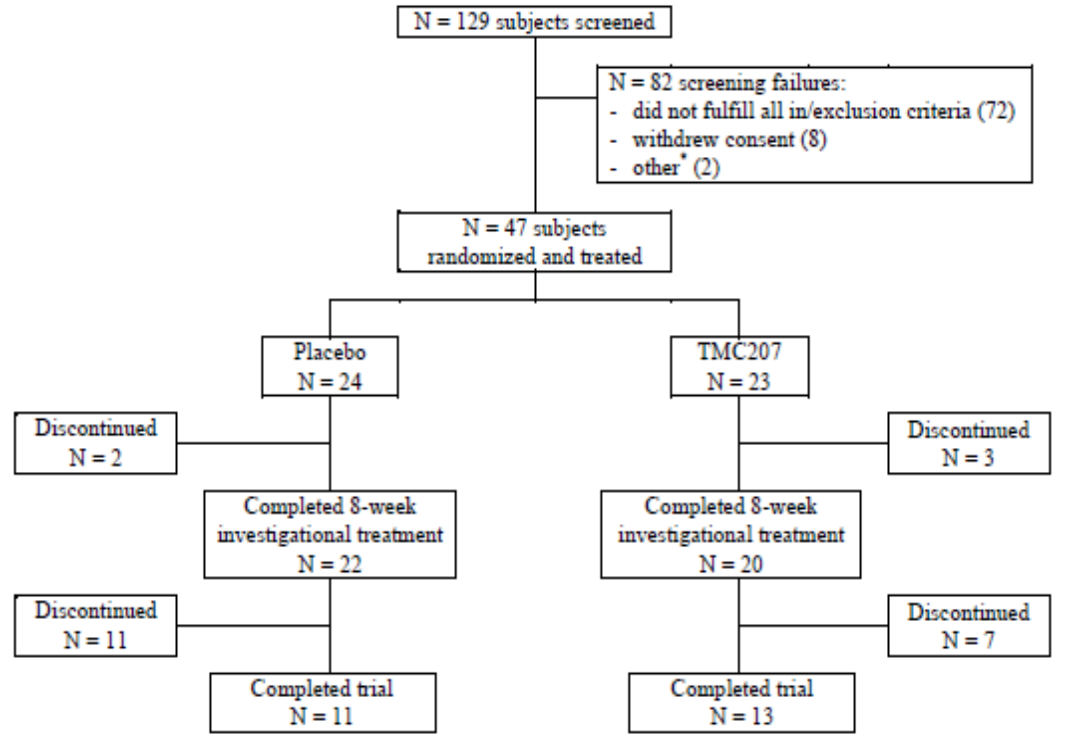
Drug susceptibility of isolates to anti-TB medications other than bedaquiline was determined by the proportion method on agar (7H11). Drug susceptibility of isolates to bedaquiline was assessed by determining MICs, using two methods: one using solid agar medium and one using liquid medium (REMA method). For bedaquiline, no critical concentration to define resistance/susceptibility is available. Therefore, subjects' isolates were considered to have decreased susceptibility to bedaquiline when they had a 4-fold increase in MIC compared to baseline. However, clinical relevance of 4-fold increase in MIC has not been established.

Drug susceptibility testing was done on Day –1, at Weeks 8 and 24, and one year after the last dose of bedaquiline or placebo (i.e., at Week 72), and also at the end of trial. Additional drug susceptibility assessments were to be made in case of failure to respond to treatment, relapse, or re-infection.

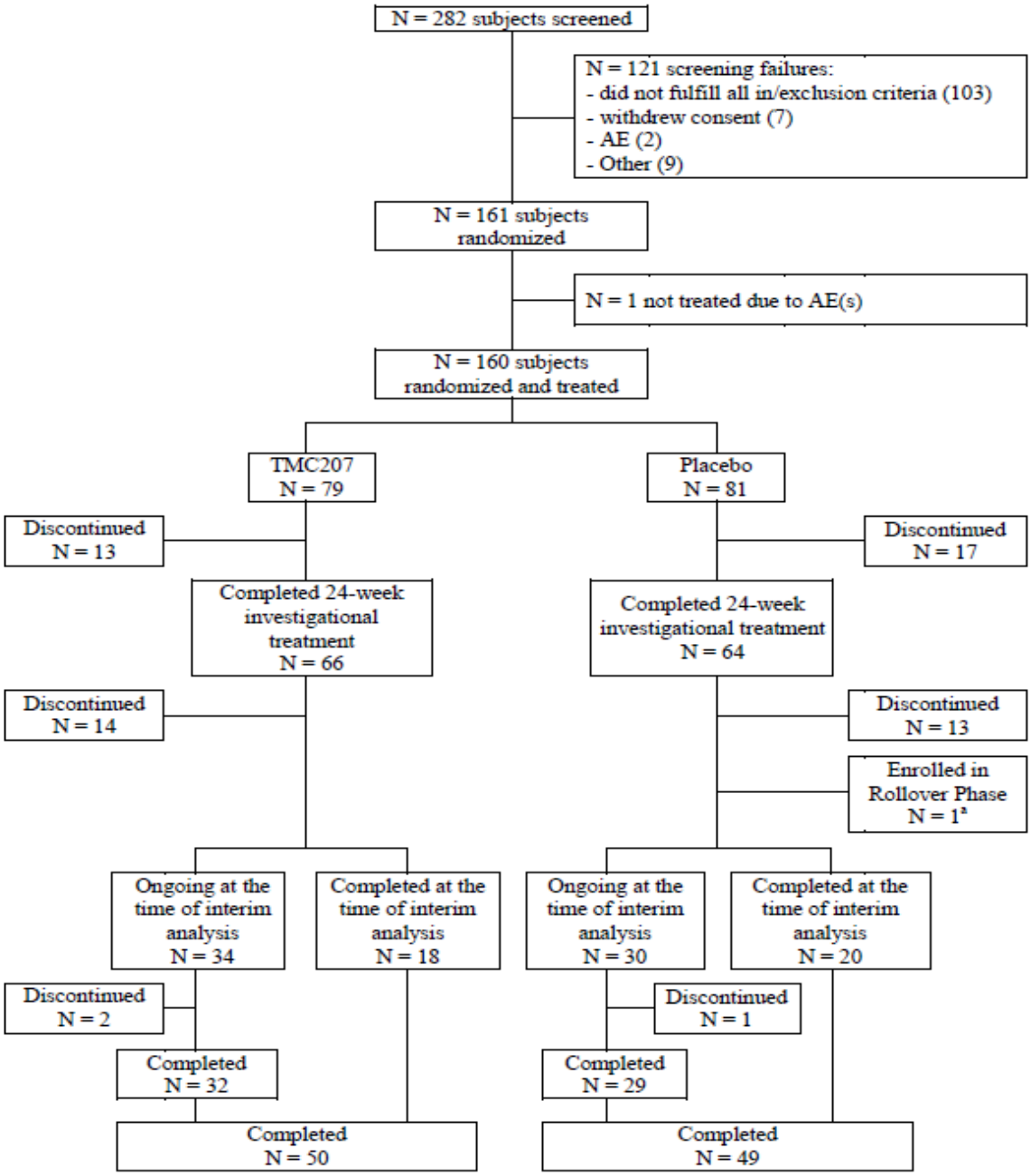
Results

Figure 3: Participant flow

C208 Stage 1



C208 Stage 2



[a] Subject was ongoing in the rollover phase at the time of database cut-off.

Recruitment

Stage 1 was initiated in June 2007 and enrolled 47 subjects (24 for placebo, 23 for bedaquiline) at 6 sites in the Republic of South Africa. The study terminated in December 2009.

A large number of discontinuations were seen during the full study period, evenly between arms (13 in the placebo group and 10 in the bedaquiline group). However, the main interest of this exploratory stage study concerned the first 8 weeks, where only 2 and 3 patients, respectively, discontinued. Although major protocol violations were common, mainly related to deviation of background regimens, this mainly occurred after the investigational period, and compliance to test agents were reportedly high. Demographics were similar between arms. The majority had cavities, BMIs were low (median 18), and the number of HIV positives were low (3 in each arm). Resistance to both R and INH was confirmed for all. In the modified ITT population (mITT), relevant for the efficacy evaluation, 3 patients were excluded (1 randomized to bedaquiline, 2 to placebo) for reasons of negative culture and XDR-TB at baseline.

Previous therapy (which had been taken by the vast majority) was similar between arms, and likewise baseline susceptibility to background agents. Importantly, the composition of background regimen was also quite similar during the investigational phase.

Stage 2 started in April 2008. The main bulk of patients were recruited in South Africa, others in South America, Eastern Europe and Asia. Main demographics were similar between arms. With regards to disease characteristics it should be noted that lung cavitations were stratified for. HIV positive status (uncommon) was more frequent in the placebo-arm, and also low baseline albumin levels, factors that are related to worse outcomes. However, HIV patients all had high CD4 counts (and not on HIV therapy), and as seen in the efficacy evaluation not a predictor for outcome within the placebo arm (where in fact a numerically better outcome was noted for those HIV co-infected). With regards to baseline albumin levels, however, this was numerically a predictor for outcomes in the placebo group, and was reported as negative predictor for TB outcomes also in other studies. The applicant was therefore asked to confirm that the outcome data could be considered robust despite the imbalance in baseline albumin grade, table 13 below. This is discussed further down. Baseline susceptibility to main second line agents and other preferred background agents, on the other hand, were similar or rather in favour of the placebo-arm.

Table 13: Demographics, C208 stage 2

Parameter Value n (%)	ITT		mITT	
	bedaquiline (79)	**Placebo (81)**	**bedaquiline (66)**	**Placebo (66)**
Positive HIV status	8 (10.1)	16 (19.8)	5 (7.6)	14 (21.2)
Cavitations both lungs	13 (16.5)	16 (19.8)	12 (18.2)	15 (22.7)
Cavitations one lung only	50 (63.3)	49 (60.5)	42 (63.6)	41 (62.1)
No cavitation	16 (20.3)	16 (19.8)	12 (18.2)	10 (15.2)
DS-TB	4 (5.1)	4 (5.2)	0	0
MDR-TB (see foot note next page)	75 (94.9)	73 (94.8)	66 (100)	66 (100)
MDRH&R-TB	*(50.6)*	*(61.0)*	*(59.1)*	*(69.7)*
pre-XDR-TB	*(20.3)*	*(15.6)*	*(22.7)*	*(18.2)*
XDR-TB	*3 (3.8)*	*4 (5.2)*	*0*	*0*
Baseline albumin grade				
Grade 0-1	59 (74.7)	51 (63.0)	49 (74.2)	38 (57.6)
Grade 2	16 (20.3)	29 (35.8)	14 (21.2)	27 (40.9)
Grade 3	4 (5.1)	1 (1.2)	3 (4.5)	1 (1.5)
Previous use of first line	72 (91.1)	70 (86.4)	60 (90.9)	58 (87.9)
PZA susceptible	(33.8)	(45.6)	(32.1)	(44.1)
Fluoroquinolone susceptible	(84.1)	(88.1)	(88.9)	(93.1)
Injectable drug susceptible	(79.4)	(82.1)	(83.3)	(86.2)
CD4 cell count for HIV positive Median (Range)	487 (340-692)	435 (310-670)	463 (352-559)	446 (310-667)

Note to previous table: For some patients, 20 subjects in the mITT population (12 in the bedaquiline group and 8 in the placebo group), no confirmation from the central laboratory of INH and R resistance was available. They were defined as MDR, based on based on previous DST. Therefore, MDR $_{H\&R}$ plus pre-XDR does not add up to 100%.

Conduct of the study

Protocol amendments

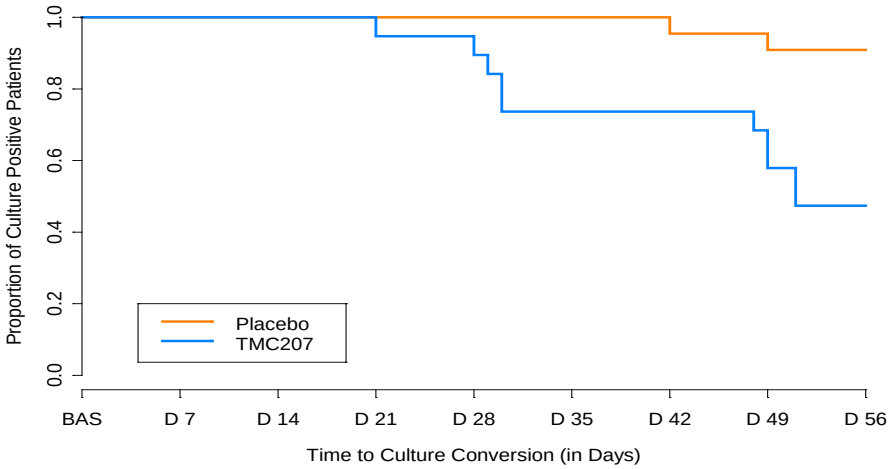
All in all 5 amendments were implemented, plus a few country-specific. The CHMP considered that these amendments do not impact on the integrity of the study. Some of the issues handled concern the difficulties related to this study population, lack of resources in low income areas, and the strong impact of National guidelines on study protocols.

Baseline data and numbers analysed

C208- Stage 1 - exploratory stage

Time to culture conversion during the investigational phase was shorter in the bedaquiline treated patients. Numbers with 2 consecutive negative triplicate cultures before the end of week 8 was 10/21 in the bedaquiline group and 2/23 in the placebo group (mITT).

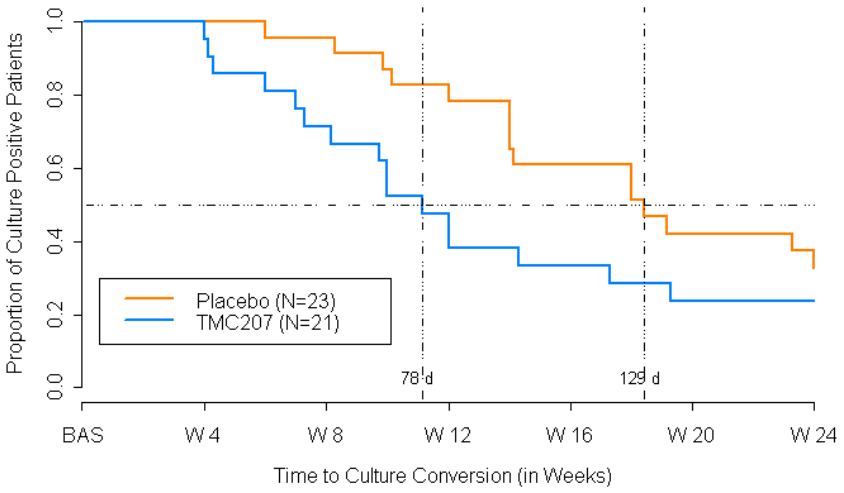
Figure 4: Proportion of culture positive subjects over time (primary stage 1 analysis) – mITT



When applying a Cox regression model adjusting for stratification variables, the treatment difference was statistically significant (p = 0.0034), with a greater probability of responding to bedaquiline treatment compared to placebo treatment within the 8-week treatment period (hazards ratio [95% CI]: 11.77 [2.26; 61.23]).

The time to culture conversion over 24 weeks (2 negative cultures, from triplicate sputa, collected at least 25 days apart) was considerably shorter for patients randomized to bedaquiline. For 50% of patients to convert, 78 days were needed in the bedaquiline arm, vs 129 days in the placebo-arm.

Figure 5: Proportion of culture positive subjects over time (24 week data, dropout = failure) – mITT



Culture conversion rates at week 24 (8 weeks of investigational treatment and total 24 weeks of background treatment) was 81.0% in the bedaquiline group and 65.2%, not statistically significant (p = 0.288).

Since bedaquiline was given for only 8 weeks in stage 1, further results in stage 1 are of low interest, and not discussed in any detail in the Overview. While a higher conversion rate was seen at week 24, no relevant difference was seen in the final conversion rates. In summary stage one was successful in showing a difference in efficacy during the investigational treatment period, which was the aim.

C208 stage 2 - single pivotal study

160 patients were randomized and treated (ITT), and the mITT population (for efficacy evaluation) consisted of 132 patients (66 in each arm). The difference between the mITT and the ITT populations was due to the exclusion of patients in the former in case of failure of cultures to grow, or XDR TB being present.

Discontinuations were common. Prior to week 24 (investigational period), 13 discontinued in the placebo arm and 17 in the placebo arm (16 and 21% respectively). At the end of study around 1/3 had left the study, evenly between arms. Stopping rates for AEs, and personal reasons (might include AEs) were similar between arms.

Table 15: Trial Termination – ITT/mITT (final results)

n (%)	ITT		mITT	
	bedaquiline N = 79	**Placebo N = 81**	**bedaquiline N = 66**	**Placebo N = 66**
Completed	**50 (63.3)**	**49 (60.5)**	**43 (65.2)**	**41 (62.1)**
Discontinued	**29 (36.7)**	**31 (38.3)**	**23 (34.8)**	**24 (36.4)**
Adverse event	9 (11.4)	6 (7.4)	8 (12.1)	5 (7.6)
Subject ineligible to continue trial	2 (2.5)	6 (7.4)	0	0
Subject is pregnant	3 (3.8)	2 (2.5)	3 (4.5)	2 (3.0)
Subject lost to follow-up	5 (6.3)	3 (3.7)	5 (7.6)	3 (4.5)
Subject non-compliant	3 (3.8)	7 (8.6)	2 (3.0)	7 (10.6)
Subject withdrew consent	6 (7.6)	7 (8.6)	5 (7.6)	7 (10.6)
Other	1 (1.3)	0	0	0
Rollover[1]	**0**	**1 (1.2)**	**0**	**1 (1.5)**

[1] The rollover arm, obviously not important for the efficacy evaluation is further mentioned in the Clinical report.

Major protocol deviations were noted in 33 % of subjects in the mITT population, i.e., in 26% of subjects in the bedaquiline group and in 39% of subjects in the placebo group. The most frequently reported major protocol deviations were BR treatment interruption of > 2weeks. More patients in the placebo arm added TB medications not formally allowed in the protocol.

Changes in the background regimen and compliance

It was allowed that the BR regimen could be somewhat adjusted during the study. At baseline and still during the investigational stage, the BR regimens were quite similar between arms. After that time point there were differences consisting of changing injectable and adding drugs (mainly PAS-C) at higher rates in the placebo arm.

In addition to cumulative frequencies, the precise number of background agents was presented during the procedure. Up to week 24 (investigational phase) the numbers and combinations used were very similar between arms. During the following phase (BR only), there was a clear trend for a higher number of agents used in the placebo-arm. With time (in practice when the injectable was stopped, previously mentioned), the BR consisted in 4 agents for the very main part of patients in the bedaquiline-arm, while in the placebo-arm a higher number of patients kept 5, or added more drugs (in total 6-7).

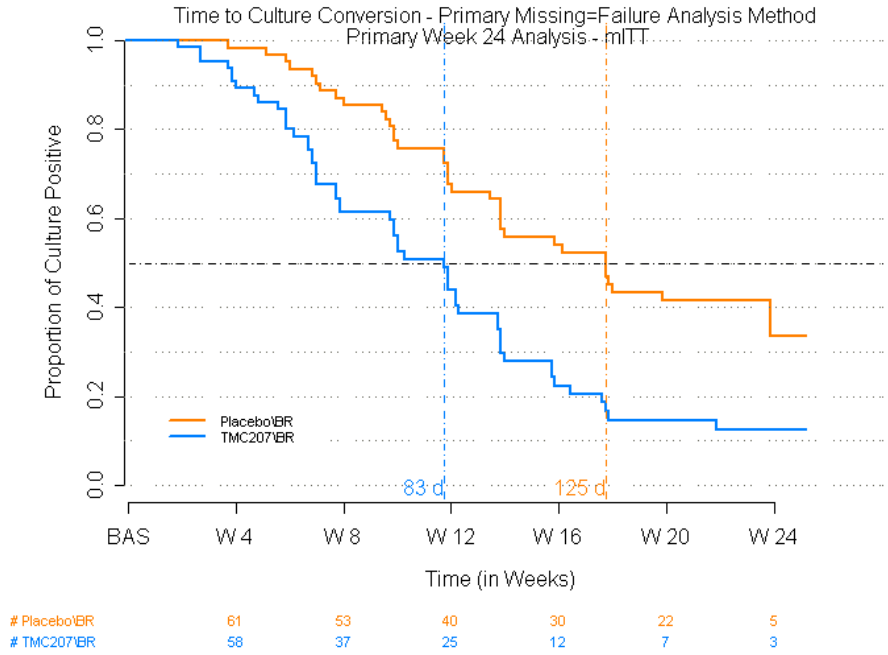
Adherence data to test agents (bedaquiline/placebo) in the mITT population was, according to the report, high (>95%) throughout the 24 weeks of investigational phase, without relevant difference between arms. The company was asked to summarize the adherence to the background regimens (including in the continuation phase). However, although DOT applied, this was with time supervised by family members, friends or certain community members, and the company was not able to provide these figures.

Outcomes and estimation

Primary Endpoint: Time to Culture Conversion

Culture conversion was faster and more frequent in the bedaquiline group compared to the placebo group; median time to culture conversion 83 vs 125 days, figure next. This was significant using a Cox proportional hazards model (p < 0.0001) [95% CI]: 2.44 [1.57; 3.80]).

Figure 6: Proportion of Culture Positive Subjects Over Time – mITT



Major secondary end point: Culture conversion rates

Culture conversion rates (missing=failure, mITT) were significantly higher in the TMC-arm by week 24 (79% vs. 58%, respectively; p = 0.008). Importantly, this difference is maintained during the study, and was still significant 62% versus 44%) 6 months after stopping treatment (final analysis).

The "No Overruling analysis" (discontinuations subsequent to culture conversion disregarded), shows stable conversion rates (i.e. without late relapses) for both arms. In patients dropping out (high rates in both arms) failure to convert or relapse was considerable more common in the placebo-arm (25/66 versus 14/66 patients in the mITT population).

Deaths occurred at higher numbers in the bedaquiline group despite the improved anti-TB efficacy. This has been carefully reviewed, and very extensive time spans from last intake of drug to deaths, and causes of deaths are not indicative for a causal relation (discussed in detail in safety section).

Table 16: Culture Conversion Rates at different time points (C208 Stage 2) – mITT

Time Point Microbiological Status, n (%)	Missing = Failure			No Overruling[1]		
	bedaquiline N = 66	**Placebo N = 66**	**p-value[c]**	**bedaquiline N = 66**	**Placebo N = 66**	**p-value[c]**
Week 24	52 (78.8)	38 (57.6)	0.008	53 (80.3)	43 (65.2)	0.049
Week 36	48 (72.7)	40 (60.6)	0.139	51 (77.3)	46 (69.7)	0.324
Week 48	49 (74.2)	42 (63.6)	0.187	53 (80.3)	48 (72.7)	0.305
Week 60	48 (72.7)	39 (59.1)	0.097	53 (80.3)	46 (69.7)	0.159
Week 72	47 (71.2)	37 (56.1)	0.069	53 (80.3)	46 (69.7)	0.159
FINAL Week 120 (≥6 months after end of therapy)	41 (62.1)	29 (43.9)	0.035	52 (78.8)	46 (69.7)	0.03
Overall non-responder	25 (37.9)	37 (56.1)				
Death - after conversion	4	0				
Death - not converted/relapse	2	1				
Discontinued - converted	7	12				
Failure to culture convert	8	14				
Relapse (as defined)	4	10				

[1] discontinuations subsequent to culture conversion disregarded.

[C] Based on a logistic regression model with treatment as covariate

As mentioned above the applicant was asked to elaborate on the issue of an imbalance in baseline albumin levels:

Firstly, it was shown that the around 20% difference in converting rates was true also when simply comparing the outcomes by albumin strata (Grade 1-2 and grade 3-4, respectively). Secondly, a logistic regression model was presented, where the estimated overall response rates correcting for baseline albumin was found to be 76.7% for BDQ/BR and 56.7% for placebo/BR, resulting in a statistically significant treatment difference of 20.0% (p-value= 0.0198).

It was also shown that imbalance in albumin levels rapidly disappeared during therapy (no main difference at week 4, and differences not present from week 6). There was no correlation with baseline albumin levels and death within study or with relapse (from conversion back to positive cultures). In conclusion, the imbalance is thus not likely to have led to an overestimation of the treatment effect in favour of bedaquiline.

Ancillary analyses

For many subgroup parameters numbers are too low for relevant comparisons. In study C208 this concerns the HIV positives, for example. Outcome by degree of lung cavitations were consistent with the overall results.

The most interesting subgroup analysis would concern the performance of bedaquiline (versus placebo) by degree of predicted background activity. This is shown in the following table and comprises the 24 week data selection. That is an adequate time point, since the study size and number of drop out in the latter part of the study would make such an analysis less clear.

Table 17: Culture Conversion Rates at Week 24 by BR activity (C208 Stage 2, C209) – mITT

No of active agents in baseline BR	C208 Stage 2				C209	
	bedaquiline/BR		Placebo/BR		bedaquiline/BR	
	N	24-week responder (missing = failure) n (%)	N	24-week responder (missing = failure) n (%)	N	24-week responder (missing = failure) n (%)
0	-	-	-	-	14	9 (64)
1	-	-	3	2 (67)	28	18 (64)
2	13	8 (61)	8	3 (37)	36	27 (75)
3	20	17 (85)	22	14 (64)	58	51 (88)
4	17	15 (88)	13	4 (31)	21	17 (81)
5	4	3 (75)	10	8 (80)	8	7 (87)
Resistance of TB strain						
MDR HR	39	32 (82)	45	28 (62)		
Pre-XDR	15	11 (73)	12	4 (33)		
PZA res	38	28 (74)	33	16 (48)		
PZA susc	18	16 (89)	25	16 (64)		

A pronounced effect of bedaquiline as compared to placebo is more obvious considering the lower activity of the BR. For patients treated with bedaquiline, high conversion rates were obtained when the number of active agents in the BR =3; 4 or 5 active agents did not seem to increase the conversion rate.

One issue for clarification is that in the analysis above (outcome by background activity) it is stated that baseline DST concerned (INH, R, EMB, SM, PZA), ETH, OFL, KAN, and CAP, while the preferred background regimen consisted of PZA, ETH,OFL, KAN, and cycloserine/terizidone. Hence, it seemed as if susceptibilities tested for did not reflect the preferred background regimen in study C208 since the same panel of drug sensibility testing was referred to, and the BR was highly individualized in that study. This was raised during the review, and for study C208, DST was performed for 4 out of the 5 drugs included in the BR; not for cycloserine/terizidone, due to the lack of a critical concentration for the latter. For study C209, in addition susceptibility to linezolid, CFZ, amoxicillin-clavulanate and thiacetazone were tested (where the susceptibility was decided based on the literature), and a summary of the number of active drugs in the background regimen was presented, shown later.

Conversion rates in (few) patients infected with a strain susceptible to PZA were high; interesting having in mind the synergistic effects of bedaquiline and PZA seen in animals.

Other secondary end point: Clinical correlates of microbiological response

The company did, in line with guidelines and advice, present analyses of change in X-ray scores, change in weight (in responders versus non-responders). As expected, they did not note any relevant differences by treatment in study C208.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of Efficacy for trial C208

Title:A Phase II, placebo-controlled, double-blind, randomised trial to evaluate antibacterial activity, safety, and tolerability of bedaquiline in subjects with sputum smear-positive pulmonary infection with multi-drug resistant Mycobacterium tuberculosis. **Final Stage 2 Analysis**		
Study identifier	bedaquiline-C208	
Design	This is an ongoing stratified, randomised, double-blind, placebo-controlled Phase II trial, comparing bedaquiline vs placebo when added to a BR of MDR-TB therapy in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection. The trial is conducted in 2 consecutive stages: an exploratory stage (Stage 1; 8 weeks of treatment with bedaquiline) and a proof-of-efficacy stage (Stage 2; 24 weeks of treatment with bedaquiline). Subjects participating in Stage 1 were not allowed to enter Stage 2. The two stages are analysed separately. After the double-blind treatment phase, subjects continue to receive their MDR-TB treatment. They are followed for safety, tolerability, PK, and microbiological efficacy for 96 weeks after receiving their last dose of bedaquiline or placebo. The results presented below reflect the final results of Stage 2 consisting of the completed 24-week investigational treatment period and the 96-week follow-up period.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 1 week 96 weeks
Hypothesis	The primary objective of Stage 2 is to demonstrate superiority in the antibacterial activity of bedaquiline compared to placebo when added to a background regimen (BR) for 24 weeks in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.	
Treatments groups	bedaquiline	24 weeks double-blind treatment with bedaquiline in addition to a BR. bedaquiline is administered as 400 mg once daily (q.d.) for the first 2 weeks, and as 200 mg 3 times/week (t.i.w.) for the following 22 weeks. After these 24 weeks of treatment with bedaquiline subjects will continue a BR of MDR-TB therapy. 79 subjects randomised

	placebo		24 weeks double-blind treatment with placebo in addition to a BR. After these 24 weeks of treatment with placebo subjects will continue a BR of MDR-TB therapy. 81 subjects randomised
Endpoints and definitions	Primary endpoint	Time to sputum culture conversion	Time to SCC during the 24-week treatment period with bedaquiline or placebo was the primary outcome parameter for Stage 2 of trial C208 and was analysed during the primary (Week 24) efficacy analysis that was performed when all subjects had completed their 24-week treatment with bedaquiline or placebo (or had discontinued earlier). This parameter was based on the qualitative assessment of culture growth in MGIT using spot sputum samples. Sputum culture conversion was defined as having 2 consecutive negative MGIT cultures from spot sputa collected at least 25 days apart.
	Secondary endpoint	Culture conversion rates	The proportion of subjects with MGIT sputum culture conversion was determined using 2 response definitions (missing = failure, and no overruling) at Week 24, Week 36, Week 48, Week 60, Week 72 and at the last available assessment time point.
	Secondary endpoint		- Time to AFB Smear Conversion and AFB Smear Conversion Rates - Time to Positive Signal in MGIT - CFU counts - Chest X-ray
Database lock	31-JAN-2012		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	**Intent-to-treat population (ITT):** includes all randomised subjects who had at least 1 intake of double blind study medication (bedaquiline/placebo). **Modified Intent-to-treat population (mITT):** is the subset of the ITT population excluding: - Subjects whose MGIT results did not allow for primary efficacy evaluation (i.e. no evidence of culture positivity prior to first intake or no results during the first 8 weeks after first intake). - Subjects infected with a DS or XDR *M. tuberculosis* strain or subjects for whom the MDR-TB status could not be confirmed based on DST results taken prior to randomisation. For the final Stage 2 analysis, the mITT population was used for efficacy analyses at Week 24 and at the end of trial.			
Effect estimate	**Treatment group**	**bedaquiline**	**Placebo**	**p-value**

	Number of subject	66 (mITT)	66 (mITT)	
	Time to conversion during first 24 weeks	Hazard Ratio=2.44 [1.57;3.80]		<0.0001
	Proportion of conversion at Week 24 (M=F)	78.8%	57.6%	P=0.008
	Proportion of conversion at Week 24 (LOCF)	80.3%	65.2%	P=0.049
	Proportion of conversion (Last available –M=F)	62.1%	43.9%	P=0.035
	Proportion of conversion (Last available –LOCF)	78.8%	62.1%	P=0.035

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

Such studies have not yet been performed, with exception for single dose studies of low relevance.

Supportive study

Study C209 - single-armed phase 2b

This study is ongoing and recruited patients in Asia including China (36%), South Africa (34%), Eastern Europe (22%) and. South America (8%). Hence, the population is more diverse than in C208, and regions differ likely with regards to resources etc.

It was started in April 2009, and final results (including 6 months follow-up post treatment) are expected to be submitted soon after granting of the Marketing authorisation.

The same dosing and duration of bedaquiline was given, as in study C208, stage 2 (i.e. 400 mg qd for 2 weeks, followed by 200 mg t.i.w for 22 weeks). BR was individualized according to national treatment guidelines (i.e. not a “preferred” BR regimen as in stud C208), for a total duration of 72-96 weeks (minimum 12 months after culture conversion).

In contrast to study C208, this study included patients with previous MDR-TB treatment, and also including those with XDR-TB, provided that the BR regimen would likely to add up to 3 active agents. Apart from this, inclusion/exclusion criteria resembled those of study C208.

Baseline regimen

The difference in baseline regimen in study C209, as compared to C209 stage 2, table 19. Capreomycin (similar to the aminoglycosides, but not formally that class) was used to a greater extent in C209; the type of fluoroquinolone used differed. Among “miscellaneous drugs”, clofazimine was used in some (but still few) patients in study C209.

From a safety point of view, the variety of BR drugs could be considered a strength; this is the way bedaquiline would be used in clinical practice for the treatment of MDR-TB. In the next table the background regimens of study C208 and C209 are compared. One drug, clofazimine, is of particular relevance, with regards to possible similarities in resistance mechanism and QT-prolongation effect, and the planned phase 3 study.

Table 19. Baseline Background Regimen in C208 Stage 2 and C209 – ITT

Drug Class anti-TB drug, n (%)	C208 - II All Subjects (N = 160)	C209 bedaquiline/BR (N = 233)
Aminoglycosides	153 (95.6)	167 (71.7)
Fluoroquinolones	159 (99.4)	208 (89.3)
Ciprofloxacin	34 (21.3)	9 (3.9)
Gatifloxacin	0	1 (0.4)
Levofloxacin	4 (2.5)	71 (30.5)
Moxifloxacin	2 (1.3)	1 (0.4)
Ofloxacin	119 (74.4)	122 (52.4)
Sparfloxacin	0	5 (2.1)
Macrolide	0	23 (9.9)
Miscellaneous drugs	159 (99.4)	233 (100)
Amoxicillin+clavulanic acid	1 (0.6)	23 (9.9)
Capreomycin	8 (5.0)	55 (23.6)
Clofazimine	0	13 (5.6)
Cycloserine	38 (23.8)	65 (27.9)
Ethambutol	104 (65.0)	120 (51.5)
Ethionamide	135 (84.4)	98 (42.1)
Imipenem	0	1 (0.4)
Isoniazid	0	30 (12.9)
Linezolid	0	13 (5.6)
Pas-C	12 (7.5)	108 (46.4)
Protionamide	21 (13.1)	85 (36.5)
Pyrazinamide	149 (93.1)	177 (76.0)
Rifampicin	0	1 (0.4)
Terizidone	29 (18.1)	70 (30.0)
Thiacetazone	0	3 (1.3)

As mentioned in section for study C208, the company was asked to further clarify how the number of active agents in the BR actually was counted. In addition to the panel of antibiotics tested in the C208 trial (INH, R, EMB, SM, PZA, ETH, OFL, KAN, CA) linezolid, CFZ, amoxicillin-clavulanate and thiacetazone were tested based on requests from the investigators. Below is a comparison of frequencies (subset of patients) for drugs without critical concentrations (but data also taken from the literature), upper cells, and restricted to drugs with validated concentrations, lower cells. It is obvious that the two ways of doing this yields similar results (i.e. restricted to validated concentrations or not). When comparing Agar vs REMA, isolates that would be deemed as susceptible to ≥3 of tested agents (sum of 3,4,5) the Agar method yielded a slightly higher frequency of such answer, than did REMA.

Table20 . Number of Active Drugs in BR at Baseline – Validated vs Unvalidated

Anti-TB Medication Number of Active Drugs	BDQ/BR					
	Agar Proportion			Rema		
	n	%	% cum	n	%	% cum
Nr of Active Drugs in BR						
0	12	7.3	7.3	15	8.9	8.9
1	23	14.0	21.3	28	16.7	25.6
2	37	22.6	43.9	48	28.6	54.2
3	63	38.4	82.3	48	28.6	82.7
4	20	12.2	94.5	29	17.3	100
5	9	5.5	100	0	0	100
Nr of Active Drugs in BR (restricted to drugs with validated critical concentrations)						
0	14	8.5	8.5	19	11.3	11.3
1	28	17.0	25.5	31	18.5	29.8
2	36	21.8	47.3	49	29.2	58.9
3	58	35.2	82.4	48	28.6	87.5
4	21	12.7	95.2	21	12.5	100
5	8	4.8	100	0	0	100

At a time when all patients had passed week 24, and around 60% week 36, some 13% of the patients had stopped, see next table. This could be compared with 19% of patients in study C208 stage 2 stopping before week 24. Hence, this trial population had better retention rates, which may have been associated with a higher overall compliance.

Table 21. Completion/Withdrawal in C209 - ITT, last available data.

Trial Termination Type[a] Reason, n (%)	**bedaquiline/BR** **N = 233**
Completed	**0**
Ongoing	**203 (87.1)**
Discontinued	**30 (12.9)**
Adverse event	8 (3.4)
Subject ineligible to continue the trial	5 (2.1)
Subject lost to follow-up	2 (0.9)
Subject non-compliant	5 (2.1)
Subject withdrew consent	8 (3.4)
Other	2 (0.9)

Results

Time to culture conversion was 57 days in this study, slightly shorter than in study C208.

Conversion rates by week 24 were around 80%, well in line with study C208. Outcome by activity in background regimen was discussed in previous section for study C208, and the analysis is questioned, for reasons mentioned. Hence, C209 supports the efficacy of bedaquiline, and have yielded important results, for example with regards to various background, that should be evaluated not at least when designing the phase 3 study.

Table22: Culture Conversion Rates (C209) – mITT

Time Point Microbiological Status, n (%)	**bedaquiline/BR N = 205**	
	Missing = Failure	**No Overruling**
Week 24 24-week responder	163 (79.5)	167 (81.5)
Last Available Time Point[c]		
Overall responder	154 (75.1)	165 (80.5)
Overall non-responder	51 (24.9)	40 (19.5)
Failure to culture convert	*33 (16.1)*	*33 (16.1)*
Relapse	*7 (3.4)*	*7 (3.4)*
Discontinued but converted	*11 (5.4)*	

Referring back to the issue around number of active drugs in BR (validated/also non-validated data) discussed previous page, the company also presented conversion rates by number of active drugs, taking into account all tested drugs (validated/non-validated), for a subset of 164 patients available for such analysis, below. Three active agents yielded maximum effect as outline din the table below.

Table 23 : Conversion rate by number of active agents (all tested) in BR (C209, week 24)

No of active drugs	**N**	**n (%)**
0	12	7 (58.3)
1	23	14 (60.9)
2	37	28 (75.7)
3	63	56 (88.9)
4	20	17 (85.0)
5	9	(77.8)

Further analyses - with data from both study C208 + C209

It is stated (SmPC) that bedaquiline should be used in combination with at least 3 other active agents. However, available agents used in MDR TB therapy are likely not considered as equally effective. The main classes are presently the injectables and fluoroquinolones (efficacy likely higher than other available second line agents). Since the proposed indication opens for therapy also in patients with pre-XDR and XDR TB (i.e. where resistance to these agents is present), and only limited data is available for pre-XDR patients (resistance to 1 main second line agent), and hardly any data for XDR-TB patients (resistance to both main classes), the company was asked to further elaborate on whether (any) 3 active agents is a safe advice also in the case of pre-XDR and XDR-TB.

When responding to this issue, the company provided data on to what extent the background regimens available for patients in study C209 yielded active agents (>3 or ≥3) by type of resistance

status, table below. It is evident, that for patients with pre-XDR and in particular XDR-TB 3 active agents in the BR was seldom the case.

Table 24. Number of Active Drugs at Baseline by TB Infection Subtype (AGAR) - C209, mITT

n (%)	BDQ/BR		
	MDR-TB	Pre-XDR-TB	XDR-TB
Number of Active Drugs in BR (restricted to drugs with validated critical concentrations)			
<3 Active Drugs	14 (15.9)	31 (72.1)	33 (97.1)
≥3 Active Drugs	74 (84.1)	12 (27.9)	1 (2.9)

However, when looking at the 24 week conversion rates (a time point when only few patients had left the studies for non-efficacy reasons) by type of regimen (next table), high conversion rates were seen also in the case a FQ or an injectable was not active/used.

In study C209 the number of patients with advanced resistance was higher. Although numbers are low, it is to be noted that high conversion rates (around 75%) were seen also for patients with <3 active agents in the background regimen, as long as either an active injectable or FQ was part of the regimen (=Pre-XDR patients, with only 1 active BR agent in addition to the injectable/FQ).

Table 25. Week 24 conversion rates by number of active drugs in the BR (mITT, M=F)

Number of active drugs at baseline Combination of background regimens	BDQ/BR		Placebo/BR	
	Responder		Responder	
	N	n (%)	N	n (%)
Study C208, stage 2				
≥3 Drugs	41	35 (85.4)	46	27 (58.7)
FQ + Injectables + Others	34	29 (85.3)	40	24 (60.0)
FQ + Others	6	5 (83.3)	4	3 (75.0)
Injectables + Others	1	1 (100)	2	0
<3 Drugs	13	8 (61.5)	11	5 (45.5)
FQ + Injectables	3	2 (66.7)	3	2 (66.7)
FQ + Others	4	3 (75.0)	4	0
Injectables + Others	5	3 (60.0)	1	1 (100)
FQ	1	0	1	1 (100)
Study C209				
≥3 Drugs	**92**	**80 (87.0)**		
FQ + Injectables + Others	74	65 (87.8)		
FQ + Others	5	4 (80.0)		
Injectables + Others	12	11 (91.7)		
Others	1	0		
<3 Drugs	**72**	**49 (68.1)**		
FQ + Injectables	12	9 (75.0)		
FQ + Others	8	6 (75.0)		
Injectables + Others	12	9 (75.0)		
FQ	1	1 (100)		
Injectable	11	8 (72.7)		
Others	16	9 (56.3)		
None	12	7 (58.3)		

Hence, it can be concluded, that available data would justify that bedaquiline can in practice be used safely (from an efficacy perspective) with 3 other active agents, definitely as long as an active injectable or FQ is part of that BR (i.e. pre-XDR TB) - and all guidelines recommends the inclusion of those classes. For patients lacking both an active injectable and FQ, can in practice hardly ever achieve an BR combination of 3 active agents, and for these patients bedaquiline may be the only chance to still cure the infection.

Resistance development to bedaquiline, and evaluation of assay (agar vs REMA)

For determination of MIC-values against bedaquiline both **agar method** (standard in an EU setting) and Resazurin Microtiter Assay **(REMA)** were used. While Agar is the standard method, REMA will likely represent the method of choice in resource poor countries given its low cost, technical simplicity and rapid results, and was endorsed by the WHO. To be noted, manipulation of REMA-plates could generate aerosols and precautions should be given to the users.

Due the lack of critical concentration to define resistance/susceptibility for bedaquiline from start, the company focused on subjects with at least a 4-fold increase in MIC from baseline to failure (using solid media, Agar method). The number of patients (or rather isolates) where such an increase was detected is still low, and concerned mainly patients with XDR-TB failing therapy in study C209, table.

Having in mind the numbers of non-responders, for example also in the bedaquiline arm in study C208, the number of patients with resistance development to bedaquiline seems low (for example 2/14 who failed to convert/relapsed with bedaquiline in C208, stage 2), table 26 below. However, as mentioned it was clarified during the review that not all isolates from those who failed to convert/relapsed where sent for DST (but in relation to predefined time points). However, the company adequately provided the reasons for such “missing samples” and will have different logistics for this in phase 3.

Table 26: Patients with ≥ 4-Fold Increase in bedaquiline MIC During Investigational Treatment – mITT

Trial Subject ID	Wk for time point	bedaquiline MIC (agar) (µg/mL)		TB Type at Baseline	N° of Active Drugs in BL BR	Overall Outcome	Time of First Culture Conversion
		BL	Time Point				
C208 I							
208-3004	8	0.06	0.24	$MDR_{H\&R}$-TB	2	relapse	Week 18
C208 II							
208-4042	8	0.03	0.12	pre-XDR-TB	2	responder	Week 7
208-4465	24	0.06	0.24	pre-XDR-TB	3	failure to convert	-
C209							
209-0038	24	0.06	> 0.48	pre-XDR-TB	2	failure to convert	-
209-0050	24	0.06	0.48	pre-XDR-TB	2	failure to convert	-
209-0070	24	0.015	0.06	$MDR_{H\&R}$-TB	5	responder	Week 8
209-0128	24	0.06	> 0.48	XDR-TB	0	failure to convert	-
209-0156	24	0.03	0.24	XDR-TB	0	failure to convert	-
209-0157	24	0.06	0.48	XDR-TB	0	responder	Week 24
209-0182	24	0.06	> 0.48	XDR-TB	1	failure to convert	-
209-0263	24	0.06	0.48	XDR-TB	2	relapse	Week 12
209-0267	24	0.06	> 0.48	XDR-TB	1	failure to convert	-
209-0269	24	0.06	0.48	pre-XDR-TB	3	failure to convert	-

Note: As mentioned, patients with XDR-TB were not included in study C208.

Based on available data, the following provisional MIC breakpoints are proposed by the EUCAST: Epidemiological Cut-Off (ECOFF) 0.25 mg/l, Clinical Breakpoints S ≤0.25 mg/l; R > 0.25 mg/l. These breakpoints concern both AGAR and REMA methods, and are reflected in the SmPC Section 5.1. The provisional breakpoints might be revised in the future when more data are available from the STREAM study.

Resistance development to other TB Drugs (study C208, stage 2)

Data is discussed only for study C208, since this study was controlled, and the same preferred backbone was used. To compare the rate of de novo resistance to BR agents is of high clinical interest as well as to evaluate to what extent bedaquiline can protect from resistance development to the other second line agents of the regimen. (Of note, not all isolates from patients who failed therapy were sent for DST testing, but that applied for both arms).

In table 27 de novo resistance (end point vs baseline), without regard to what agents the BR contained, is shown. Paired results were available for 12 patients in the bedaquiline group and for 31 in the placebo group.

De novo resistance to at least 1 of the tested drugs had emerged in isolates from only 2/10 patients in the bedaquiline group, to be compared to in 16/31 patients in the placebo group.

These results are of main interest, and are further proof for bedaquiline showing relevant activity to MDR-TB. IT is however acknowledged that verifying effects in a population with high dropout rates and low adherence is difficult.

Table 27: Emergence of Resistance to Anti-TB Drugs in study C208 stage 2– final analysis mITT

	Agar proportion			
	bedaquiline / BR		Placebo / BR	
Drug	N	n	N	n
Any compound	12	2	31	16
Ofloxacin	10	0	27	7
Kanamycin	7	0	25	1
Capreomycin	8	1	25	1
Pyrazinamide	2	0	11	2
Ethionamide	11	0	28	2
Ethambutol	4	1	15	6
Streptomycin	2	1	5	1
PAS-C	10	0	29	1
INH (high dose)	-	-	1	1

N = number of subjects' isolates having paired data and whose isolate was susceptible at baseline for the considered drug; n = number of subjects' isolates with emerging resistance for the given drug;

Cross resistance

Analyses could not show any signs for cross resistance causing reduced susceptibility to bedaquiline. Looking the other way around, a not confirmed trend for increased MICs to clofazimine was noted in isolates with higher MICs to bedaquiline. There is currently not enough clinical data to confirm that finding, which will be studied as one aspect within the confirmatory study.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In view of study C202, the CHMP considered that the ethics of performing exploratory studies for a new agent in monotherapy (first time efficacy studies in infected humans) in such patients, who have other effective treatment options, is quite questionable. The design and conduct of the submitted studies C208 and C209 were considered satisfactory.

Efficacy data and additional analyses

Clinically relevant antimycobacterial efficacy of bedaquiline in patients with various amounts of resistance to other TB agents has been demonstrated in a phase IIb trial. Time to culture conversion as well as conversion rates were superior with bedaquiline as compared to placebo. De novo resistance to agents in the background regimen was more commonly seen in non-responders in the placebo group, than in those treated with bedaquiline. In summary, this may support the conclusion that TMC-207 when appropriately used would contribute to a higher efficacy, or make possible shorter treatment duration with maintained efficacy, when used for the treatment of TB with significant resistance to presently available agents.

Results obtained in the controlled study (C208 stage 2) are supported by the data from the un-controlled study of larger size (C209).

The vast majority of patients who entered the phase 2 studies had failed previous therapy with first line agents. To what extent they were initially infected with TB resistant to part of that first line therapy (overall cure rates well over 90%), or whether resistance developed due to first line treatment failure, is unknown.

Additional efficacy data needed in the context of a conditional MA

Phase 3 study

The company is applying for a conditional approval based on the data from phase 2b studies. Having the limited data base of phase 2b in mind, both with regards to efficacy and safety, a phase 3 study is of crucial importance to get further insights into the efficacy of bedaquiline. The need for a phase 3 study, following such an approval, has also been stressed as part of the CHMP scientific advice.

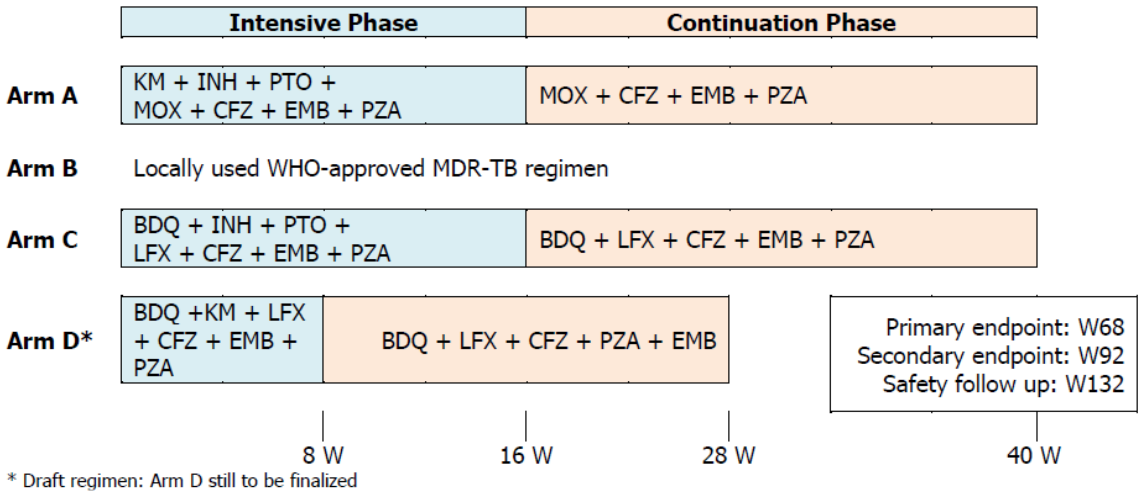
The company has proposed a confirmatory phase III study, where the mentioned Bangladesh regimen (Van Deun 2010) will be compared to two different simplified bedaquiline based regimens. This will be done as part of an already ongoing, much cited, study called STREAM.

Only patients with $MDR_{H\&R}$ TB will be included, not patients with pre-XDR or XDR TB. This is endorsed, having in mind the effectiveness already proven for bedaquiline in phase 2b.

The STREAM study regimen is based on the regimen described by Van Deun in 2010; it consists of a potent fluoroquinolone (FQ) (moxifloxacin [MOX] or levofloxacin [LFX]), clofazimine (CFZ), ethambutol (EMB) and pyrazinamide (PZA) given for nine months (40 weeks), supplemented by kanamycin (KM), isoniazid (INH) and protionamide (PTO) in the first four months (16 weeks), i.e., the intensive phase. All drugs are given daily (seven days a week) except for KM, which is given three times per week from week 12 onwards. The intensive phase can be extended from 16 to 20 or 24 weeks for patients whose AFB smear has not converted by 16 or 20 weeks respectively.

In the already ongoing stage 1 of STREAM, patients are randomized to either the study regimen (Arm A) or the locally-used WHO-approved MDR-TB regimen (Arm B), now referred to as stage 1. 400 subjects are intended to be randomized to the Bangladesh or WHO regimen in a 2:1 ratio (267 versus 133 subjects).

In stage 2 of STREAM (the confirmatory phase III study), two additional experimental arms will be included, i.e. an all oral Bangladesh-modified regimen (Arm C, N = 250 subjects) and a 28-week regimen (Arm D, N = 250 subjects). These will be compared to patients concurrently randomized to the 40 week regimen (Arm A), figure below. Randomization of stage 2 will likely be started before stage 1 randomization is completed and will be done in a 2|2|2|1(WHO) ratio until 133 subjects in the WHO arm are recruited, which is the targeted sample size for performing the stage 1 analysis. After this, randomization will continue for the remaining 3 arms in a 2/2/2 ratio.



* Draft regimen: Arm D still to be finalized

The drug doses in both regimens will be the same as those given in the 40-week control regimen (Arm A). In Arm A, weigh based MOX is used (400-800 mg daily). In arms C and D LFX is used (750-1000 mg daily). The reason for having levofloxacin rather than moxifloxacin in the bedaquiline arms pertains to the possible added risk for QT-prolongation with moxifloxacin (as compared to levofloxacin). Based on the current enrolment in stage 1, LFX is also the most commonly used fluoroquinolone in the WHO-approved MDR-TB regimen (Arm B).

The primary efficacy outcome is status at the end of follow-up (i.e. the proportion of patients with a favourable outcome) 68 weeks after randomization. Secondary efficacy endpoints concern weeks 92 and 132.

The CHMP considers that the study design is adequate and informative:

In arm C bedaquiline will replace the injectable during the intensive phase (and be part of the regimen throughout the 9 months treatment). Injectables are problematic with regards to safety and logistics; and an all oral regimen without the need for the presently available injectables would have great advantages provided that efficacy is not negatively affected.

In Arm D bedaquiline replaces PTO and INH during the intensive phase, and the treatment duration is shortened from 40 weeks to 28 weeks. PTO and high dose INH are associated with tolerability problems (e.g., hepatotoxicity concerns), and the effect of at least high dose INH (in patients with INH resistance) can hardly be considered well established. A shortened treatment duration is of considerable practical importance, and may translate into a higher real life effectiveness.

The final synopsis for the study includes for stage 2 a primary week 68 analysis, a week 92 follow-up analysis and the final week 132 analysis.
Due dates for reports to be submitted to EMA/CHMP as part of the Specific Obligation will be as follows:

- Interim IDMC analysis when half of the patients reach W68: Q1 2018
- W68 primary analysis – Clinical Study Report 3Q 2020
- W92 analysis – Clinical Study Report 1Q 2021
- W132 final analysis – Clinical Study Report Nov 2021

In addition to evaluating the efficacy (including resistance development) and safety (including the follow up on mortality for at least 2 years after stopping therapy), a number of PK issues should be addressed within the study. Overall the CHMP consider that the confirmatory phase III study adequately addresses the remaining list of outstanding issues, as part of a conditional approval, and that the time lines are acceptable.

Other planned studies

Longer term treatment in early access programmes (EAP)

Bedaquiline 100mg tablets are available under nominative Temporary Authorisation for Use (ATU) (named-patient use) granted by the ANSM (Medicine and Health Products Safety Agency, France) since March 2011.

An EAP is therefore currently on-going in France, which is the only early access program where extension of treatment >24 weeks occurred.
Preliminary information have been provided which showed that up to 14 September 2013, out of the 81 patients currently in the French program, 34 patients have been treated for > 6 months (of

which 22 patients have been treated for more than 9 months and 6 patients for more than 12 months). However, no formal assessment of these data has yet been conducted.

Paediatric trial

The planned paediatric development program has been agreed with the EMA Paediatric Committee (PDCO). This concerns a phase I/II trial in TB-infected subjects (< 18 years old), evaluating pharmacokinetics, efficacy, and safety and tolerability of bedaquiline in pulmonary MDR-TB infected children and adolescents.

2.5.4. Conclusions on the clinical efficacy

In first line therapy high cure rates are achieved with a moderate number of very efficient drugs taken for 6 months (3 drugs for 2 months, and 2 drugs for the following 4 months). Bedaquiline seems to share similar qualities to the main first line drugs, for example in terms of its sterilizing activity in various animal models.

Considering that the evidence of efficacy is based on a surrogate endpoint and that the overall data from the phase II trial are limited, further confirmation of efficacy is considered as a condition for the approval. This is considered to be adequately addressed in a coming phase 3 study that the company commits to perform as outlined above, which will provide complementary information on the efficacy of bedaquiline in regimens aimed at simplifying and shortening of treatment.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

To gather additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (“STREAM-study stage”).

In addition, the CHMP made the following recommendations for future development:

- The applicant should submit the final study report for study C209 after granting of the Marketing Authorisation
- Efavirenz is a key drug for HIV therapy, both in Europe and in particular in lower income regions globally - where MDR-TB is prevalent. It is considered a better drug than nevirapine, both for reasons of efficacy and safety. A dose recommendation is would therefore be of high value. Based on preliminary DDI data, efavirenz is presently to be avoided with bedaquiline according to the SmPC, and will not be used in the STREAM study. According to published modelling data for this combination, it may indeed be possible to dose adjust in order to maintain adequate exposure to bedaquiline (Svensson et al, AAC 2013), although the safety implications of changed metabolite exposures (M2, M3) would need to be taken into account. The applicant is encouraged to perform a DDI study of adequate duration. A study protocol for the latter is recommended to be reviewed by the CHMP prior to the start of such a study.

- At present there is only one packet size; a bottles containing 188 tablets, that is to say a full treatment for 24 weeks duration. The CHMP is aware that the applicant is currently working on revising the packaging (with collecting corresponding stability data), this is indeed necessary and should be made in a timely manner.

2.6. Clinical safety

Introduction

Complicated background regimen with potential toxicity

Cure rates in the treatment of MDR-TB are generally lower as compared to first line therapy for drug sensitive TB. Treatment is much more complex, including at least 5 second-line anti-TB drugs for an extended period of time, lasting up to 2 years. As understood from prior sections attempts are presently taken with shorter therapies, but then with an even higher number of “second line drugs” included, none of which were initially developed for the treatment of TB.

The two most important classes of second-line anti-TB drugs are the injectable drugs (i.e., capreomycin and the aminoglycosides amikacin and kanamycin) and the fluoroquinolones. In addition there are a number of miscellaneous drugs, less efficacious and in many cases with poor tolerability/safety.

Unlike the first-line drugs, the second-line drugs and combinations of these have not been formally tested in randomized controlled trials, making the safety profile of individual drugs or combinations very difficult to assess.

Toxicitites of bedaquiline - data from preclinical studies

The following target organs and systems for bedaquiline were seen in pre-clinical studies. The NOAEL margin for bedaquiline as dosed in phase 2b is around 1, while that exposure margin to verified toxicities in animals are around 4 or higher (pending on species and organ system). The same margins for M2 (which seemed to be the main driver of toxicity in animals) were many times higher.

- skeletal muscle (mouse, rat, and dog)
- heart muscle (dog),
- liver (mouse, rat, and dog),
- inflammation in lymph node tissues (mouse, rat, and dog),
- pancreas (mouse, dog)
- stomach (mouse, dog).

Effects in mice were considered species-specific as mice showed much higher concentrations of the main metabolite (M2) relative to the parent compound bedaquiline and direct dosing of the metabolite showed that the toxicity observed in mice was probably related to M2.

Based on these findings, clinical trials included specific safety monitoring for liver, pancreas, musculoskeletal system, heart muscle (including cardiac rhythm disturbances), and the gastrointestinal system.

Patient exposure

The evaluation of the clinical safety of bedaquiline for the treatment of pulmonary MDR-TB in adults is predominantly based on data from 11 phase I trials and 3 phase II trials.

The total number of subjects exposed to bedaquiline in these trials was 645 (table 28): 265 non-TB infected subjects received bedaquiline in Phase I trials and 380 TB-infected subjects received bedaquiline in Phase II trials.

Table 28: Overview of Exposure to bedaquiline

Healthy subject in the Phase I trials	265
Single dose (maximum 800 mg)	208
Multiple dose (14 days duration, 400 mg qd in the vast majority)	57
Treatment naïve patients (EBA-study, 25-400 mg, 7 days)	45
MDR-TB-infected patients	335
C208 stage 1 (8 weeks of bedaquiline therapy)	23
C208 stage 2 (24 weeks of bedaquiline therapy)	79
C209 (un-controlled study) (24 weeks of bedaquiline therapy)	233

Adverse events

The main safety data originated from the phase 2b studies. When comparing controlled (of highest interest, but low numbers) and un-controlled data the following should be noted:

Disease severity (numbers with cavitations etc.) was similar between studies, but known XDR-TB was allowed only in C209 (around 20% in ITT population).

The same preferred background regimen (BR) was recommended for all patients in study C208, and no relevant difference in BR agents were noted between the arms (bedaquiline versus placebo) here. In contrast, the BR was individualized in study C209. Hence, background regimens differed.

In study C209 85% of the patients were already on second line TB therapy at time of study entry, while study C208 only included patients naïve to such therapy, and with a minimum of 7 days wash out from first line agents.

During the investigational phase (bedaquiline or placebo) serious adverse events were more common with bedaquiline than with placebo in study C208, but not with a permanent treatment

discontinuation as a result (see table 29 below). Similar or lower numbers of AEs were seen in study C209 (despite the more diverse background regimens). This is likely because the latter patients were in the vast majority of cases already on second line treatment when entering the study, while patients in study C208 were naïve to such therapy.

Table 29. Phase IIb Trials: Summary Table of AEs During the *Investigational* Treatment Phase

	C208				C209
	bedaquiline		placebo		
	Stage 2 N = 79	Stage1+2 N = 102	Stage 2 N = 81	Stage 1+2 N = 105	N =233
Number of subjects with at least one					
AE	77 (97.5)	98 (96.1)	77 (95.1)	100 (95.2)	284 (91.0)
SAE	6 (7.6)	7 (6.9)	1 (1.2)	2 (1.9)	20 (6.4)
AE leading to death	1 (1.3)	1 (1.0)	0	0	3 (1.0)
AE of at least grade 3	22 (27.8)	28 (27.5)	19 (23.5)	24 (22.9)	66 (21.2)
AE leading to permanent stop of bedaquiline/placebo	4 (5.1)	4 (3.9)	5 (6.2)	5 (4.8)	10 (3.2)
AE leading to temporary stop of bedaquiline/placebo	2 (2.5)	2 (2.0)	3 (3.7)	3 (2.9)	6 (1.9)
AE at least possibly related to bedaquiline/placebo	55 (69.6)	69 (67.6)	56 (69.1)	68 (64.8)	130 (41.7)

bedaquiline/placebo was given for 8 weeks in stage 1, 24 weeks in stage 2 and 24 weeks in study C209.

When looking at any AE in study C208 stage 2, regardless of severity and including AEs with a frequency of 5% in either arm, arthralgia (33 vs 22%), headache (28 vs 12%), increased transaminases (5 vs 0%) and perhaps anaemia (6 vs 2.5%) were more frequently reported in the bedaquiline-arm. For other AEs no relevant difference between arms were noted.

When comparing stage 2 of C208 and study C209, AEs show the same pattern, but in a lower frequency in study C209 for reasons speculated on previous page. This may be reassuring with regards to the use of bedaquiline in combination with a variety of background agents (individualized in study C209).

Table 30. C208 Stage 2 and C209, AEs in > 10.0% (any arm), investigational treatment phase.

	C208-Stage 2		C209
SOC Preferred Term, n (%)	**bedaquiline (79)**	**Placebo (81)**	**bedaquiline (233)**
Any AE	***77 (97.5)***	***77 (95.1)***	***207 (88.8)***
Gastrointestinal disorders	**50 (63.3)**	**50 (61.7)**	**72 (30.9)**
Nausea	30 (38.0)	26 (32.1)	25 (10.7)
Vomiting	20 (25.3)	21 (25.9)	20 (8.6)
Gastritis	6 (7.6)	13 (16.0)	9 (3.9)
Diarrhoea	3 (3.8)	11 (13.6)	18 (7.7)
Abdominal pain upper	9 (11.4)	7 (8.6)	3 (1.3)
Metabolism / nutrition disorders	**30 (38.0)**	**31 (38.3)**	**56 (24.0)**
Hyperuricaemia	19 (24.1)	26 (32.1)	32 (13.7)
Decreased appetite	8 (10.1)	3 (3.7)	9 (3.9)
Musculoskeletal / connective tissue disorders	**35 (44.3)**	**32 (39.5)**	**56 (24.0)**
Arthralgia	26 (32.9)	18 (22.2)	27 (11.6)
Investigations	**17 (21.5)**	**17 (21.0)**	**58 (24.9)**
Nervous system disorders	**32 (40.5)**	**21 (25.9)**	**42 (18.0)**
Headache	22 (27.8)	10 (12.3)	20 (8.6)
Dizziness	10 (12.7)	10 (12.3)	10 (4.3)
General disorders	**23 (29.1)**	**23 (28.4)**	**41 (17.6)**
Chest pain	9 (11.4)	6 (7.4)	10 (4.3)
Infections and infestations	**25 (31.6)**	**28 (34.6)**	**44 (18.9)**
Respiratory, thoracic, mediastinal disorders	**25 (31.6)**	**23 (28.4)**	**29 (12.4)**
Haemoptysis	14 (17.7)	9 (11.1)	11 (4.7)
Ear and labyrinth disorders	**24 (30.4)**	**26 (32.1)**	**32 (13.7)**
Deafness unilateral	9 (11.4)	6 (7.4)	0
Tinnitus	2 (2.5)	10 (12.3)	13 (5.6)
Skin and subcutaneous tissue disorders	**19 (24.1)**	**21 (25.9)**	**45 (19.3)**
Pruritus	10 (12.7)	11 (13.6)	14 (6.0)
Psychiatric disorders	**15 (19.0)**	**11 (13.6)**	**24 (10.3)**
Insomnia	11 (13.9)	9 (11.1)	13 (5.6)
Eye disorders	**10 (12.7)**	**14 (17.3)**	**26 (11.2)**
Blood and lymphatic system disorders	**8 (10.1)**	**4 (4.9)**	**13 (5.6)**

Serious adverse event / deaths / other significant events

Serious adverse events

Serious adverse events possibly related to drug toxicity were uncommon, and without any major findings when comparing bedaquiline and placebo, table next page. There was no obvious imbalance between bedaquiline and placebo in the frequency of SAEs. A number of SAEs reported are likely unrelated to therapy, for example thoracic disorders and infections.

Table 31. Pooled Phase IIb Trials: SAEs Reported During the Investigational Treatment Phase

	Controlled				Controlled + Uncontrolled	
	bedaquiline		Placebo		bedaquiline	
	24 Weeks N = 79	Any N = 102	24 Weeks N = 81	Any N = 105	24 Weeks N = 312	Any N = 335
Any SAE	***6 (7.6)***	***7 (6.9)***	***1 (1.2)***	***2 (1.9)***	***20 (6.4)***	***21 (6.3)***
Respiratory, thoracic and mediastinal disorders	**2 (2.5)**	**2 (2.0)**	**0**	**1 (1.0)**	**6 (1.9)**	**6 (1.8)**
Bronchiectasis	1 (1.3)	1 (1.0)	0	0	1 (0.3)	1 (0.3)
Haemoptysis	1 (1.3)	1 (1.0)	0	0	1 (0.3)	1 (0.3)
Chronic obstructive pulmonary disease	0	0	0	0	1 (0.3)	1 (0.3)
Dyspnoea	0	0	0	0	1 (0.3)	1 (0.3)
Hydropneumothorax	0	0	0	0	1 (0.3)	1 (0.3)
Pneumothorax	0	0	0	1 (1.0)	1 (0.3)	1 (0.3)
Blood and lymphatic system	**1 (1.3)**	**1 (1.0)**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Anaemia	1 (1.3)	1 (1.0)	0	0	1 (0.3)	1 (0.3)
Ear and labyrinth disorders	**1 (1.3)**	**1 (1.0)**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Conductive deafness	1 (1.3)	1 (1.0)	0	0	1 (0.3)	1 (0.3)
Infections and infestations	**1 (1.3)**	**1 (1.0)**	**0**	**0**	**4 (1.3)**	**4 (1.2)**
Pyothorax	1 (1.3)	1 (1.0)	0	0	1 (0.3)	1 (0.3)
Lung infection	0	0	0	0	1 (0.3)	1 (0.3)
Pneumonia	0	0	0	0	1 (0.3)	1 (0.3)
TB	0	0	0	0	1 (0.3)	1 (0.3)
Psychiatric disorders	**1 (1.3)**	**1 (1.0)**	**0**	**0**	**2 (0.6)**	**2 (0.6)**
Suicidal ideation	1 (1.3)	1 (1.0)	0	0	1 (0.3)	1 (0.3)
Hallucination	0	0	0	0	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders	**0**	**1 (1.0)**	**0**	**0**	**3 (1.0)**	**4 (1.2)**
Diabetic ketoacidosis	0	1 (1.0)	0	0	0	1 (0.3)
Decreased appetite	0	0	0	0	1 (0.3)	1 (0.3)
Dehydration	0	0	0	0	1 (0.3)	1 (0.3)
Diabetes mellitus inadequate control	0	0	0	0	1 (0.3)	1 (0.3)
Hyponatraemia	0	0	0	0	1 (0.3)	1 (0.3)
Gastrointestinal disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Vomiting	0	0	0	0	1 (0.3)	1 (0.3)
Hepatobiliary disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Cholelithiasis	0	0	0	0	1 (0.3)	1 (0.3)
Investigations	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
ECG QT prolonged	0	0	0	0	1 (0.3)	1 (0.3)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Pain in extremity	0	0	0	0	1 (0.3)	1 (0.3)
Pregnancy, puerperium and perinatal conditions	**0**	**0**	**1 (1.2)**	**1 (1.0)**	**0**	**0**
Abortion spontaneous	0	0	1 (1.2)	1 (1.0)	0	0
Renal and urinary disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Renal impairment	0	0	0	0	1 (0.3)	1 (0.3)

Note. "Any" (column heading) refers to pooling of stage 1 + 2 (8 weeks and 24 weeks of test agents) and the pooling of the entire C208 + C209 (column to the far right)

Deaths in study C208

An updated report of all deaths was retrieved on 16 November 2012. This includes the final results for study C208 (both stages) plus available data for study C209. The data in table 32 and onwards refers to that report.

In study C208, there was an imbalance in the number of deaths between the bedaquiline group and the placebo group (12 vs. 4 patients) in stage 1 + 2, and for stage 2 only (pivotal study, bedaquiline vs. placebo for 24 weeks) these figures where 10 versus 2 (see table below). Apart from following patients within study C208 (and study C209), the company collected data on follow-up survival for all patients who left the phase 2b studies for reasons other than withdrawing consent. They managed to follow the majority of such patients. Hence, the figures below concern all deaths, also those in patients who had left the study.

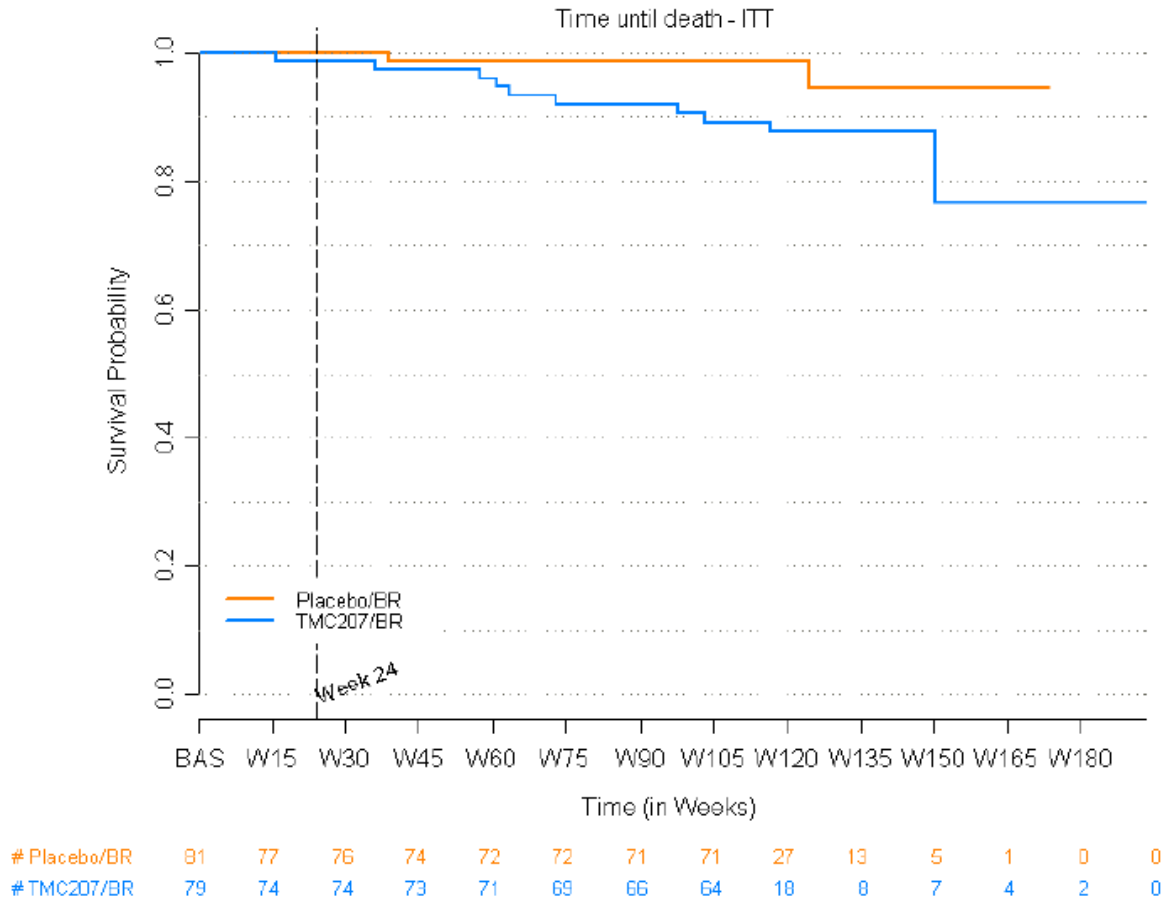
Table 32. Overall Death rate in study C208, final analysis (ITT)

MDR-TB infected subjects in Phase IIb – C208						
	bedaquiline		Placebo		Diff, %	p-value
	N	N (%)				
C208 Stage 2 - *within study*	79	6 (7.6)	81	1 (1.2)	6.4	0.062
C208 Stage 2 - in premature withdrawals		4 (5.1)		1 (1.2)	3.9	
Subtotal C208 Stage 2	79	10 (12.7)	81	2 (2.5)	10.2	0.017
C208 Stage 1 - in study	23	1 (4.3)	24	0	4.3	0.489
C208 Stage 1 - in premature withdrawals		1 (4.3)		2 (2.4)	1.9	
Subtotal C208 Stage 1	23	2 (8.7)	24	2 (8.3)	0.4	1.000
Overall deaths C208, Stage 1 + 2	**102**	**12 (11.8)**	**105**	**4 (3.8)**	**8.0**	

Time to death from last intake of bedaquiline, study C208 stage 2

The difference in death rates was not obvious within the investigational phase (i.e. during the 24 weeks of bedaquiline or placebo), but started to differ a long time after bedaquiline/placebo had been stopped (see figure 7 below).

Figure 7 Kaplan-Meier Survival Plot C208 Stage 2 – ITT



Causes of deaths in patients exposed to bedaquiline in C208, stage 2.

Deaths in patients allocated to bedaquiline in study C208 occurred with 1 exception, (patient found dead at road side, with a blood alcohol content of 3.73), in patients who had already stopped bedaquiline since very long (range 86 days to 911 days; median 329 days).

Out of the total 10 deaths, 5 were linked to worsened TB. All 5 occurred in patients with non-response to the MDR TB therapy (2 who never had converted, 3 relapsers). They occurred 281-787 days after last intake.

The remaining 5 deaths, seemingly non-TB related, where all different and without any obvious connection to the potential safety concerns of bedaquiline, (see table 33 for diagnoses). With the exception of the early case occurring 2 days after intake, mentioned above, all other cases were late (86-911 days after last intake of bedaquiline).

None of the patients who died, had been recorded to QTc of >500 ms during ECG recordings which were regularly monitored.

Table 33. Narratives on all deaths in study C208 final analyses, ITT

ID	Treatment	Sputum Converted	Cause of Death	Duration of Exposure to bedaquiline/ placebo	Days Since Last Intake of Study Medication
C208 stage 1 - patients in study					
208-3079	bedaquiline	yes	Myocardial infarction (autopsy confirmed)	168	115
C208 stage 1 - premature withdrawal					
208-3100	bedaquiline	no	TB	6	504
208-3010	Placebo	no	TB	NA	427
208-3049	Placebo	no	TB	NA	267
C208 stage 2 - patients in study					
208-4041	bedaquiline	yes	Alcohol poisoning (autopsy done, BAC 3.73)	109	**2**
208-5069	bedaquiline	yes	Hepatitis/ hepatic cirrhosis	168	86
208-5067	bedaquiline	yes	Septic shock/peritonitis	170	513
208-4399	bedaquiline	yes	Cerebrovascular Accident	168	556
208-4153	bedaquiline	relapse	TB	168	344
208-4224	bedaquiline	relapse	TB	163	281
208-4120	Placebo	no	Haemoptysis	168	105
C208 stage 2 - premature withdrawal					
208-4378	bedaquiline	relapse	Motor vehicle accident	142	911
208-4127	bedaquiline	no	TB	29	787
208-4145	bedaquiline	relapse	TB	168	262
208-4464	bedaquiline	no	TB	90	314
208-4155	Placebo	no	TB	NA	709

Hence, the numbers of deaths were higher in the bedaquiline group in this randomized study. During careful evaluation of narratives neither the pattern of deaths, nor the duration from last intake are indicative for a causal relation per se.

Although a causal relation was not likely in phase 2 (above), this issue must also be adequately followed up in the confirmatory phase III study.

Deaths in study C209

To be noted all patients have passed week 24 (where bedaquiline was stopped) in study C209 (n=233).

In the updated report (including data up to mid-July 2012), 12 deaths were reported in patients while in study, and another 4 in patients followed after study discontinuation. The pattern of deaths was similar to that described above for study C208. Hence, worsened TB dominated (10/16), and deaths typically occurred a long time after bedaquiline had been stopped (13/16 > 1 month after, and typically much longer). No death related to hepatic events was reported.

Laboratory findings

To repeat, based on pre-clinical findings, clinical trials included specific safety monitoring for liver, pancreas, musculoskeletal system, heart muscle (including cardiac rhythm disturbances), and the gastrointestinal system. Hence, these organ systems and relevant lab chemistry for related events are of particular interest.

A number of enzymes/parameters related to the specific safety issues mentioned above were followed. For common blood chemistry, and the specifically monitored tests, relevant differences (bedaquiline versus placebo) were seen only for liver enzymes, table 34

Table 34. Treatment-emergent worst toxicity for liver parameters in phase 2b.

	Investigational Treatment Phase		
	Controlled Trials		**Controlled + Uncontrolled Trials**
Laboratory parameter, Abnormality, n (%)	**bedaquiline**	**Placebo**	**bedaquiline**
	24 Weeks	**24 Weeks**	**24 Weeks**
ALT increased,	**78**	**80**	**307**
Grade 3	4 (5.1)	1 (1.3)	8 (2.6)
Grade 4	1 (1.3)	0	2 (0.7)
Any Grade	19 (24.4)	6 (7.5)	45 (14.7)
ALP increased, N	**78**	**80**	**307**
Grade 3	2 (2.6)	0	2 (0.7)
Any Grade	10 (12.8)	6 (7.5)	12 (3.9)
AST increased, N	**78**	**80**	**307**
Grade 3	3 (3.8)	0	9 (2.9)
Grade 4	4 (5.1)	0	6 (2.0)
Any Grade	39 (50.0)	31 (38.8)	99 (32.2)
GGT increased, N	**78**	**80**	**307**
Grade 3	3 (3.8)	2 (2.5)	4 (1.3)
Grade 4	2 (2.6)	0	4 (1.3)
Any Grade	7 (9.0)	4 (5.0)	37 (12.1)

When plotting liver enzymes over time AST, to some extent ALT, and GGT showed modest mean increases, with a quite slow onset, which returned to baseline values after stopping therapy.

To be noted levels of bilirubin were not relevantly affected, and mean ALP values decreased slightly over time.

This slow onset, also seen for QTc changes (discussed next) might be associated to the phospholipidogenic potential of the drug.

However in summary the CHMP concluded during the procedure (mainly based on non-clinical data as discussed above) that firstly, significant phospholipidosis is unlikely to occur with the exposure seen in humans, and was not a consistent finding in animals with sign of toxicity (liver, muscle). Secondly, longer term animal data does not support an accumulation of bedaquiline or M2 in tissues,

and plasma levels in patients (C208, stage 1) was slightly lower at week 8 (200 mg thrice weekly) than at the end of the second week (400 mg daily). Finally, neither in vitro studies, nor in vivo data, nor EM studies on mice, were indicative for a mitochondrial toxicity.

While 3 patients (out of 102 patients) stopped bedaquiline due to a hepatic event in study C208 (none in the placebo group), none of the 233 patients in study C209 did so. For those who stopped bedaquiline, no linkage was found to any specific background agent (more or less identical during the investigational phase in study C208).

Any case which fulfilled the definition of HY´s law was searched for. One questionable case was found, who fullfilled the defintion. The event occured at week 24 right at the end of bedaquiline treatment period, with rapid recovery. However, the very same reaction occurred also at week 84, now with the background regimen only. The man had a heavy alcohol intake, including a history of alcohol hepatitis, and the case seems cofounded.

In summary, monitoring for liver toxicity should be continued in future studies, and during therapy with bedaquiline. This is adequately handled in the proposed labelling.

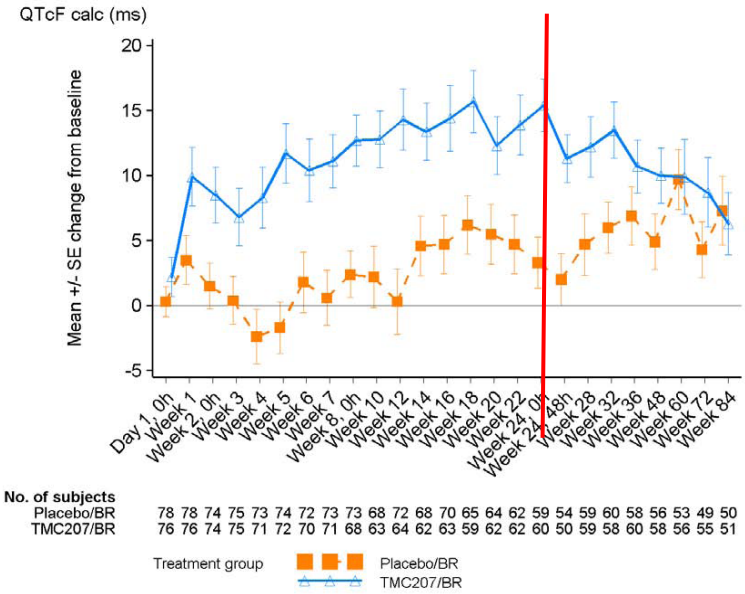
QT-findings during therapy with bedaquiline

A positive hERG assay was seen in non-clinical studies, and QT prolongation was noted in a 6-month study in dogs using a high dose of bedaquiline. In contrast, a thorough QT study using a single dose of 800 mg was negative.

In study C208 ECGs were followed at pre-specified time points. It was obvious that QTc-intervals increased significantly in the bedaquiline-group (versus placebo). In line with changes in liver enzymes there was a slow and gradual onset, maximum at around week 18, and stable until week 24 (here bedaquiline was stopped). The largest mean increase in QTcF was 15.7 ms in the bedaquiline group (at Week 18), versus 6.2 ms in the placebo group (at Week 18).

1 patient in the bedaquiline group showed a QTc > 500 ms (none in the placebo group).

Figure 8 Stage 2: Mean (SE) changes from reference in QTcF over time



Similar increases in QTc were seen in study C209 (around + 15 ms). Here a significant finding was seen with regards to background regimen; increases were substantially larger in patients with concomitant clofazimine (n=13) (Week 24, 31.94 ms versus 12.28 ms in patients without that drug).

Although bedaquiline does have an impact on QTc, changes as compared to placebo (background regimens very similar) are still moderate (mean difference around 10 ms at week 18, when maximum increase was achieved). Total increase, around 15 ms, is also moderate, although above the common threshold of 10 ms referred to in drug development.

To put in perspective, during methadone therapy (opioid substitution therapy) a mean increase in QTc of 34 ms was reported in one controlled study, where 6/56 (11%) had a QT-prolongation > 500 ms after longer term therapy (Andrew et al, Cardiology Journal 2009).

This issue has also been discussed in relation to the confirmatory phase III study, where clofazimine will be a part of the background regimen. In that study there will be a close monitoring of ECGs, and a DSMB will review data regularly. In the present SmPC the risk for increased QtC prolongations with this agent is stated.

Safety in special populations

Such studies have not yet been performed, with exception for single dose studies of low relevance.

Safety related to drug-drug interactions and other interactions

In all DDI studies, safety observations in the treatment phase in which the respective concomitant medication was co-administered with bedaquiline was comparable with those in the treatment phase where bedaquiline was administered alone. By SOC and preferred term, no clinically relevant differences in the incidence of AEs were observed between both treatment phases.

Discontinuation due to adverse events

AEs leading to permanent discontinuation of bedaquiline /placebo in the pooled Phase IIb trials are presented in the table below.

Table 35: Pooled Phase IIb Trials: AEs leading to permanent stop of bedaquiline /placebo during the Investigational Treatment phase

	Controlled Trials				Controlled + Uncontrolled Trials	
	TMC207		Placebo		TMC207	
SOC Preferred term, n (%)	24 Weeks N = 79	Any N = 102	24 Weeks N = 81	Any N = 105	24 Weeks N = 312	Any N = 335
Any AE leading to permanent stop of TMC207/placebo	*4 (5.1)*	*4 (3.9)*	*5 (6.2)*	*5 (4.8)*	*10 (3.2)*	*10 (3.0)*
Investigations	**3 (3.8)**	**3 (2.9)**	**1 (1.2)**	**1 (1.0)**	**4 (1.3)**	**4 (1.2)**
Transaminases increased	3 (3.8)	3 (2.9)	0	0	3 (1.0)	3 (0.9)
Blood amylase increased	0	0	1 (1.2)	1 (1.0)	0	0
ECG QT prolonged	0	0	0	0	1 (0.3)	1 (0.3)
Lipase increased	0	0	1 (1.2)	1 (1.0)	0	0
Injury, poisoning and procedural complications	**1 (1.3)**	**1 (1.0)**	**1 (1.2)**	**1 (1.0)**	**2 (0.6)**	**2 (0.6)**
Alcohol poisoning	1 (1.3)	1 (1.0)	0	0	1 (0.3)	1 (0.3)
Drug exposure during pregnancy	0	0	1 (1.2)	1 (1.0)	1 (0.3)	1 (0.3)
Gastrointestinal disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Vomiting	0	0	0	0	1 (0.3)	1 (0.3)
Infections and infestations	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Tuberculosis	0	0	0	0	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Diabetes mellitus inadequate control	0	0	0	0	1 (0.3)	1 (0.3)
Pregnancy, puerperium and perinatal conditions	**0**	**0**	**2 (2.5)**	**2 (1.9)**	**0**	**0**
Pregnancy	0	0	2 (2.5)	2 (1.9)	0	0
Psychiatric disorders	**0**	**0**	**0**	**0**	**1 (0.3)**	**1 (0.3)**
Hallucination	0	0	0	0	1 (0.3)	1 (0.3)
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (1.2)**	**1 (1.0)**	**0**	**0**
Urticaria	0	0	1 (1.2)	1 (1.0)	0	0

N = number of ITT subjects with data; n = number of ITT subjects with this observation

Of note, One subject discontinued due to lipase increased (grade 3) which is an AE of special interest for bedaquiline in the phase I studies. However, based on these limited data no specific safety signals could be detected.

In study C208, there was one discontinuation due to a fatal myocardial infarction, where highly pathological coronary artery vessels were confirmed (as detailed above).

Of note, during the first 24 weeks in C209, one grade 3 AE of ECG QT-prolongation was reported, and led to permanent discontinuation of bedaquiline, however no AEs with preferred term torsade de pointes were reported in this study.

Overall, the frequency of AEs leading to discontinuation of study drug in the Phase IIb trials was low in the controlled trials and it was slightly higher for subjects in the placebo group than for the bedaquiline group (4.8% vs. 3.9% in the Any Placebo group and Any Bedaquiline group, respectively).

It is noted that for the AEs of special interest; more patients discontinued in the Any Bedaquiline group than in the Any Placebo group due to “transaminases increased” (3 subjects - 2.9% vs. 0%, respectively). These 3 events started on Day 142, 11 and 49, respectively. For 2 of these subjects the AE hepatitis B was concurrently reported.

In the pooled controlled + uncontrolled trials, 1 subject in the Any Bedaquiline group discontinued because of ECG QT prolonged. However, for blood amylase and lipase increased there was 1.0% (in total 2 subjects) in the Any Placebo group that discontinued versus none in the Any Bedaquiline group. The number of discontinuations is low in total and no apparent trends could be observed.

Post marketing experience

No post marketing safety data was submitted during the review of this application.

2.6.1. Discussion on clinical safety

When discussing the safety profile of bedaquiline, the severity of the disease to be treated, and the safety (and suboptimal efficacy) of other second-line agents should be kept in mind.

In the study with relevance for a present approval, C208 stage 2, a higher number of deaths were seen in patients randomized to bedaquiline, (n=10), than in the placebo group (n=2). During careful evaluation of narratives neither the pattern of deaths, nor the duration from last intake are indicative for a causal relation per se, but an effect of a small size study. However, it is crucial that survival will be followed adequately in phase III, with special reference to patients leaving the study; the company is requested discuss the details on this issue. It should be noted that the reported on-study death rates in studies/cohorts on MDR TB therapy is reported to be 10-15%. In an EU cohort concerning around 1200 patients who had been treated for 24 months, this figure was 16% (reported in 2008 by the ECDC). Hence, from this perspective the death rate in the placebo arm in study C208 was low.

Serious adverse events were few, and not markedly different between bedaquiline and placebo. A slight effect on liver enzymes was noted (transaminases, GGT), with a slow and gradual onset. This did not translate into any clinical events, and no case adequately fulfilling Hy´s law has been seen so far. A moderate QT effect, with the same slow onset and without relation to exposure parameters (AUC or Cmax), was seen in phase 2b. The increase in QTc seemed to stabilize after around 18 weeks (out of total 24 weeks) of therapy.

The metabolism of bedaquiline is not fully elucidated; CYP3A is the main pathway. Lacking adequate interaction studies, inducers (potentially lowering efficacy) and inhibitors (potentially increasing

toxicity) were not allowed in phase 2b. Since TB patients also commonly are infected with HIV where inducers (NNRTIs) and inhibitors (PIs) generally would be part of the HIV therapy, this is a very important issue for the company to study further. A number of post approval measures pertaining to pharmacokinetics are therefore requested (PAMs, section 7.1), and the company is requested to perform DDI studies within the coming confirmatory study.

In summary, based on the available data, the safety issues do not preclude a positive benefit-risk. However, based on the limited number of patients studied, and some remaining uncertainties around the safety of bedaquiline, the benefit risk is presently considered positive for a more restricted indication (i.e. patients who cannot achieve a fully active MDR TB regimen for reasons of resistance or tolerability).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

In the confirmatory phase III study, QT prolongation will be monitored throughout. Follow up on mortality will be done for at least 2 years on all patients, as requested by the CHMP. After stopping therapy it is intended to have a long-term mortality follow-up.

In addition to the STREAM study, a multi-country MDR TB registry is planned for by the applicant and is reflected in the RMP. This registry will compare safety issues, some efficacy measures and non-regulatory end points in patients who receive or not bedaquiline as part of MDR-TB therapy.

2.6.2. Conclusions on the clinical safety

In summary, based on the available data, the safety issues do not preclude a positive benefit-risk, and can be handled by appropriate labeling and further follow up in future studies.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

In the confirmatory phase III study, QT prolongation will be monitored throughout. Follow-up on mortality will be done for at least 2 years on all patients, as requested by the CHMP. After stopping therapy it is intended to have a long-term mortality follow-up.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.5, the PRAC considers by consensus that the risk management system for bedaquiline indicated for use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability is acceptable.

Advice on conditions of the marketing authorisation

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The following safety concerns were identified:

Table 36. Summary of the Safety Concerns

Important identified risks	Electrocardiogram QT prolonged
Important potential risks	Severe hepatotoxicity
	Pancreatitis
	Myopathy
	Myocardial injury
	Development of drug resistance
	Off-label use, including prolonged treatment duration
	Medication error
Missing information	Long term effects of bedaquiline treatment on mortality
	Use in subjects with severe hepatic impairment
	Use in subjects with severe renal impairment
	Use in paediatric subjects
	Use in elderly
	Use during pregnancy
	Use in nursing mothers
	Use in subjects with cardiovascular risk factors
	Use in HIV coinfection
	Effects on fundic glands in humans
	Drug-drug interactions with potent inhibitors of drug metabolising enzymes and transporters

- **Pharmacovigilance plans**

Table 37. Ongoing and planned studies in the PhV development plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
STREAM The evaluation of a standardised treatment regimen of anti-tuberculosis drugs for patients with MDR-TB. Category 2	To investigate the efficacy and safety, including mortality, of the adapted 'Bangladesh' regimen and of bedaquiline in combination with the background regimen followed by a treatment-free follow-up.	Electrocardiogram QT prolonged, Severe hepatotoxicity, Pancreatitis, Myopathy, Myocardial injury, Development of drug resistance, Off-label use, including prolonged treatment duration, Long-term effects of bedaquiline treatment on mortality, Use in elderly patients, Use in HIV coinfection, Effects on fundic glands, Drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Yearly updates on study progress: aggregate reports (PSUR/DSUR) Interim IDMC analysis when half of the patients reach W68: 1Q 2018 Report W68 primary analysis: 3Q 2020 Report W92 analysis: 1Q 2021 Report W132 final analysis: November 2021
bedaquiline-0049281/ FK 10493, In vitro study on the OATP1B1 and OATP1B3 uptake and inhibition of bedaquiline and its M2 metabolite in human hepatocytes in suspension Category 3	To assess the potential of bedaquiline and M2 to inhibit OATP1B1 and OATP1B3 and to be substrates for OATP1B1 and OATP1B3.	Missing information drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Submission final report: 1Q 2014
bedaquiline-0049280/ FK 10497, In vitro study on the OCT1 uptake and inhibition of bedaquiline and its M2 metabolite in human hepatocytes in suspension Category 3	To assess the potential of bedaquiline and M2 to inhibit OCT1 and to be substrates for OCT1.	Missing information drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Submission final report: 1Q 2014
bedaquiline-005447, Transport ABC (bedaquiline and M2 as substrates of MRP2, BCRP, BSEP) Category 3	To assess whether bedaquiline and M2 are substrates for BCRP, BSEP and MRP2.	Missing information drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Submission final report: 1Q 2014

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
bedaquiline0054807/ FK 10542, CYP2C8 and CYP2C9 inhibition by bedaquiline (microsomes) Category 3	To assess the potential of bedaquiline to inhibit the enzymes CYP2C8 and CYP2C9.	Missing information drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Submission final report: 1Q 2014
bedaquiline-0055364, In vitro study on the BCRP and OAT1 inhibition of bedaquiline and its M2 metabolite Category 3	To assess the potential of bedaquiline and M2 to inhibit BCRP and OAT1.	Missing information drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Submission final report: 1Q 2014
bedaquiline-0055365, In vitro study on the OAT3 inhibition of bedaquiline and its M2 metabolite Category 3	To assess the potential of bedaquiline and M2 to inhibit OAT3	Missing information drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Submission final report: 1Q 2014
bedaquiline-0055366, In vitro study on the OCT2,MATE1 and MATE2 inhibition of bedaquiline and its M2 metabolite Category 3	To assess the potential of bedaquiline and M2 to inhibit OCT2, MATE1 and MATE2.	Missing information drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters.	Planned	Submission final report: 1Q 2014
Preclinical experiments to explore mechanisms of resistance other than that known to date. Category 3	Explore mechanisms of resistance other than that known to date.	Development of drug resistance	Planned	Submission final report: 1Q 2015
TBC3001 (EAP) Early access of bedaquiline in combination with other anti- TB drugs in subjects with XDR or pre-XDR pulmonary TB. Category 3	Provide access to bedaquiline to subjects with XDR or pre-XDR pulmonary TB.	Electrocardiogram QT prolonged, Severe hepatotoxicity, Pancreatitis, Myopathy, and Myocardial injury.	Trial started January 2012	Submission final report: 2017

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Multi-Country MDR-TB Disease Registry Category 3	A multi-country prospective multi-drug resistant tuberculosis patient registry to monitor bedaquiline safety, utilization, and emergence of resistance.	Electrocardiogram QT prolonged, Severe hepatotoxicity, Pancreatitis, Myopathy, and Myocardial injury, Development of drug resistance, Off-Label use, including prolonged treatment duration, Medication error, Long-term effects of bedaquiline treatment on mortality, Use in elderly patients, Use in HIV coinfection, Effects on fundic glands, Drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters,	Planned	Interim reports: semi-annual Final study report: Q2 2020

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

Table 38. Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Electrocardiogram QT prolonged	Adequate information and guidance to help the prescriber is provided in Sections 4.2, Posology and method of administration; 4.4, Special warnings and precautions for use; 4.5, Interaction with other medicinal products and other forms of interaction; and 4.8, Undesirable effects, of the SmPC.	None
Important potential risks:		
Severe hepatotoxicity	Adequate information and guidance to help the prescriber is provided in Sections 4.2, Posology and method of administration; 4.4, Special warnings and precautions for use; and 4.8, Undesirable effects, of the SmPC.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Pancreatitis	Adequate information and guidance to help the prescriber is provided in Section 5.3, Preclinical safety data, of the SmPC.	None
Myopathy	Adequate information and guidance to help the prescriber is provided in Section 5.3, Preclinical safety data, of the SmPC.	None
Myocardial injury	Adequate information and guidance to help the prescriber is provided in Section 5.3, Preclinical safety data, of the SmPC.	None
Development of drug resistance	Adequate information and guidance to help the prescriber is provided in Sections 4.2, Posology and method of administration; and 5.1, Pharmacodynamic properties, of the SmPC.	None
Off-label use, including prolonged treatment duration	Adequate information and guidance to help the prescriber is provided in Sections 4.1, Therapeutic indications; 4.2, Posology and method of administration; and 4.4, Special warnings and precautions for use, of the SmPC.	None
Medication error	Adequate information and guidance to help the prescriber is provided in Section 4.2, Posology and method of administration, of the SmPC.	None
Missing information		
Long-term effects of bedaquiline treatment on mortality	Adequate information and guidance to help the prescriber is provided in Sections 4.1, Therapeutic indications, 4.4, Special warnings and precautions for use; and 4.8, Undesirable effects, of the SmPC.	None
Use in patients with severe hepatic impairment	Adequate information and guidance to help the prescriber is provided in Sections 4.2, Posology and method of administration; 4.4, Special warnings and precautions for use; and 4.8, Undesirable effects, of the SmPC.	None
Use in patients with severe renal impairment	Adequate information and guidance to help the prescriber is provided in Section 4.2, Posology and method of administration, of the SmPC.	None
Use in paediatric patients	Adequate information and guidance to help the prescriber is provided in Section 4.2, Posology and method of administration, of the SmPC.	None
Use in elderly patients	Adequate information and guidance to help the prescriber is provided in Section 4.2, Posology and method of administration, of the SmPC.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use during pregnancy	Adequate information and guidance to help the prescriber is provided in Section 4.6, Fertility, pregnancy and lactation, of the SmPC.	None
Use in nursing mothers	Adequate information and guidance to help the prescriber is provided in Section 4.6, Fertility, pregnancy and lactation, of the SmPC.	None
Use in patients with cardiovascular risk factors	Adequate information and guidance to help the prescriber is provided in Sections 4.2, Posology and method of administration; 4.4, Special warnings and precautions for use; 4.5, Interaction with other medicinal products and other forms of interaction; and 4.8, Undesirable effects, of the SmPC.	None
Use in HIV coinfection	Adequate information and guidance to help the prescriber is provided in Section 4.4, Special warnings and precautions for use, of the SmPC.	None
Effects on fundic glands	Adequate information and guidance to help the prescriber is provided in Section 5.3, Preclinical safety data, of the SmPC.	None
Drug-drug interactions with potent inhibitors of drug-metabolising enzymes and transporters	Adequate information and guidance to help the prescriber in Section 4.5, Interactions with other medicinal products and other forms of interaction, of the SmPC.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The PRAC considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures and that no additional risk minimisation measures will be necessary for the safe and effective use of the medicinal product.

The CHMP endorsed this advice without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted

by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The main evidence for the efficacy of bedaquiline in the treatment of *M. tuberculosis* infection derives from the C208 study, in which patients with MDR or pre-XDR TB were randomized to receive bedaquiline or placebo as add on to a background regimen including an injectable, a fluoroquinolone, and other anti-TB drugs. In this phase IIb study, the primary endpoint was time to culture conversion. This was statistically significantly shorter in patients randomized to bedaquiline (median 83 versus 125 days for placebo). Consequently, culture conversion rates at week 24 of treatment were significantly higher in the bedaquiline arm (mITT: 79% vs. 58%, respectively; p = 0.008). The inference of clinically relevant activity, increasing the efficacy of the regimen to which it was added, is supported by a significantly higher cure rate (62.1 versus 43.9%, p=0.035). Subgroup analysis showing a numerically greater increment in treatment response with bedaquiline in patients with fewer active drugs in their regimens is further supportive of the reality of the demonstrated anti-TB efficacy. Also, the proportion of patients failing therapy with bedaquiline that demonstrated de novo resistance to components of the treatment regimen was considerably lower than in the placebo group, which is further indicative of activity, and may also be clinically relevant in case of subsequent rescue therapy. Further complementary evidence of efficacy is provided by an ongoing single arm study also including patients with XDR-TB (C209). These clinical data together with the high antimycobacterial efficacy observed in several relevant animal models, indicate that bedaquiline would likely provide clinically relevant activity as part of multi-drug regimens against TB.

Bedaquiline is a new active agent of a unique class, and the activity is specific for Mycobacteria. No relevant cross resistance is seen to other available agents. This is of major importance in a situation of a great need for new active therapies to improve outcomes of MDR TB therapies.

Uncertainty in the knowledge about the beneficial effects.

The low number of patients hitherto studied, and for whom outcomes are available, makes estimates of the precise magnitude of the added effect of bedaquiline uncertain.

Also, the optimal use of bedaquiline for the treatment of drug resistant pulmonary TB (the indication sought), has not yet been characterized. Animal models indicate that bedaquiline is a sterilizing agent that might significantly reduce the number of drugs and/or treatment duration required. An appropriately designed phase III study is required to further define the optimal use of this agent, both with regards the number and types of agents that are needed in combination, and the optimal

treatment duration. The upcoming confirmatory phase III study with recruitment planned to start within 2014, is considered to include the adequate elements for these activities. The final protocol of the phase III study is still to be decided, and this may occur after an approval.

Bedaquiline has been studied only in a small number of MDR TB patients co-infected with HIV. This is an important TB population. The pertinent issue relating to this population is not the efficacy of bedaquiline per se, but rather adequate guidance on how to safely use bedaquiline in combination with certain antiretroviral agents that may display significant drug-drug interactions with bedaquiline. Due to the limitations of the pharmacokinetic characterization of bedaquiline, it is difficult to make reliable predictions about its full potential for clinically significant DDIs (see also below).

Patients with extra-pulmonary TB, including TB meningitis, have not been studied. However, the indication presently sought by the applicant only includes the indication pulmonary tuberculosis.

Risks

Unfavourable effects

Side effects with available second line agents, such as those included in the background regimens in the studies of bedaquiline, are numerous and problematic. In the placebo controlled study (with a specified background regimen) adverse events were not markedly different between arms. However there was a slow increase in mean transaminase levels over time in the bedaquiline group, with a higher frequency of patients with increase in liver enzymes was noted in patients treated with bedaquiline compared to placebo. Two patients potentially fulfilled Hy's law. However, one case was heavily confounded by alcoholism, and in the other case a reaction to recently introduced protionamide (with a well-established risk for liver toxicity) was deemed the likely causative agent. Liver enzymes are generally monitored during TB therapy, as liver toxicity is common for a number of other TB agents.

Furthermore, QTc prolongation was noted during treatment with bedaquiline, also with a slow onset of the effect, reaching a mean maximum of approximately 15 ms at week 18. One patient showed a QTc > 500 ms, and no clinical events related to QTc were reported. QTc prolongation requires monitoring and judicial consideration of benefit-risk when combining bedaquiline with other antimycobacterial drugs that are also significant prolongators of the QTc-interval.

Uncertainty in the knowledge about the unfavourable effects

In the phase II C208-study , pivotal to this application for conditional approval, there was an imbalance in mortality, with 12/102 patients randomized to bedaquiline, versus 4/105 randomised to placebo, dying during the study or during the follow-up (10 versus 2 deaths in the "pivotal study, C208 stage 2). In all but one case, the patients died 3 months to >2.5 years after discontinuing bedaquiline (median 329 days). Neither the temporal pattern nor the distribution of attributed causes of deaths within the relatively small C208 study, are supportive of a causal relation to bedaquiline therapy. This conclusion should be verified post approval in the phase III study , where

survival will be followed up to 2 years after stopping therapy, including in the patients who discontinue early.

The mortality data from study C208 highlight the fact that the safety data base for bedaquiline is limited; indeed, the company is applying for a conditional approval on the basis of phase 2b studies, where some 300 patients were exposed for bedaquiline for 24 weeks of therapy (the presently proposed treatment duration with this agent). Hence, uncommon but serious side effects may so far be unknown. Also, the safety profile for exposure beyond 24 weeks, which is to be studied in the proposed phase III trial, has not hitherto been investigated, except in a very few patients being part of the Early Access Program in France.

Presently, as stated above, there is limited knowledge about how bedaquiline and M2 (major metabolite) are eliminated. Thus, drug-interactions resulting in increased exposure may only be partially predicted. The same is true for potential genetic subpopulations with increased exposure. There is no safety data on higher doses than the recommended clinical dose. The exposure of metabolites in plasma has not been extensively investigated (as there is no mass-balance study). Thus, the relevance of the preclinical species in terms of metabolite exposure cannot be assessed, neither can, with the exception of M2, absence of major metabolites with target (or off target) pharmacological activity be concluded.

Benefit-risk balance

Present treatment of MDR or XDR-TB is complicated, including a considerable number of drugs with varying tolerability and in some cases serious safety issues. Treatment durations are long, which yields a high risk for patients not completing therapy. The mortality in patients with MDR- or XDR-TB is considerable and there is an urgent need of new agents, to increase efficacy, to reduce long term exposure to potentially toxic substances and to shorten therapy. Furthermore, drug resistant TB is a recognized public health hazard; in this respect also a decreased time to sputum culture negativity may be seen as a potentially valuable drug effect. In phase 2 bedaquiline has shown convincing and relevant activity for the treatment of MDR TB. Apart from higher cure rates, bedaquiline also provided a shield to resistance development to the other background agents, which may be of considerable clinical importance.

The benefit provided by the availability of bedaquiline for the treatment of drug-resistant tuberculosis are weighted against safety concerns and uncertainties, including QTc prolongation, potential hepatotoxicity and a higher total mortality compared to placebo in patients treated in the phase IIb study. There is no safety data on increased exposures and due to the lack of knowledge on the elimination of bedaquiline and formation and elimination of the active metabolite M2, situations with increased exposure due to drug interactions may not be predicted. In summary, there are no safety concerns that would necessarily preclude a conditional approval, provided that a number of post approval measures are fulfilled.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of SIRTURO in the treatment of pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability as part of an appropriate combination regimen is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH will evaluate additional efficacy and safety data of bedaquiline in different treatment regimen compared to a regimen that does not include bedaquiline (confirmatory phase III study) following an agreed protocol.	• Annual updates on study progress in the frame of annual renewal submissions • Interim IDMC analysis when half of the patients reach W68: 1Q 2018 • W68 primary analysis - Clinical Study Report 3Q 2020 • W92 analysis - Clinical Study Report 1Q 2021 • W132 final analysis - Clinical Study Report November 2021

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that bedaquiline fumarate is qualified as a new active substance.

Paediatric Data

No significant studies in the agreed paediatric investigation plan PIP P/55/2011 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.