Bedaquline Clinical data

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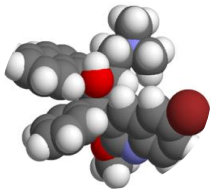
Brussels, Belgium

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson



Bedaquiline development plan

2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016

Non Clinical — Non-clinical

Phase I — 11 trials

Phase II

- C202 75 pts
- C208 Stage 1 47 MDR-TB pts
- C208 Stage 2, 160 MDR, pre-XDR-TB pts
- C209, 233 MDR, pre-XDR, XDR-TB pts

Phase III

- C210, ~600 MDR , pre-XDR-TB pts

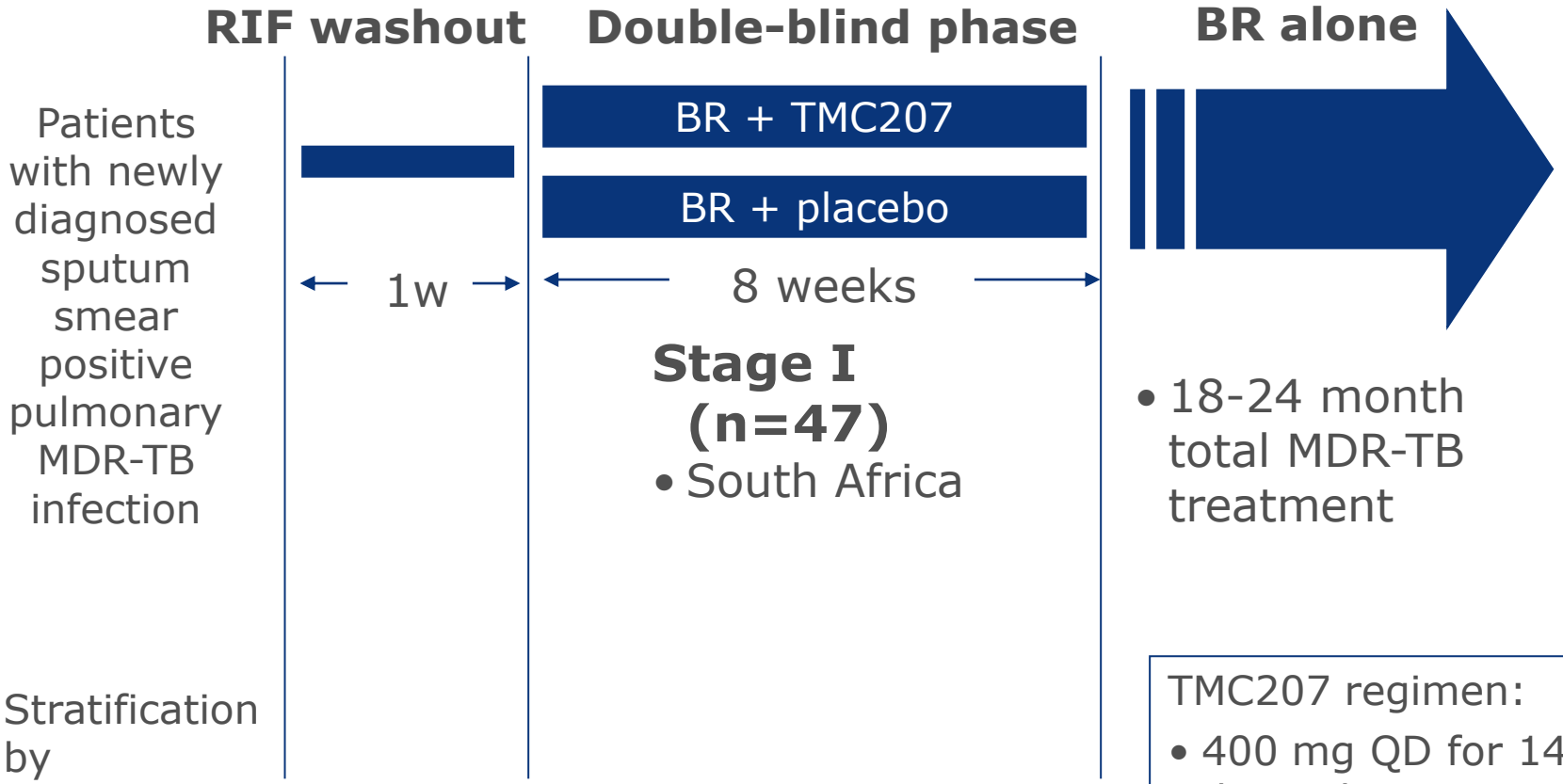
CLINICAL: Phase I studies

Key PK characteristics of TMC207

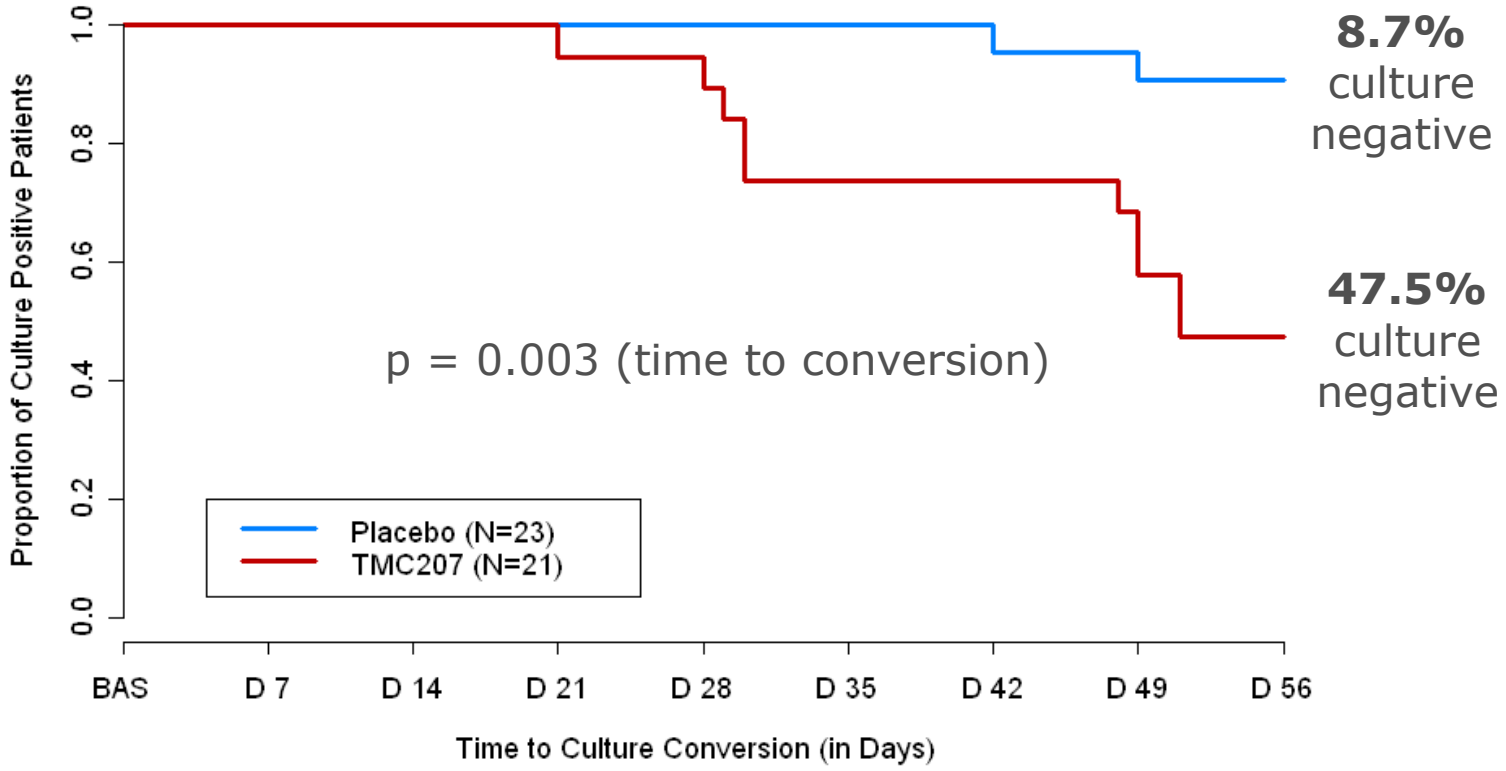
- Positive food effect
  - 2-fold increase in exposure with food versus fasted
- Dose proportional increase in exposure
  - Up to 700 mg after single dose, up to 400 mg after multiple dose
- Major metabolite is N-monodesmethyl-TMC207 (M2)
  - Exposure to M2 is about 25-30% of TMC207 upon repeated dosing
- Potential for DDIs via CYP3A
  - ↑ exposure with ketoconazole, LPV/r, ↓ exposure with rifampicin
  - No clinically relevant DDIs with a range of second-line TB drugs (pyrazinamide, ethambutol, kanamycin, ofloxacin, cycloserine)
- Slow elimination of TMC207 and M2
  - Terminal elimination half-life about 5.5 months (slow release from peripheral tissues; CAD)

CLINICAL: design and results of Phase II studies

C208 Stage 1: trial design randomized, controlled, multicenter

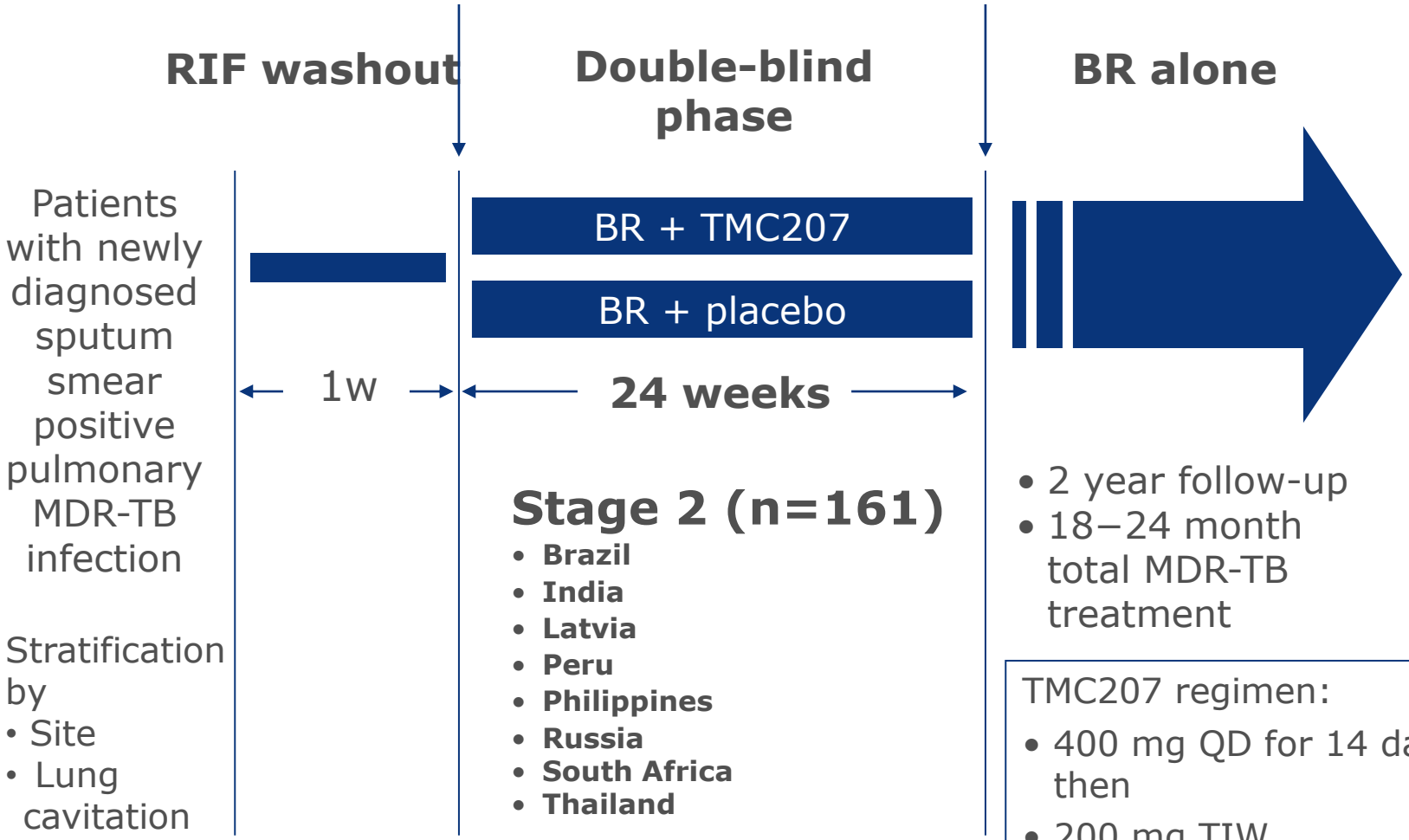


TMC207-C208 Stage 1 primary analysis at Week 8



Placebo = background regimen only
p-value from Cox proportional model adjusting for strata

C208 Stage 2: trial design randomized, controlled, multicenter



C208 Stage 2: objectives

- Demonstrate superiority of TMC207 compared to placebo at 24 weeks of treatment in the mITT population
  - Primary analysis = **time to sputum culture conversion**
    - sputum culture conversion is defined as 2 consecutive negative MGIT cultures collected at least 25 days apart and not followed by a confirmed positive culture
    - Patients who drop out during the 24weeks are considered failed, irrespective of their culture status at time of dropout
  - Secondary analysis = **culture conversion rates at 24 weeks**

C208 Stage 2: populations for analysis

Screened (282)		
	TMC207	**Placebo**
Randomized (161)	80	81
ITT (160)	79	81
Modified ITT (132)	66	66

ITT population: *Randomized patients who had at least one dose of TMC207 or placebo*

Modified ITT population (mITT) = *ITT excluding:*

- Non-MDR patients **(4 TMC207 + 8 placebo)**
- XDR patients **(3 TMC207 + 4 placebo)**
- MGIT results not evaluable **(7 TMC207 + 4 placebo)**

- In the mITT 20 patients (12 TMC207 + 8 placebo) were considered MDR patients based on local DST results

C208: background regimen

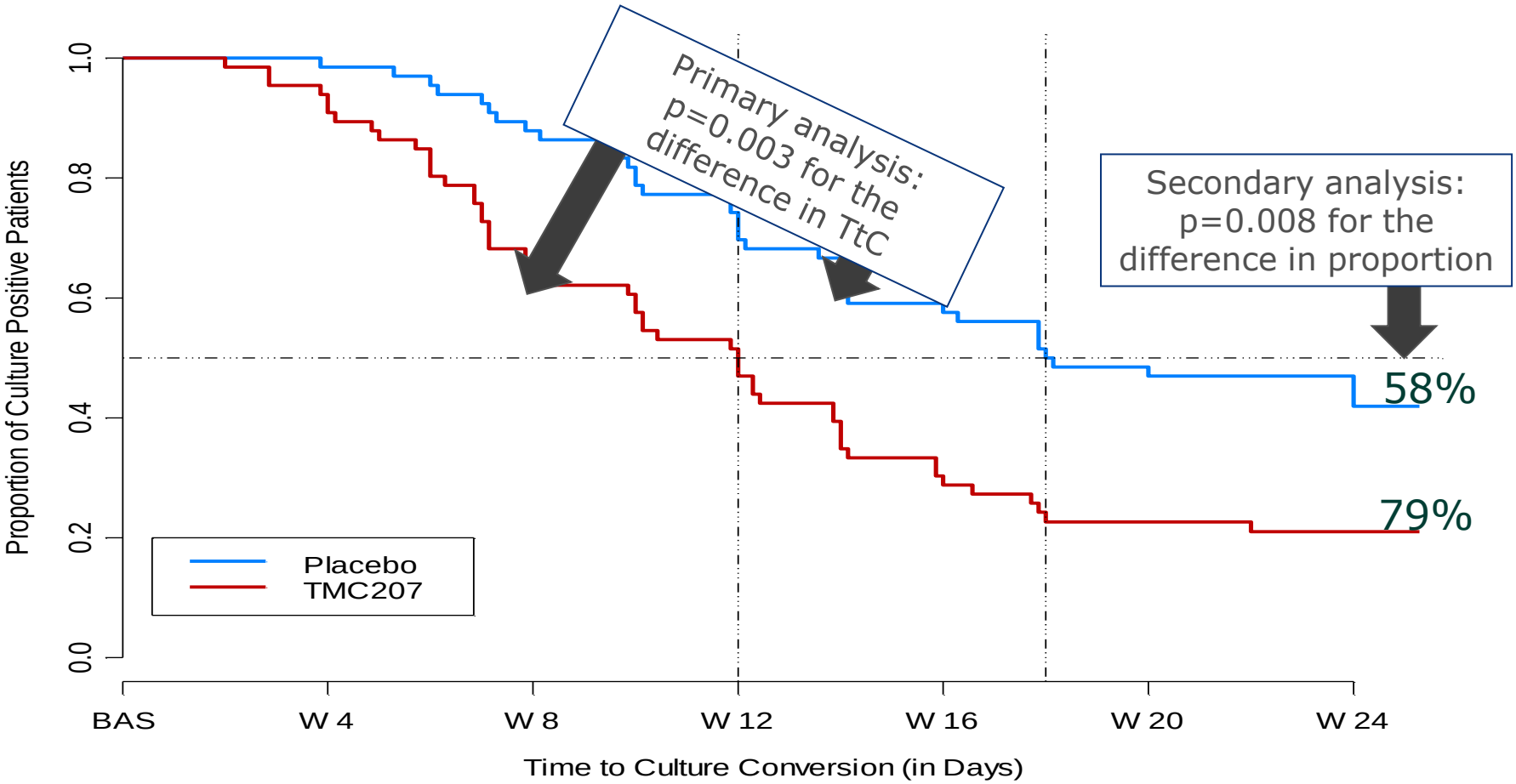
- The preferred 5-drug BR* consisted of
  - Ethionamide, pyrazinamide, ofloxacin, kanamycin and terizidone/cycloserine
- Changes in the BR occurred over time due to
  - DST results and side effects
  - Switches within the same drug class (due to shortage on site)
- Per protocol BR substitution was similar by Tx group
  - Cipro 21.5% vs 21.0%; OFL was most common FQ 74.4%
  - EMB 67.1% vs 63.0%
  - Protionamide for ETH: 10% vs 16%
  - CS 22.8% vs 24.7%
  - TRD 16.5% vs 19.8%

*BR was consistent with WHO recommended drugs at the time of study start (2006) and consistent with National TB program guidelines.

C208: efficacy analysis time points

- Four analysis time points were considered, including all data up to
  1. Week 24 (the time point of the primary analysis of the trial)
  2. Week 72 (key time point of this analysis)
  3. All available data (up to trial termination or the cut-off date, whichever occurred first)
  4. Final data (120 weeks)
- At every time point, only the data available up to that time point were included to derive and evaluate the following efficacy endpoints

C208: time to conversion (TtC) – mITT



Median time to culture conversion was 12 weeks in the TMC207 group and 18 weeks in the placebo group

p-value from Cox proportional model adjusting for strata

C208 Stage 2: safety

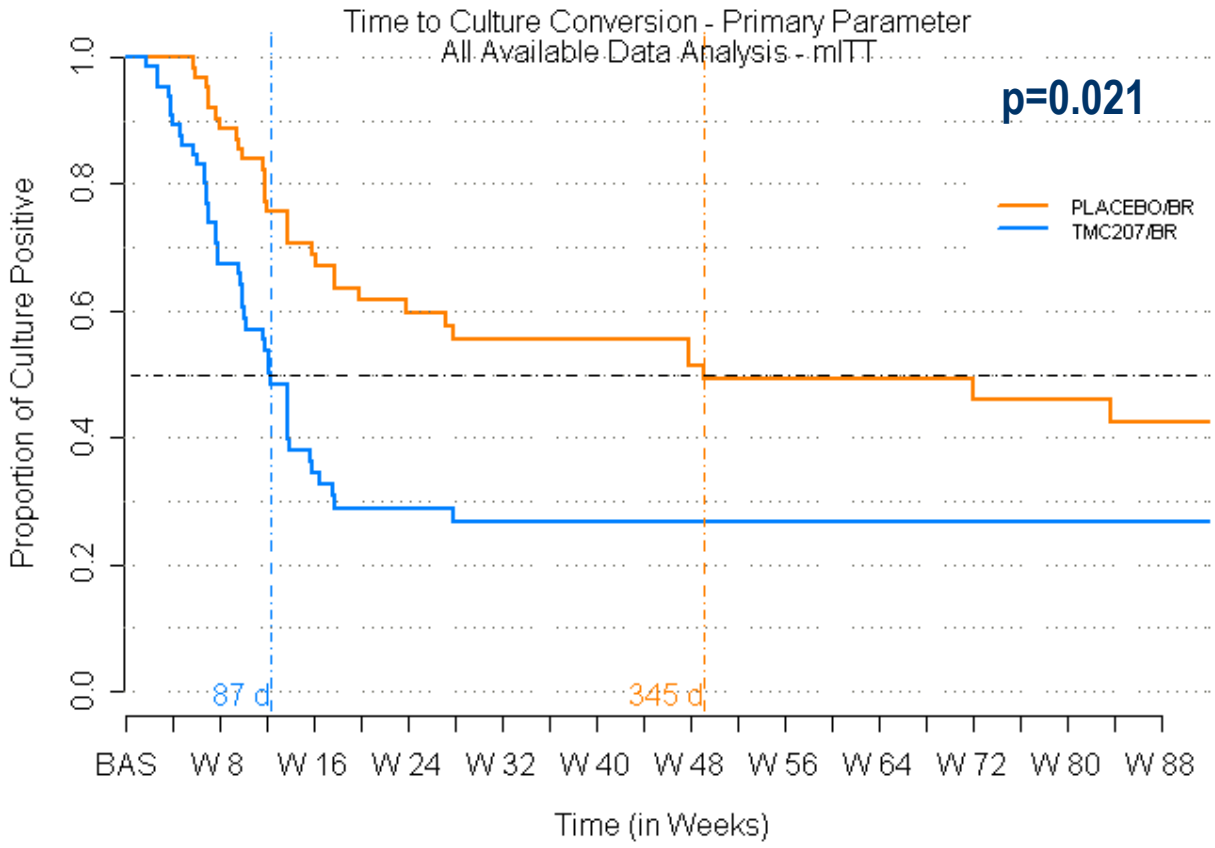
TMC207 was generally safe and well tolerated

- Incidence of adverse events were similar across treatment groups occurring in 97.5% in TMC207 and 95.1% in placebo
- Adverse events leading to permanent discontinuation of TMC207/placebo were recorded in 5.1% in the TMC207 group and 6.2% in the placebo group
  - Adverse events leading to permanent discontinuation of any BR drug were recorded in 11.4% in the TMC207 group and 12.3% in the placebo group
- One serious adverse event possibly related to TMC207, 1 possibly related to placebo
- Four deaths in TMC207 group, all considered not related; 1 death in placebo group
- Most frequently reported adverse events (>15%) during the inv. phase were nausea (38%/32%), arthralgia (33%/22%), hyperuricaemia (24%/32%), headache (28%/12%), vomiting (25%/26%), haemoptysis (18%/11%) for TMC207/placebo
- Except for transaminases there were no clinically significant differences in laboratory tests
- More QTcF prolongation was seen with TMC207 vs placebo – Approx. 10 ms difference
  - No reports of serious cardiac arrhythmias such as ventricular tachycardia or Torsade de pointes

Durability of the effect

72 week interim analysis and final analysis

C208: all available data
time to culture conversion – primary

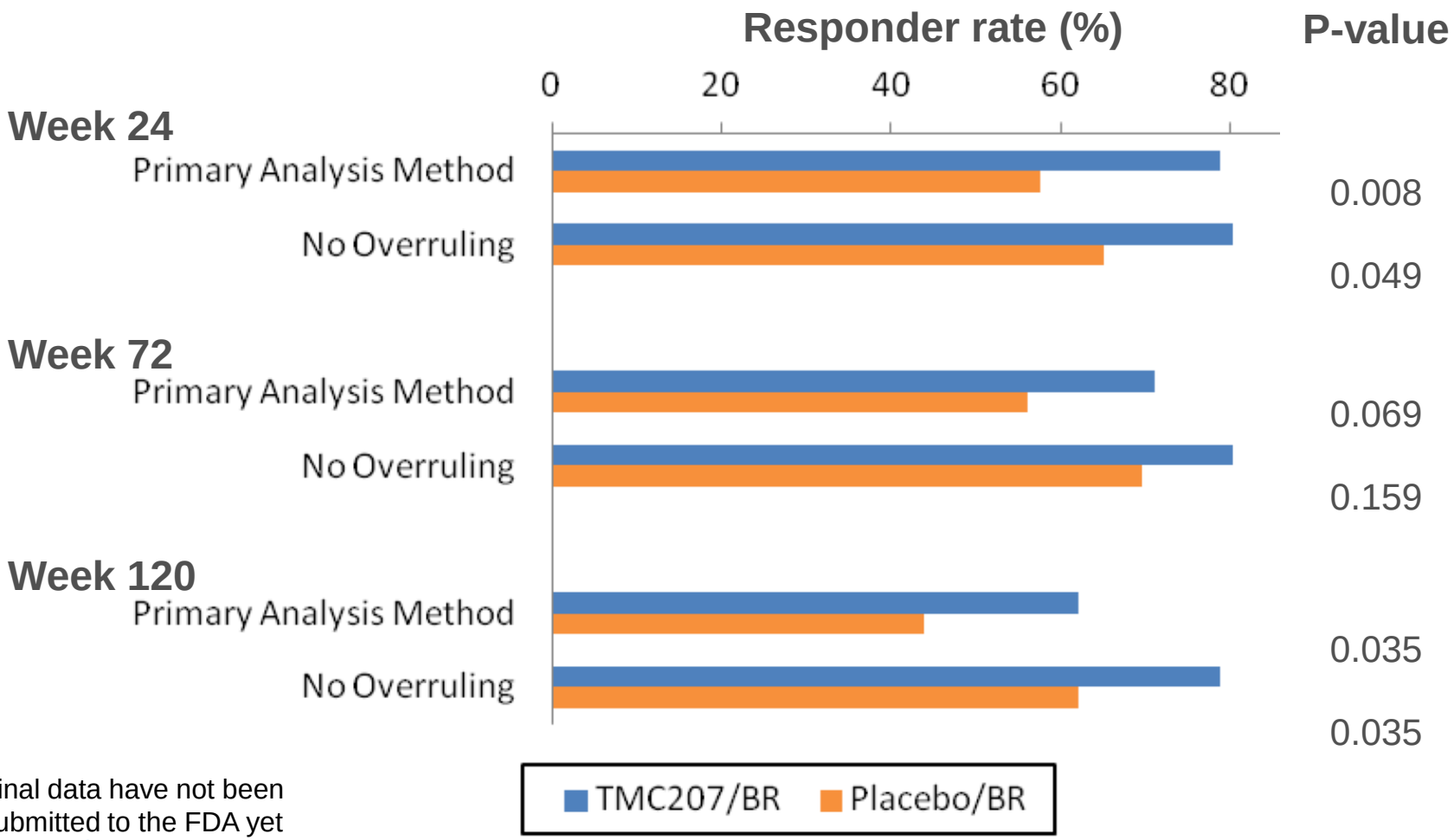


C208 Stage 2: final analysis culture conversion rates at Week 120 MGIT – mITT

Outcome at Week 120 (%)	TMC207/ BR (N=66)	Placebo/ BR (N=66)	P-value
Responder	41 (62.1)	29 (43.9)	0.035*
Non-responder	25 (37.9)	37 (56.1)	
Discontinued but converted	11 (16.7)	12 (18.2)	
Failure to convert	8 (12.1)	15 (22.7)	
Relapse	6 (9.1)	10 (15.2)	

*Based on a logistic regression model with treatment as the only covariate
Final data have been submitted to the FDA

C208 Stage 2: final analysis
culture conversion rates over time



Final data have not been submitted to the FDA yet

WHO treatment outcomes

1. Cured
2. Treatment completed
3. Died
4. Failed
5. Defaulted
6. Transferred out

Treatment Outcomes

Cured

A Category IV patient who has completed treatment according to program protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart

C208 Stage 2: outcome based on WHO definition (final data) – mITT

Cure rate n (%)	TMC207/BR (N=66)	Placebo/BR (N=66)	
Treatment success	38 (57.6)	21 (31.8)	p*=0.003
Treatment failure	5 (7.6)	20 (30.3)	
Death	6 (9.1)	1 (1.5)	
Transfer out/default	17 (25.8)	24 (34.8)	

p-value is based on logistic model with treatment is the only covariate
Final data have not been submitted to the FDA yet

Review of mortality

C208 Stage 2: summary of deaths on trial

	BDQ	Placebo
Fatal SAEs	N=6/79	N=1/81
Micro response	• 4 converters • 2 relapsers**	Non-converter
Reported causes of death	• TB (n=2)** • Alcohol poisoning • Hepatitis/hepatic cirrhosis* • Septic shock/peritonitis* • Cerebrovascular accident	• Hemoptysis
Duration of study drug exposure	5/6 completed full course of study drug	Completed full course
Days since last study drug intake	2–556 days (median: 313 days)	105 days
AEs of interest: QTcF prolongation/Grade 3 or 4 LFTs or liver AEs	• None with QTcF >500 ms • 2/6 with abnormal LFTs or liver AEs (complicated by alcohol abuse, indicated by * above)	None
Investigator causality	6/6 not related	Doubtfully related

C208 Stage 2: summary of deaths in premature discontinuations (survival data[1])

	BDQ	Placebo
Fatal SAEs	N=4/17	N=1/23
Micro response	• 2 non-converters • 2 relapsers	Non-converter
Reported causes of death	• TB-related illness (n=3) • Motor vehicle accident*	TB-related illness
Duration of study drug exposure	1/4 completed full course of study drug	Completed full course
Days since last study drug intake	262–911 days (median 551 days)	709 days
AEs of interest: QTcF prolongation/Grade 3 or 4 LFTs or liver AEs	• None with QTcF >500 ms • 1/4 with abnormal LFTs or liver AEs (designated with * above)	None

[1]Survival outcomes were collected every 6 months for patients who prematurely withdrew from the trial and consented to survival follow up until last patient last visit

C208 Stage 2: summary of non-TB deaths

Patient	Micro response	Cause of death[a]	Duration of exposure TMC207/ placebo (days)	Days since last study drug intake	QTcF ≥500 ms/ Grade 3 or 4 LFTs or liver AEs?	Risk factors/ prohibited con meds/comments
BDQ						
208-4041	Converter	Alcohol poisoning	109	2	-/-/-	Alcohol intoxication confirmed at autopsy; TB: cavitations
208-5069	Converter	Hepatitis/ hepatic cirrhosis	168	86	-/+/+	Alcoholic liver cirrhosis as cause of death on hospital record; TB: cavitations
208-5067	Converter	Septic shock/peritonitis	170	513	-/+/+	Heavy alcohol consumption; TB: pre-XDR; <3 active drugs in BR at BL; cavitations, met Hy's law lab criteria
208-4399	Converter	CVA	168	556	-/-/-	Hypertension (source: CIOMS)
208-4378* AE: increased transaminases	Relapse	Motor vehicle accident	142	911	-/+/+	TB: cavitations

[a]All deaths in the TMC207 group were considered not related to TMC207 by the investigator
*Patient prematurely discontinued from the study

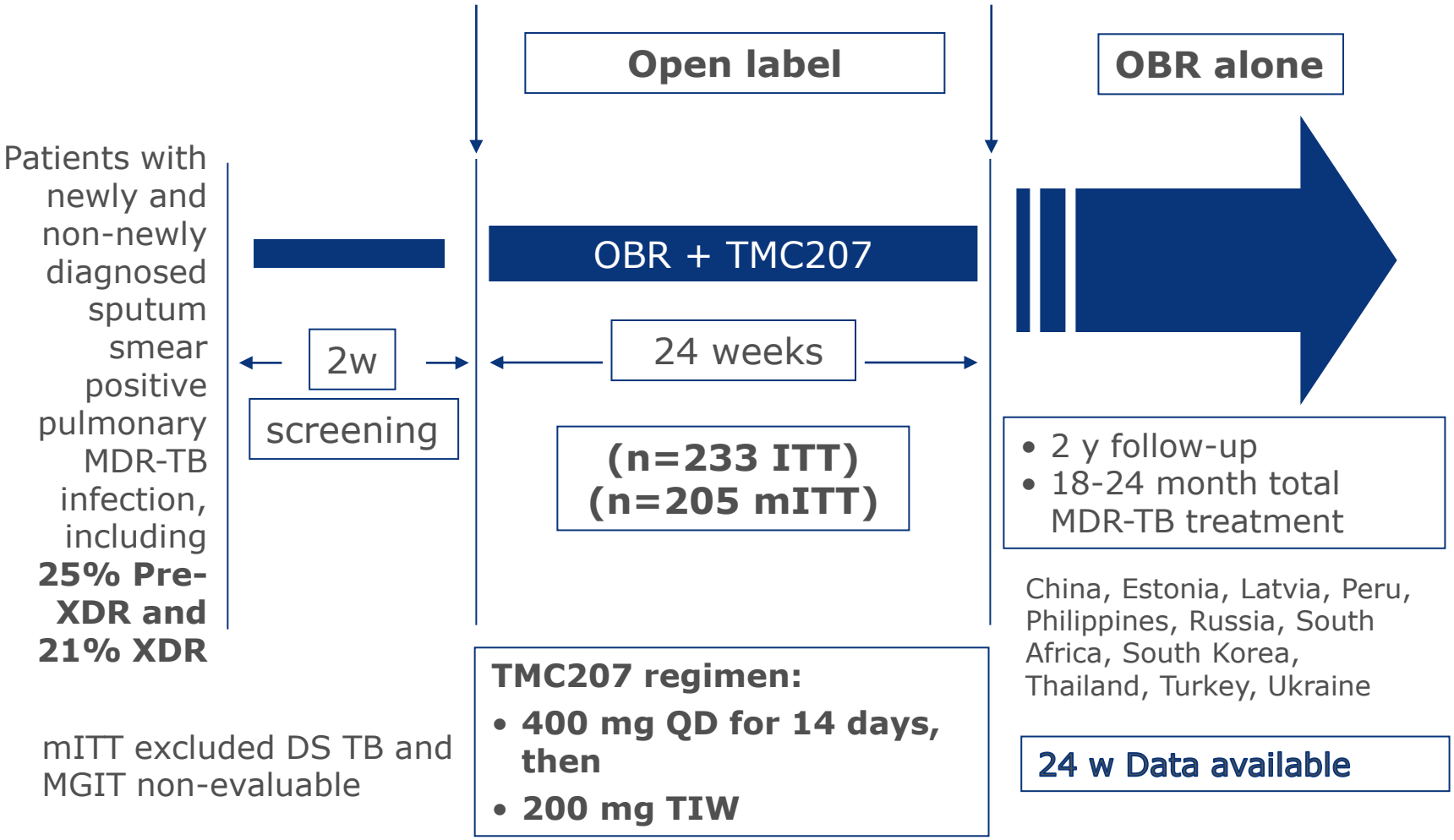
Discussion of mortality in the BDQ program

- Trial C208 Stage 2 (BDQ arm: 5 deaths TB-related, 5 due to other causes)
  - No pattern to the cause of deaths (other than TB in non-responders/relapsers)
  - Long and varied time to death after BDQ was stopped
  - No QTcF prolongation >500 ms in patients who died
  - No liver related toxicity without concomitant alcohol abuse or hepatotoxic background medications in patients who died (viral hepatitis not documented)
  - No difference in BDQ plasma exposure (AUC) between survivors and non-survivors
  - No relevant difference in baseline demographic factors and disease characteristics (including BMI, extent of resistance, HIV, alcohol abuse, liver-related adverse events, baseline hepatic parameters or diabetes mellitus) to explain the mortality data in treatment arms
- Additional Phase IIb trials
  - C208 Stage 1 trial had equal number of deaths in each treatment arm
    - 1 BDQ subject died during the trial (MI, autopsy confirmed)
    - 3 prematurely withdrawn subjects (1 BDQ + 2 Placebo) died of TB
  - No additional insights from ongoing open label C209 study (5 deaths due to TB, 11 due to other causes)
- Data reviewed by 2 external bodies (study DSMB and external panel of MDR-TB experts) and no cause was identified

Safety conclusions

- The most frequent ADRs were nausea, arthralgia, headache, vomiting, and dizziness. ADRs of at least grade 3 in severity were reported in at most 1 patient in the BDQ group, except for arthralgia and transaminases increased
- There was a low number of discontinuations due to ADRs; the most common were related to transaminase increases
- Mean QTcF intervals showed a moderate increase of 10 to 15 ms over the 24-week treatment period with BDQ and values decreased after the end of BDQ treatment
  - Our analysis does not suggest QT prolongation contributed to the deaths
- Increased hepatic transaminases were observed
  - No severe cases of liver toxicity were attributed to bedaquiline by the investigators
  - Two deaths had hepatic injury complicated by alcohol related complications

C209 open label study: trial design



C209: background regimen

- The majority of patients were on a background regimen at baseline consisting of
  - Fluoroquinolones (89%)
  - Ethionamide/Protionamide (79%)
  - Pyrazinamide (76%)
  - Aminoglycosides (72%)
  - Cycloserine/Terizidone (58%)
  - Ethambutol (52%)
- A large number of other miscellaneous anti-TB drugs were used
- Changes in the background regimen occurred over time due to
  - DST results
  - Side effects
  - Switches within the same drug class (due to shortage on site)

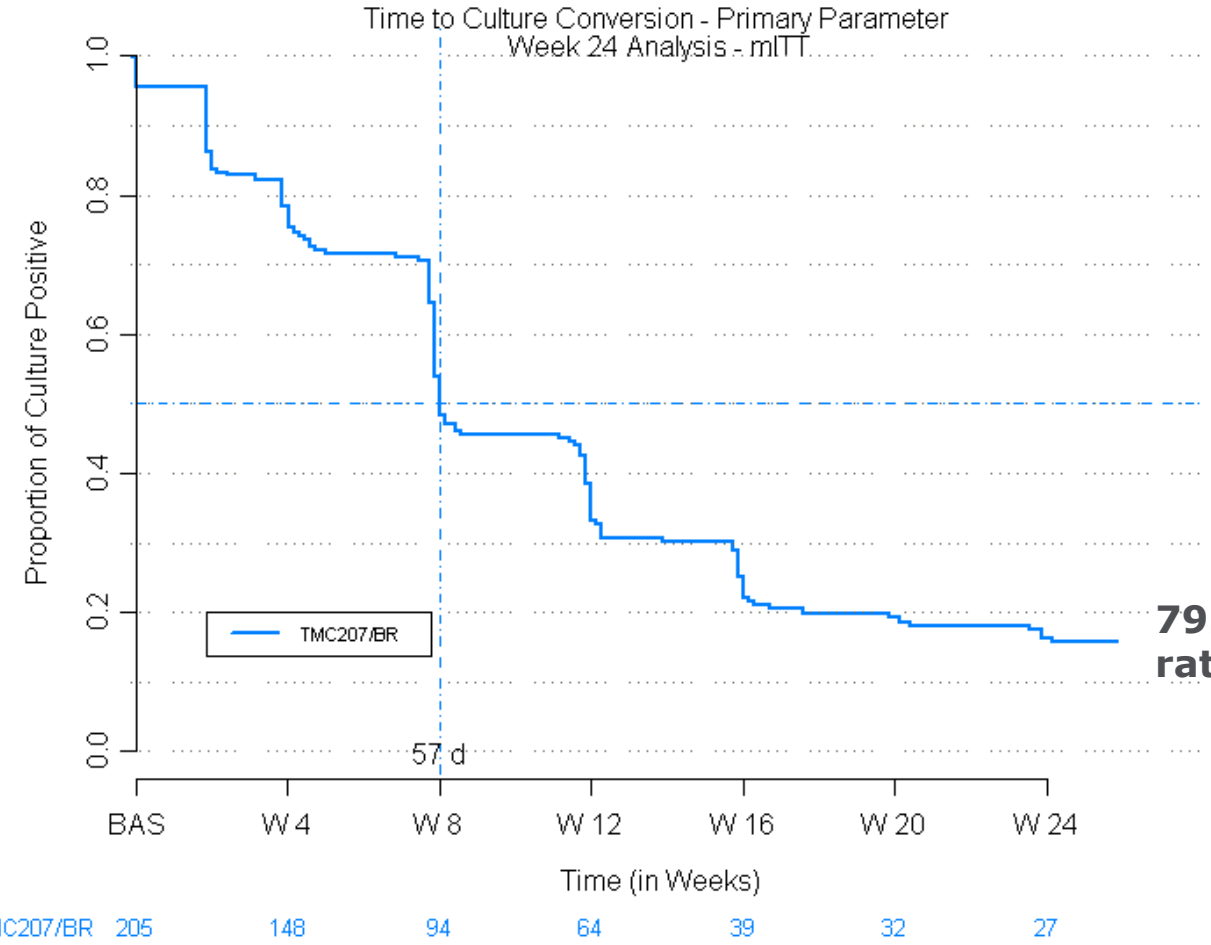
*Approx. 86% of the MDR TB patients were already on TB treatment with a median duration of 36 days prior to baseline

C209: safety

TMC207 was generally safe and well tolerated

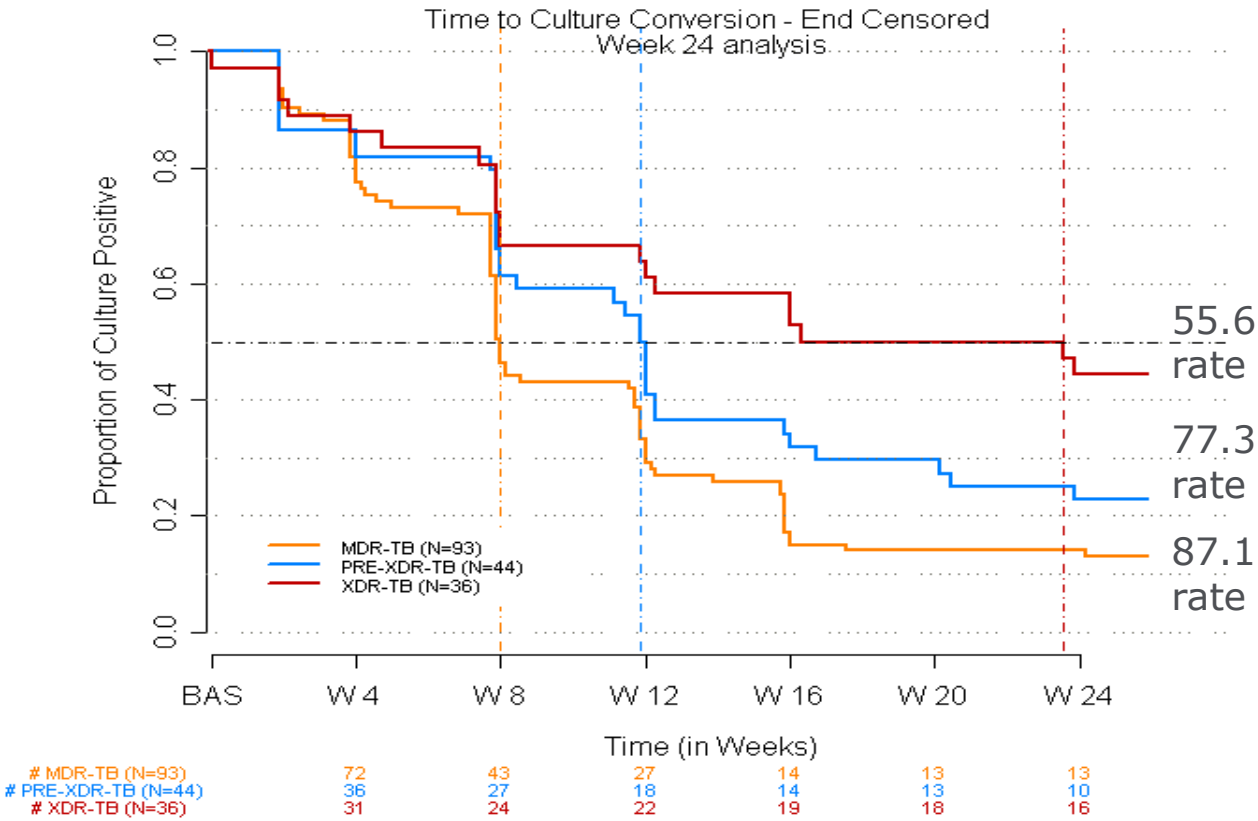
- 88.8% of patients reported an adverse event during the investigational treatment phase
- 3% of the patients stopped TMC207 prematurely due to an AE
  - 22% of the patients stopped a background TB drug due to an AE
- 6% of patients reported a SAE during the investigational treatment phase, only 1 was considered related (ECG QT prolonged)
- 5 patients died, of which 1 (renal impairment) was considered doubtfully related to TMC207 and 4 not related
- Most frequently reported adverse events (>10%) during the investigational phase were: nausea (11%), arthralgia (12%) and hyperuricaemia (14%)
- Clinically significant laboratory changes were infrequent, except for transaminases increased
- QTcF prolongation seen – with mean changes from baseline ~10 ms by week 2, trend towards increase within the first 24 weeks and decrease thereafter
  - Co-administration with clofazimine increases the mean change from baseline to ~ 30 ms
  - There were no reports of serious cardiac arrhythmias such as ventricular tachycardia or Torsade de pointes

C209: conversion rates (MGIT)
Week 24 analysis – mITT



79.5% response rate

C209: time to conversion by subgroup (1)



The intersection of horizontal dotted line and each treatment arm represents the median time to sputum conversion

Conclusions from Study C209 at 24 w

- Addition of TMC207 to an individualized MDR-TB regimen
  - Was generally safe and well-tolerated
    - Co-administration with clofazimine increases the mean change from baseline to ~ 30 ms
    - There were no reports of serious cardiac arrhythmias such as ventricular tachycardia or Torsade de pointes
  - Resulted in a 79.5% culture conversion rate at Week 24
- Responder rates were higher for
  - Patients with no cavitations (p* = 0.0157)
  - Patients with lower extent of resistance (p* = 0.0006)
  - Patients on 3 or more active drugs in their BR (p* = 0.0376)

*Cox proportional hazards model

Culture Conversion Rates: Week 24 and Endpoint

TEFCR01I: Culture Conversion Rates; mITT

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

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WHO Definition of Cure

TEFCR08I: WHO Definition of Cure; mITT

	Treatment group
	TMC207/BR
Analysis Set: Number of Subjects	205
Cure	125 (61.0%)
Death	14 (6.8%)
Transfer out/default	31 (15.1%)
Treatment completed	3 (1.5%)
Treatment failure	32 (15.6%)

;#Deaths shown are those which occurred up to and including the week 120 analysis window.;
#

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BACKUPS

Clinical data

EMA training event September 2013

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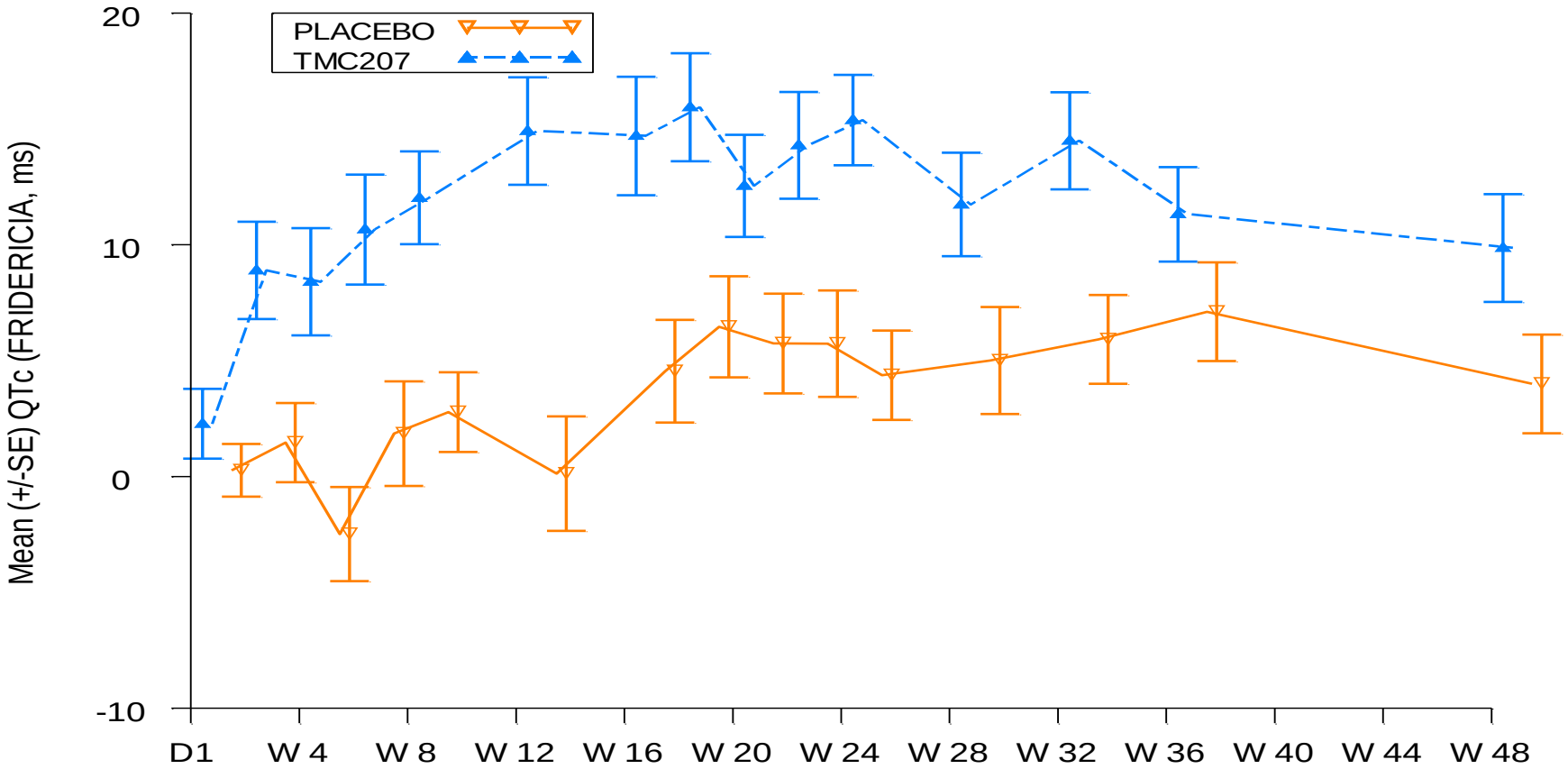
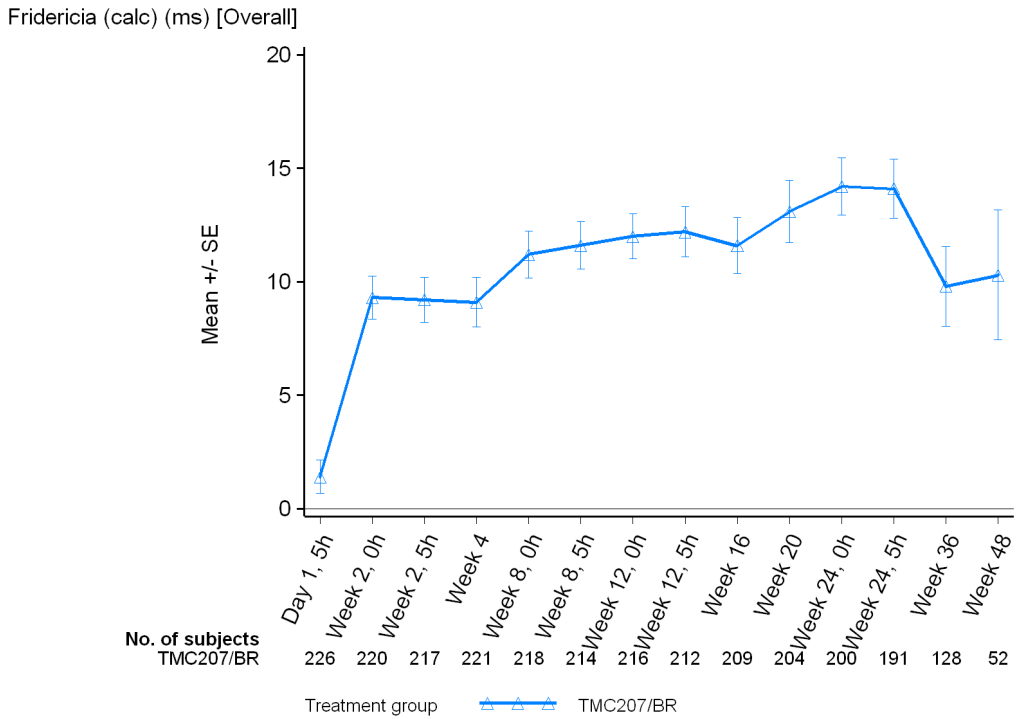
C208: QTcF changes from ref – ITT



PLACEBO	79	78	75	74	76	73	71	67	69	64	63	61	61	61		46
TMC207	78	76	73	72	73	67	65	61	64	64	63	62	62	63		48

C209: ECG: QTcF(calc) changes over time



QTcF prolongation was observed, with mean changes from baseline ~10ms by Week 2, with a trend towards increase within the first 24 weeks during TMC207 dosing followed by a trend to decrease after dosing. There have been no reports of serious cardiac arrhythmias such as ventricular tachycardia or Torsade de pointes

Mean Change in QTcF over Time