TMC207

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TMC207 (R207910): Diarylquinoline- a New Class of TB Drug

Novel MoA: selectively active against Mycobacteria; inhibits Mycobacterial ATP synthase

Active against multi-drug resistant strains

Metabolized by CYP3A4

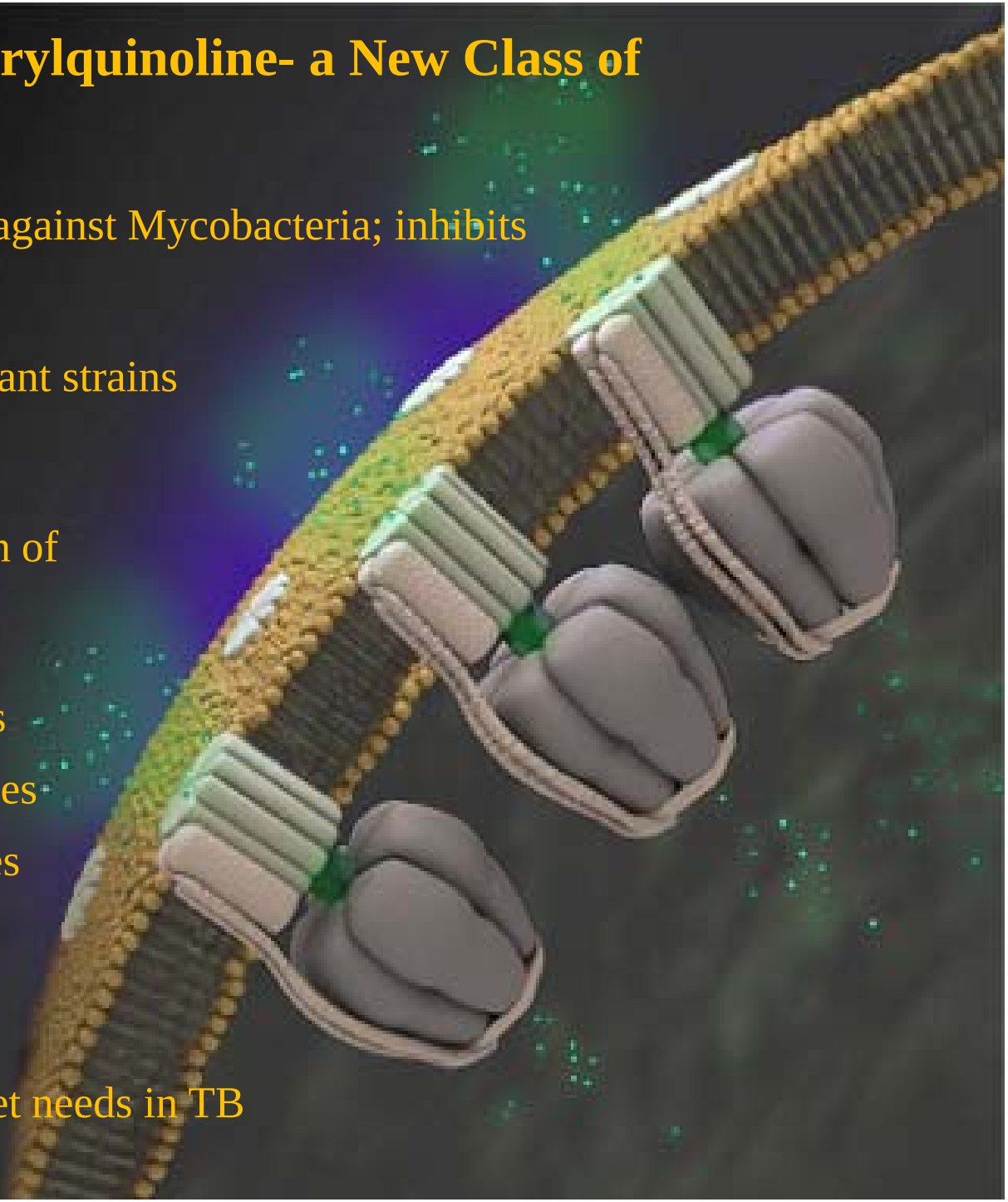
- No inhibition or induction of CYP3A4 in vitro

Potent activity in mouse models

- Early bactericidal properties
- Late bactericidal properties

Safe and well-tolerated in healthy volunteers

Potential to address major unmet needs in TB



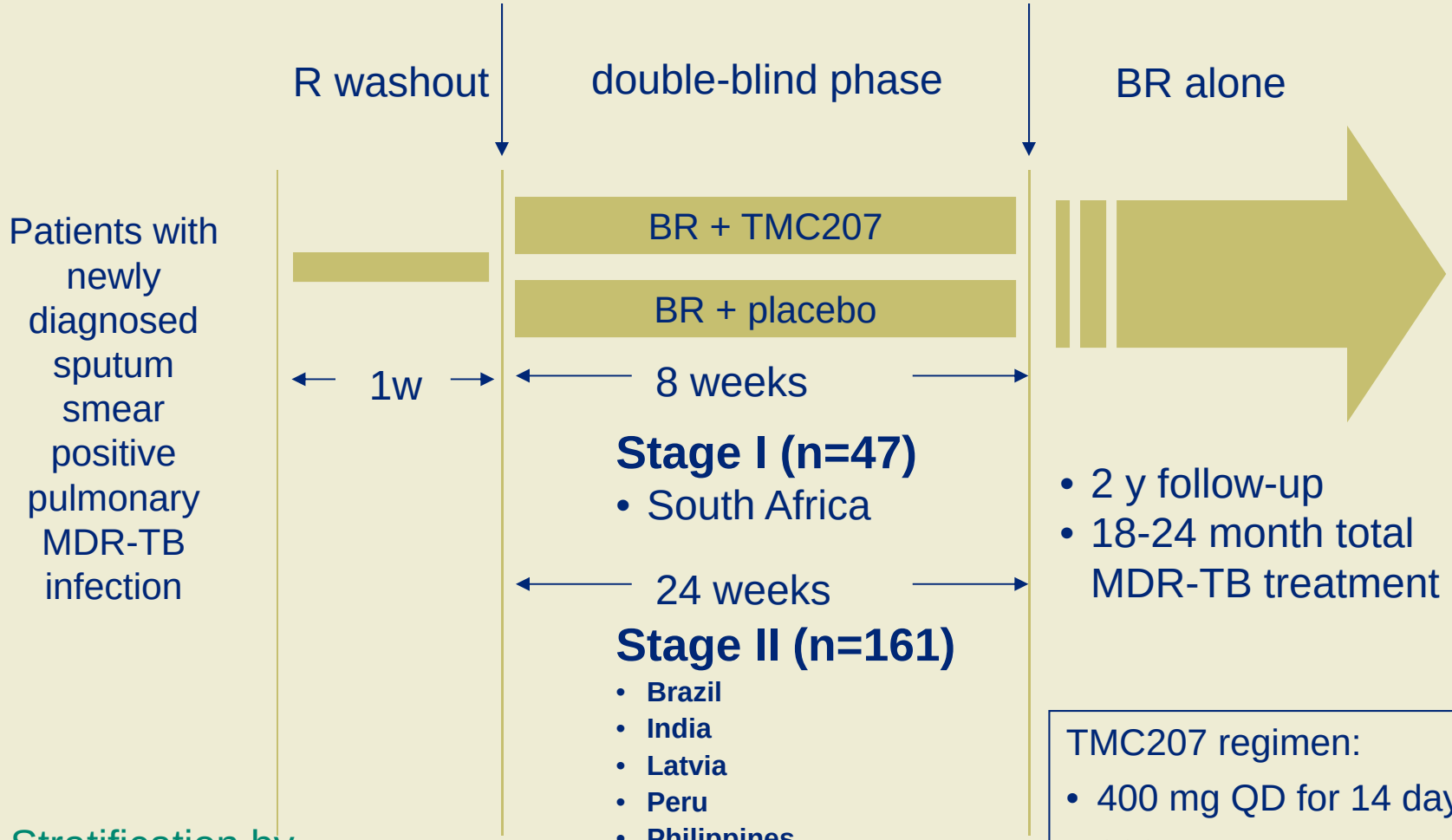
Clinical Development Status PhIIb

McNeeley D, et al. IUATLD 2006. oral
Van Heeswijk et al., ICAAC 2007, A-780
Van Heeswijk, et al., IUATLD 2007, PS-71358-11
Van Heeswijk et al, IAS 2010, WEPE0097
Van Heeswijk et al, IAS 2011, MOPE172
Rustomjee et al., AAC 2008, 52, 2832
Diacon et al., NEJM 2009, 360, 2397
McNeeley et al, IUATLD, 2010 Session N.00189

- Key Phase I PK findings
  - Linear PK
  - Positive food effect (2-fold increase in exposure)
  - Administration of Rif lowers TMC207 levels 50% (CYP3A4)
  - Administration of LPV/r modestly increased TMC207 exposure (22%).
  - Administration of NVP does not affect TMC207 exposure
  - Long terminal elimination half-life (steady state levels not achieved by day 14)

- Key Phase II findings
  - TMC207-C202: Proof of Principle demonstrated in a one-week EBA trial
  - TMC207-C208 Stage I: TMC207 added to a 5-drug BR increased culture conversion by ~40% at 8 weeks in MDRTB
  - TMC207-C208 Stage II: TMC207 added to a 5-drug BR resulted in faster culture conversion at 24 weeks ($p = 0.003$) and higher proportion of conversion 79% vs 58% ($p=0.008$) versus placebo.

C208 – Trial Design – randomized controlled multi-center



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C208 Stage 2 Objectives

- Demonstrate superiority of TMC207 compared to placebo at 24 W of treatment

- 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.

  - Subjects who drop out during the 24W are considered failed, irrespective of their culture status at time of dropout.

- Secondary analysis = **culture conversion rates at 24 W**

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Baseline

	Placebo N=81	TMC207 N=79
Gender - male (%)	61	66
Age - median (yrs)	35	31
HIV negative (%)	82	91
Body weight - median (kg)	53	54

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C208 - Populations for Analysis

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

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

Modified ITT population (mITT): *ITT subjects excluding:*
- Non-MDR subjects **(8 placebo + 4 TMC207)**
- XDR subjects **(4 placebo + 3 TMC207)**
- MGIT results not evaluable **(4 placebo + 7 TMC207)**

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Background Regimen

The preferred 5-drug background regimen consisted of:

- Ethionamide, Pyrazinamide, Ofloxacin, Kanamycin and Terizidone/Cycloserine.

Changes in the background regimen occurred over time due to:

- DST results and side effects
- Switches within the same drug class (due to shortage on site)

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C208 - Baseline Drug Resistance

Second Line Drug Resistance n (%)	Asia N = 11	Europe N = 15	South America N = 32	South Africa N=71
Ethionamide	1 (9 %)	1 (7 %)	0 (0 %)	9 (13%)
Kanamycin	0 (0 %)	10 (67 %)	10 (31 %)	2 (3 %)
Ofloxacin	4 (36 %)	3 (20 %)	6 (19 %)	5 (7 %)
Pyrazinamide	4 (36 %)	11 (73 %)	16 (50 %)	46 (65%)

Similar distribution of resistance in TMC and Placebo groups
No resistance to TMC207

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Safety

- Adverse events evenly distributed across treatment groups
- Discontinuations due to adverse events were unrelated to the study drug
  - Placebo: 4 DO's during the treatment phase
    (drug exposure during pregnancy, amylase/lipase increase, urticaria and pregnancy)
  - TMC207: 3 DO's during the treatment phase
    (transaminase increases: 2 acute Hep B infections and 1 alcoholic binge)
- No serious adverse events related to study drug
- No clinically significant differences in laboratory tests
- QTcF prolongation seen - relevance unclear
  - no adverse events associated with QTcF changes
  - no pathologically prolonged QT intervals (> 500 msec)

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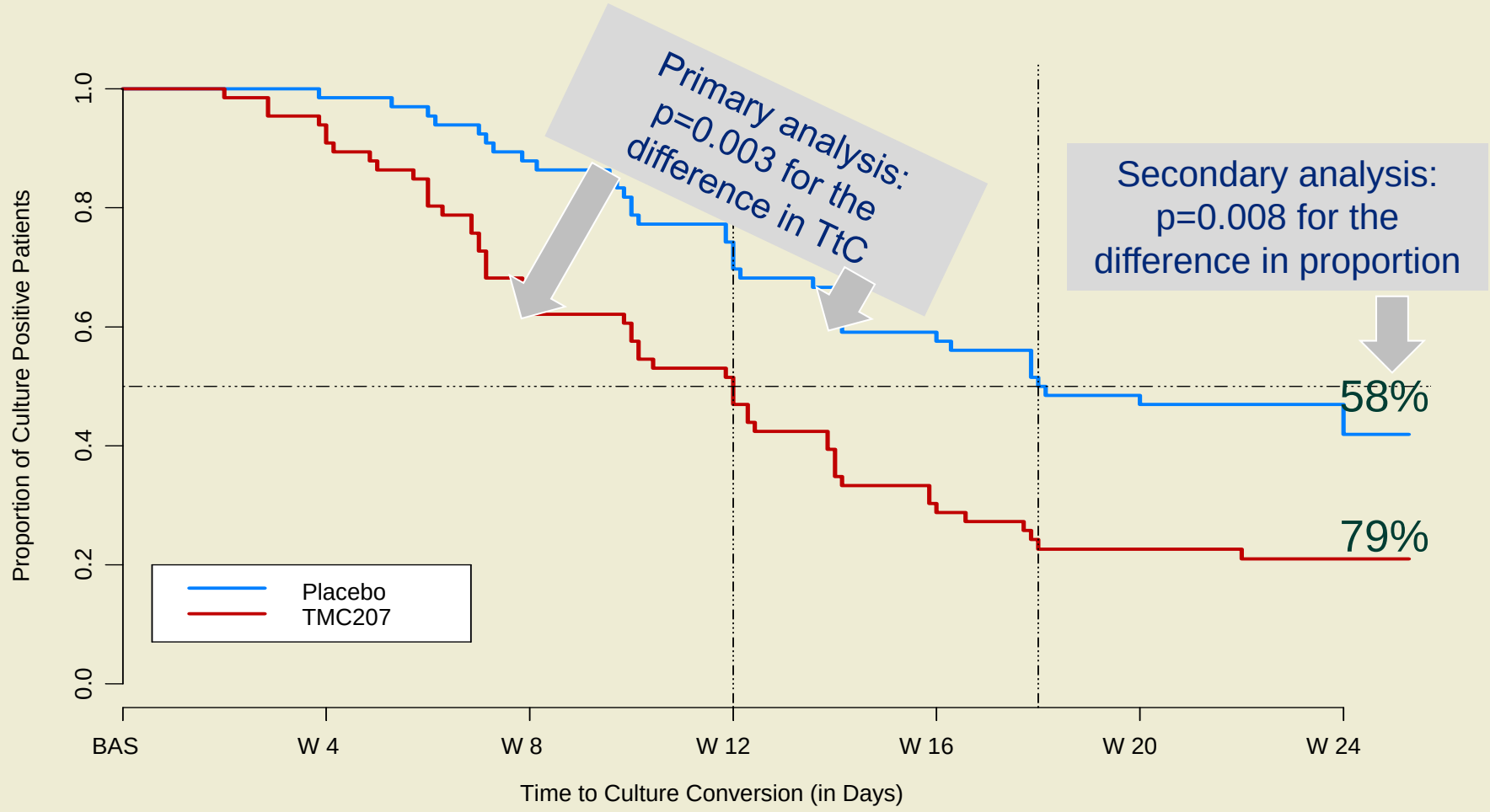
C208 - Time to Conversion(TtC)- mITT



Time to 50% culture conversion: 12 weeks in the TMC207 group
Time to 50% culture conversion 18 weeks in the placebo group

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Conclusions from study TMC207- C208

TMC207 was safe and well-tolerated over 24 weeks

Addition of TMC207 to a 5-drug MDR-TB regimen resulted

- In faster culture conversion within 24 weeks (p=0.003)
- In median time to culture conversion of 12 versus 18 weeks.
- In a higher sputum conversion rate at 24 weeks 79% vs 58% (p=0.008)

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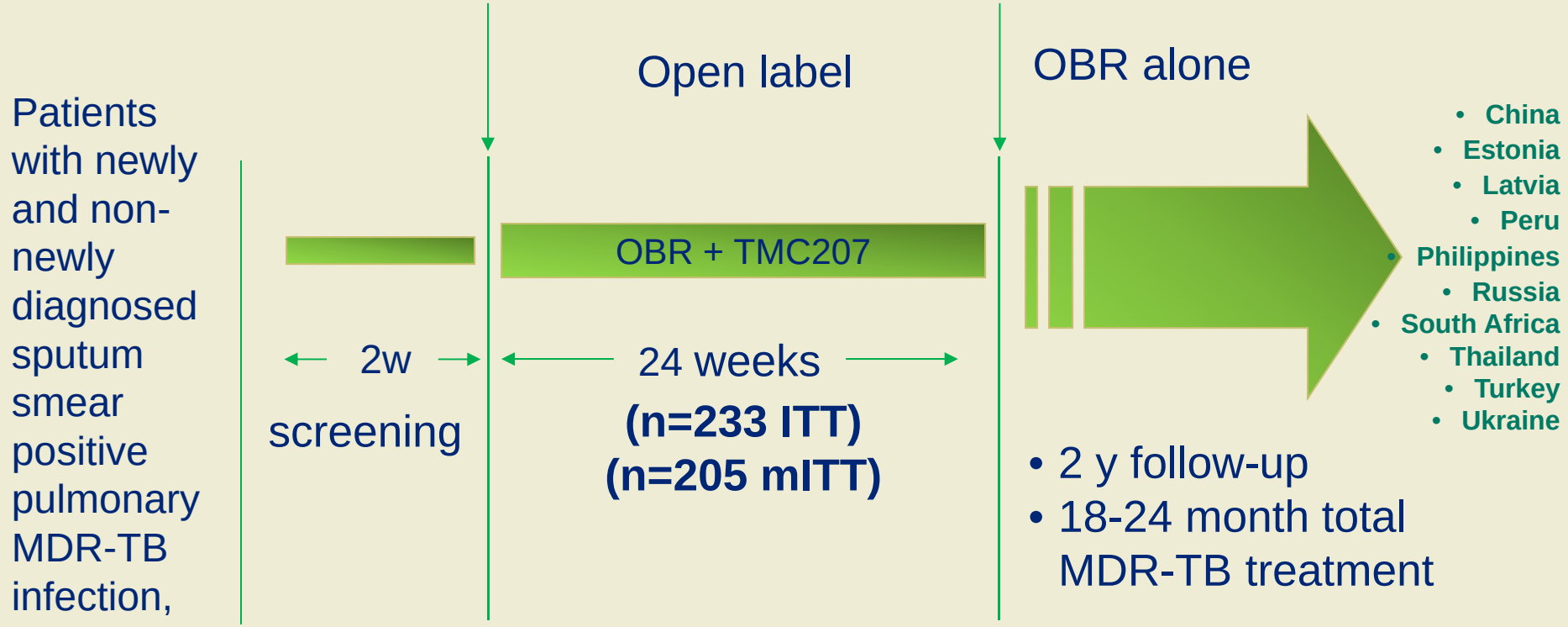
BREATHE STUDY (TMC207-TiDP13-C209)

Bringing T**REAT**ment wit**H** TMC207 to MDR-Tub**E**rculosis

TMC207-C209 Open label study: Trial Design



TMC207 regimen:

- **400 mg QD for 14 days, then**
- **200 mg TIW**

24 w Data available

OBR= optimized background regimen

mITT excluded DS TB and MGIT non-evaluable

Next Steps

- Health Authority submission planned in 2012
- Compassionate use program ongoing in Pre-XDR/XDR TB
  - Countries participating as of 10/2011: South Africa, Switzerland, Nepal, Bangladesh, Georgia, Italy, Germany, Greece, UK, France
  - EAP clinical trial Russia, China, Lithuania (FPFV October 2011)
- Phase III clinical trial mid 2012

Questions?