

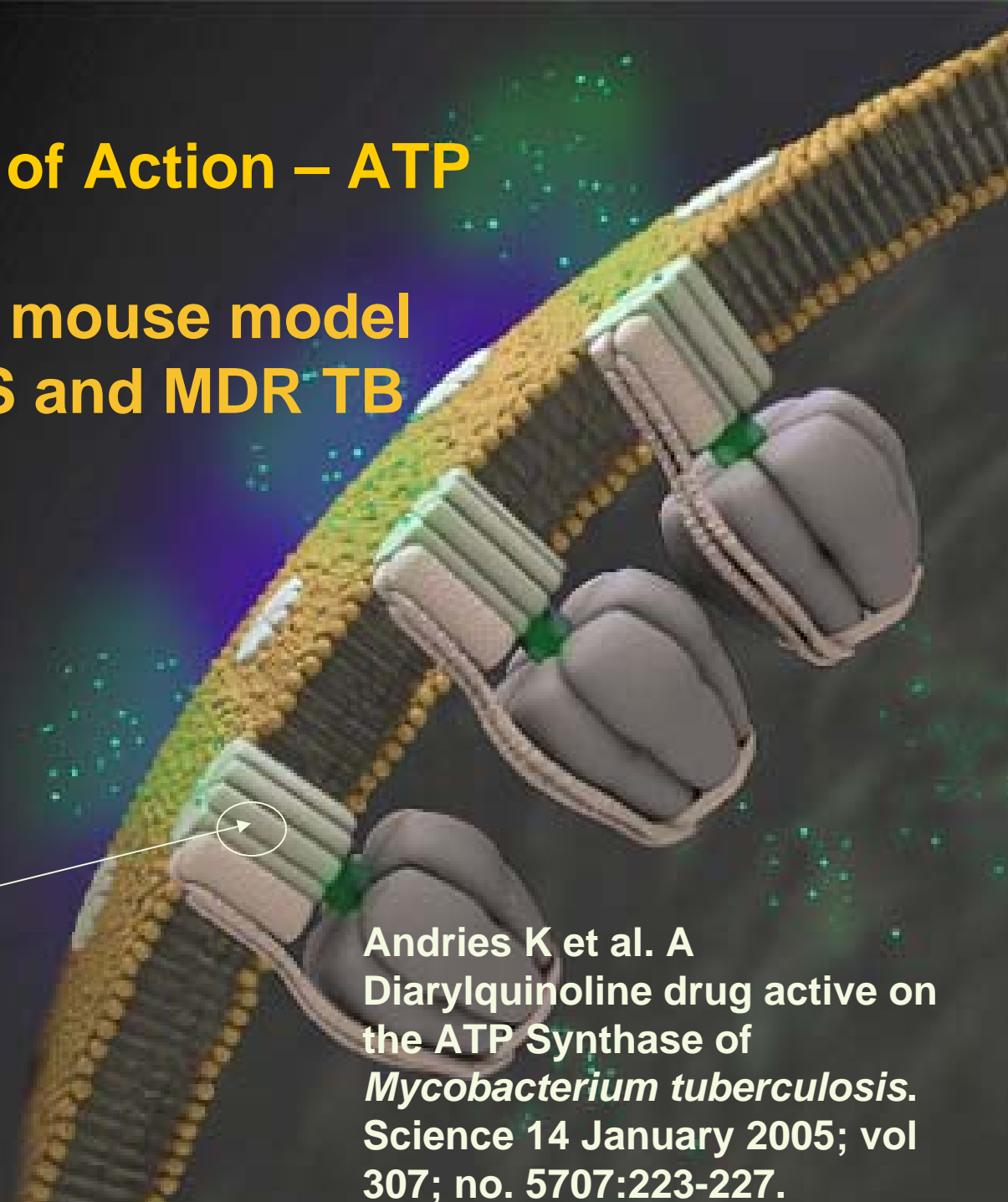
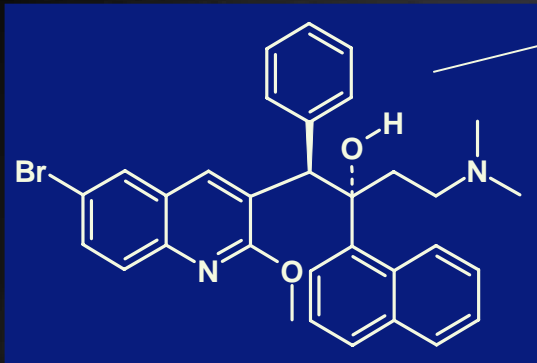


Update on TMC207
Recent Advances in Development

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TMC207

- Novel mechanism of Action – ATP synthase inhibitor
- Highly effective in mouse model
- Bactericidal for DS and MDR TB



A 3D molecular model of the ATP synthase enzyme embedded in a lipid bilayer membrane. The enzyme is shown in a light grey color, with its stator and rotor domains protruding from the membrane. A white circle highlights the stator domain, with a white arrow pointing from the chemical structure of TMC207 to this specific region.

Andries K et al. A
Diarylquinoline drug active on
the ATP Synthase of
Mycobacterium tuberculosis.
Science 14 January 2005; vol
307; no. 5707:223-227.

TMC207 Phase I Trials

- Single ascending dose (25-700mg)
- Multiple ascending dose (25-400mg, 14 days)
- Interactions studies with R, H and Z
- Interaction study with ketoconazole

Key Phase I PK findings

- Linear PK profile
- Positive food effect (2-fold increase in exposure)
- Metabolism by CYP3A4
- Administration of rifampin lowers TMC207 levels 50%
- Long terminal elimination half-life (steady state levels not achieved by day 15)

Clinical Safety

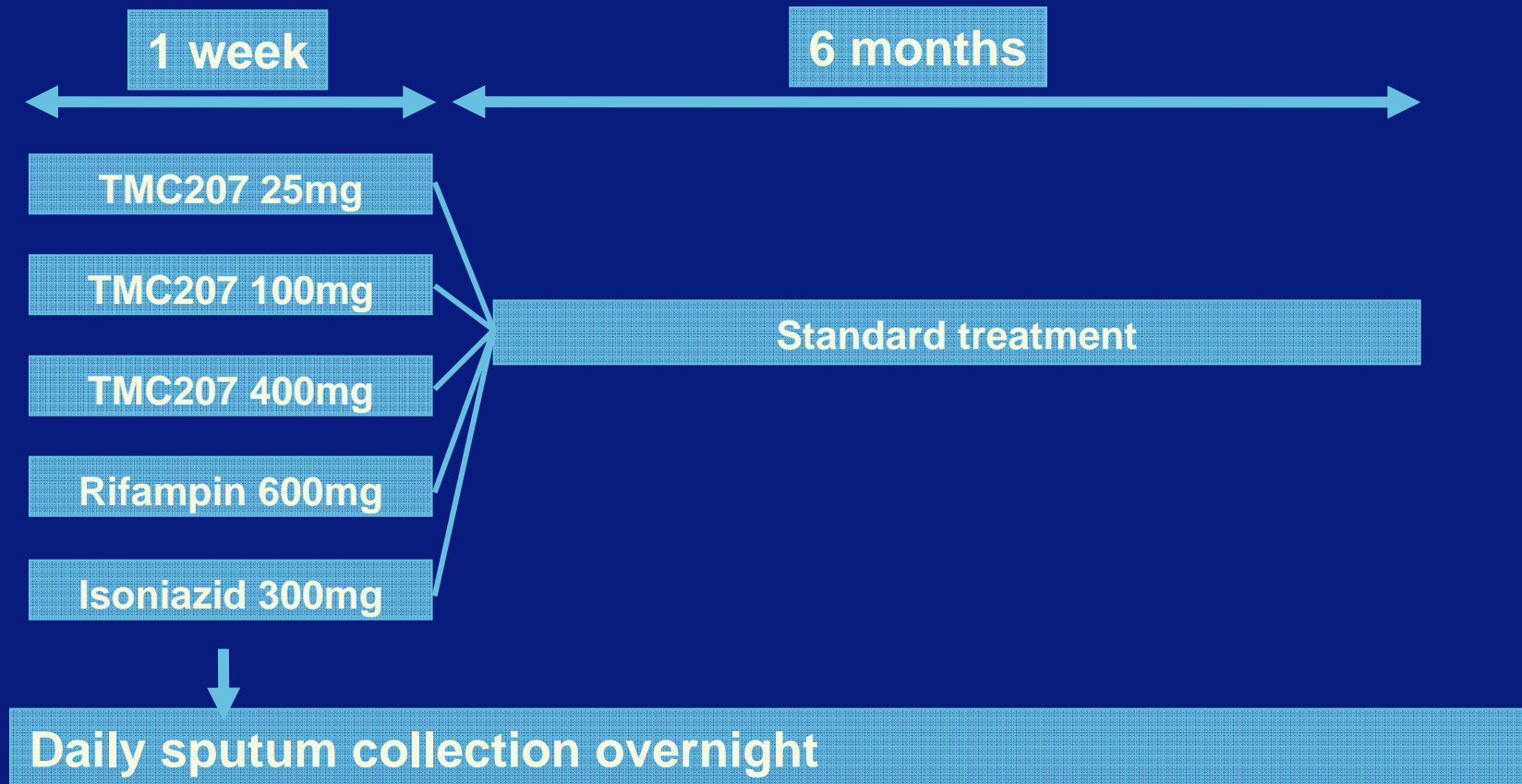
- 189 subjects treated in all trials to date
- No serious adverse events related to TMC207

Early Bactericidal Activity, Tolerability, and Pharmacokinetics of the Investigational Diarylquinoline TMC207

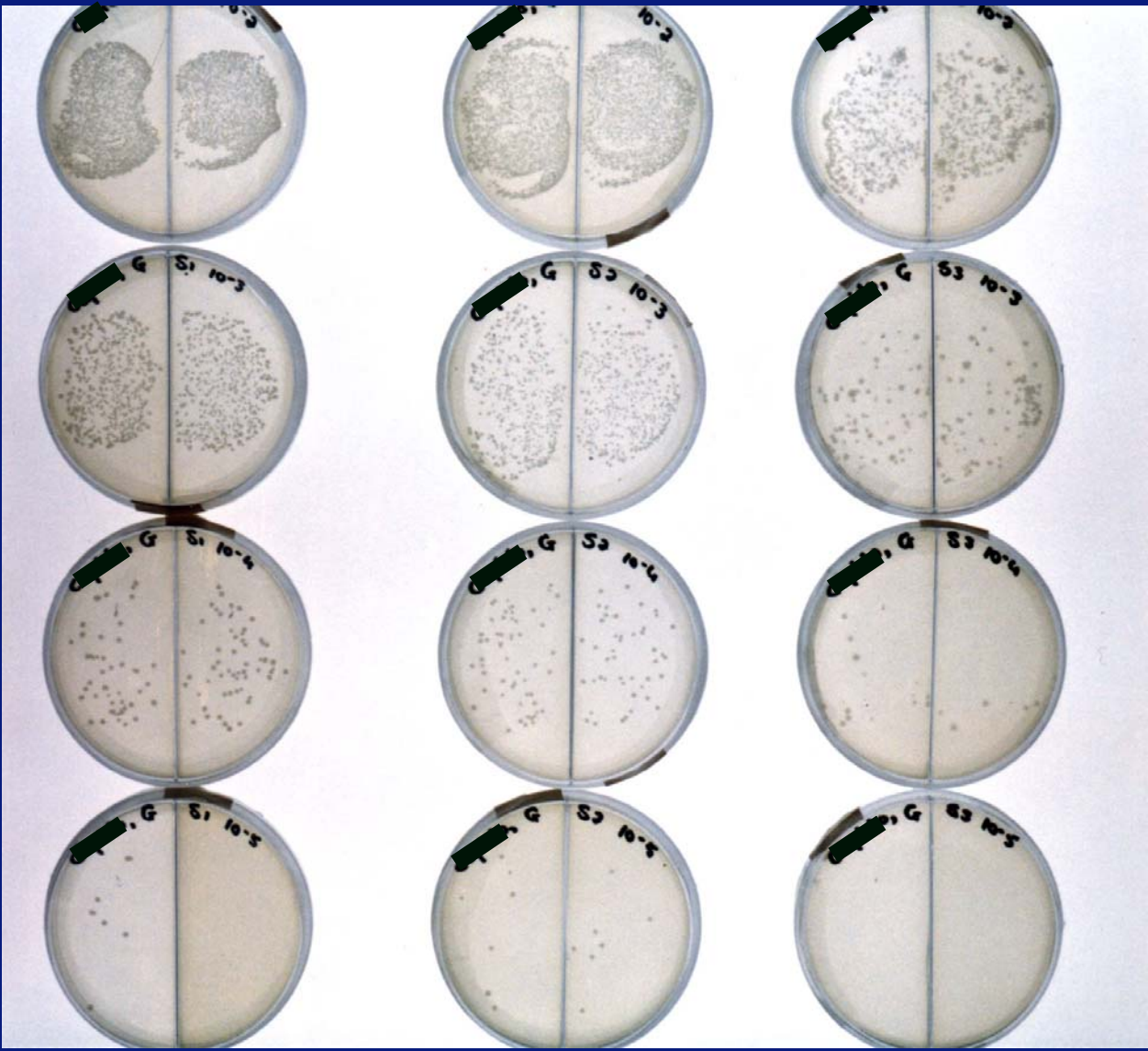
Dr. Andreas Diacon

Phase IIa proof of concept study

Multicenter, randomized, open-label, extended EBA



Serial CFU counting



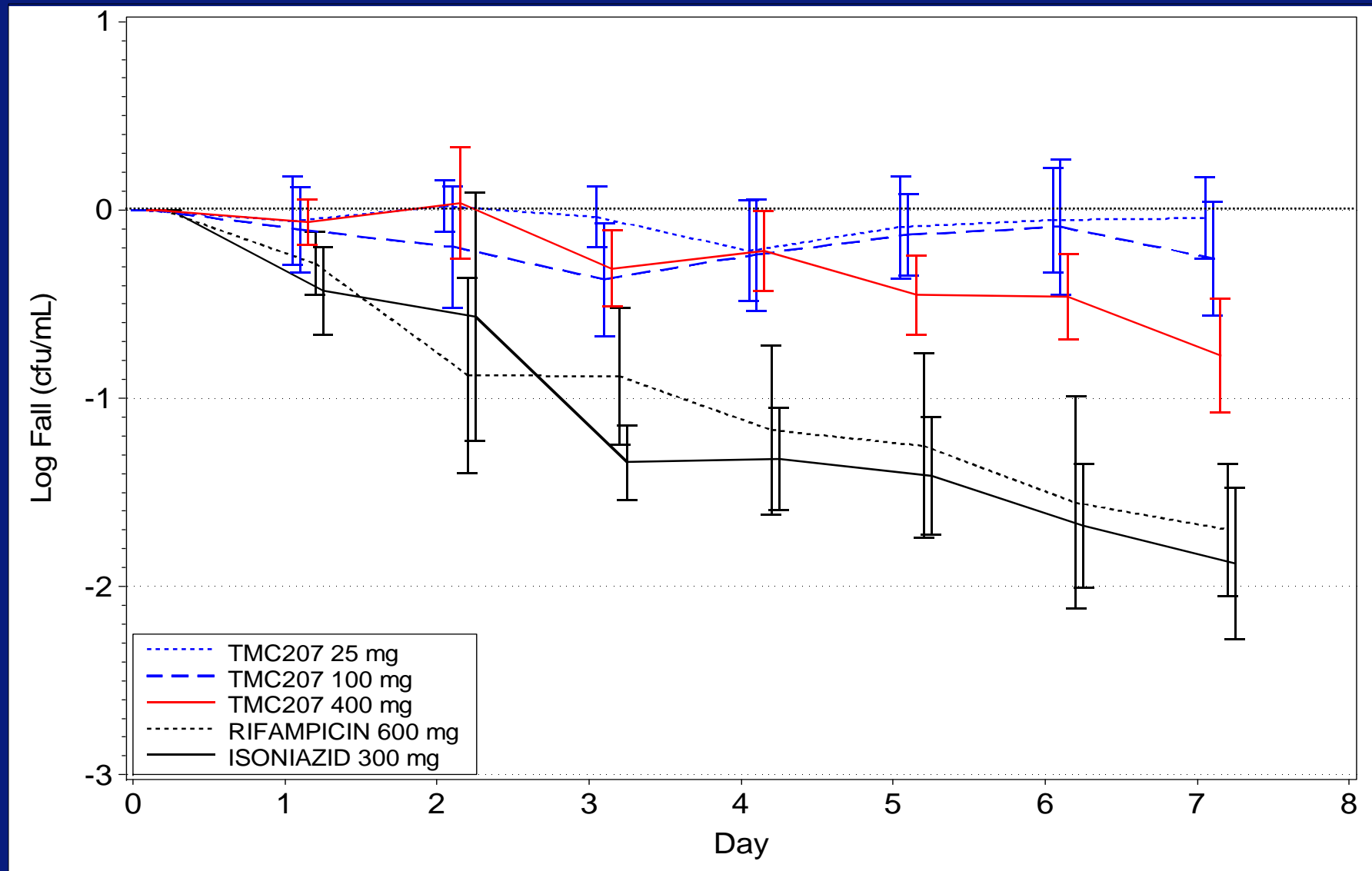
Inclusion Criteria

- Male or female, 18 - 65 years old
- Treatment naïve pulmonary TB
- At least 1+ positive sputum smear
- At least 15ml sputum overnight
- Not on or in need of antiretroviral therapy

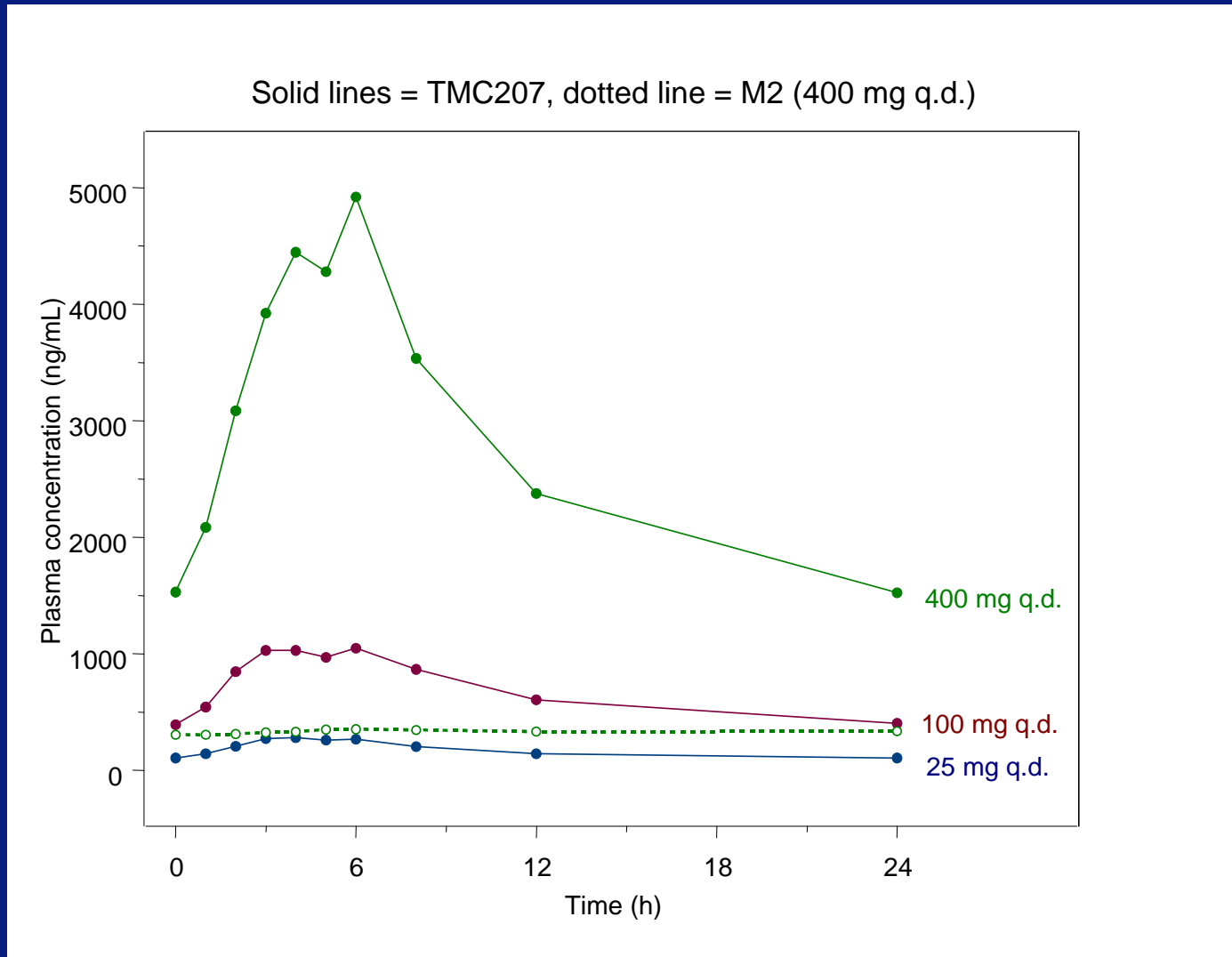
Baseline

- 75 subjects
- 60% male
- Median age 35 years (range 18-61 years)
- 31% HIV-positive
- Mean baseline sputum count 6.6 (± 1) \log_{10} cfu/ml sputum

TMC207 400 mg dose bactericidal activity from day 4



Linear PK in TB patients



Safety and Tolerability

- TMC207 was well tolerated
- During follow up, two deaths unrelated to TMC 207

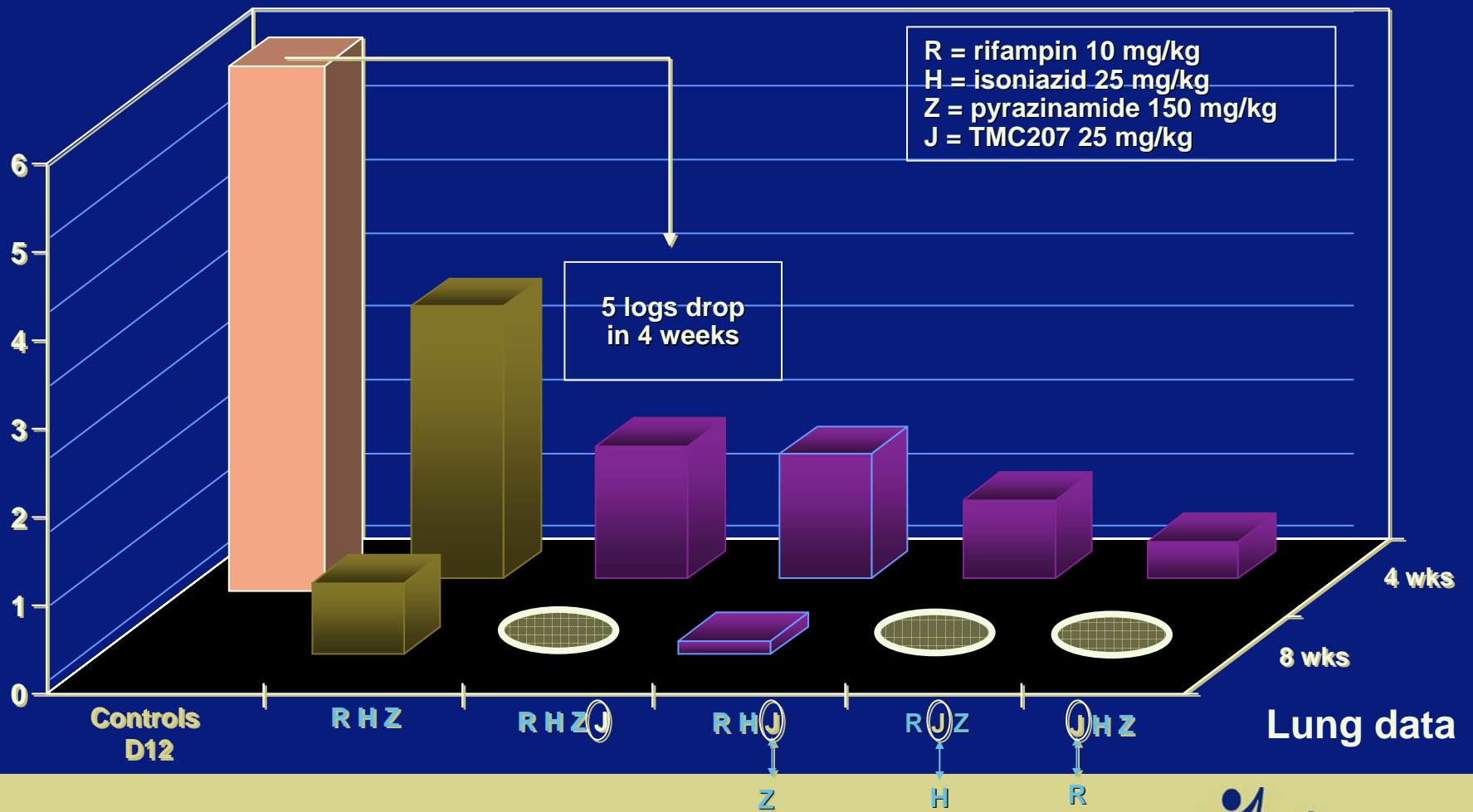
Conclusions from study TMC207- C202

- Bactericidal activity of TMC207 demonstrated at 400mg
- Steady state levels not reached within 7 day exposure
- Linear pK in patients, comparable to volunteer data
- No safety alerts
- Activity of TMC207 beyond 7 days needs to be studied

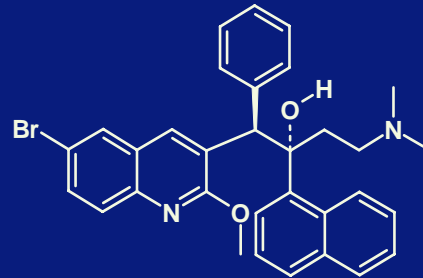
Poster Display Session

Vaccines, clinical trials and TB treatment
Today 12:45 to 13:45

TMC207 (J) in combination resulted in culture negativity in 8 weeks

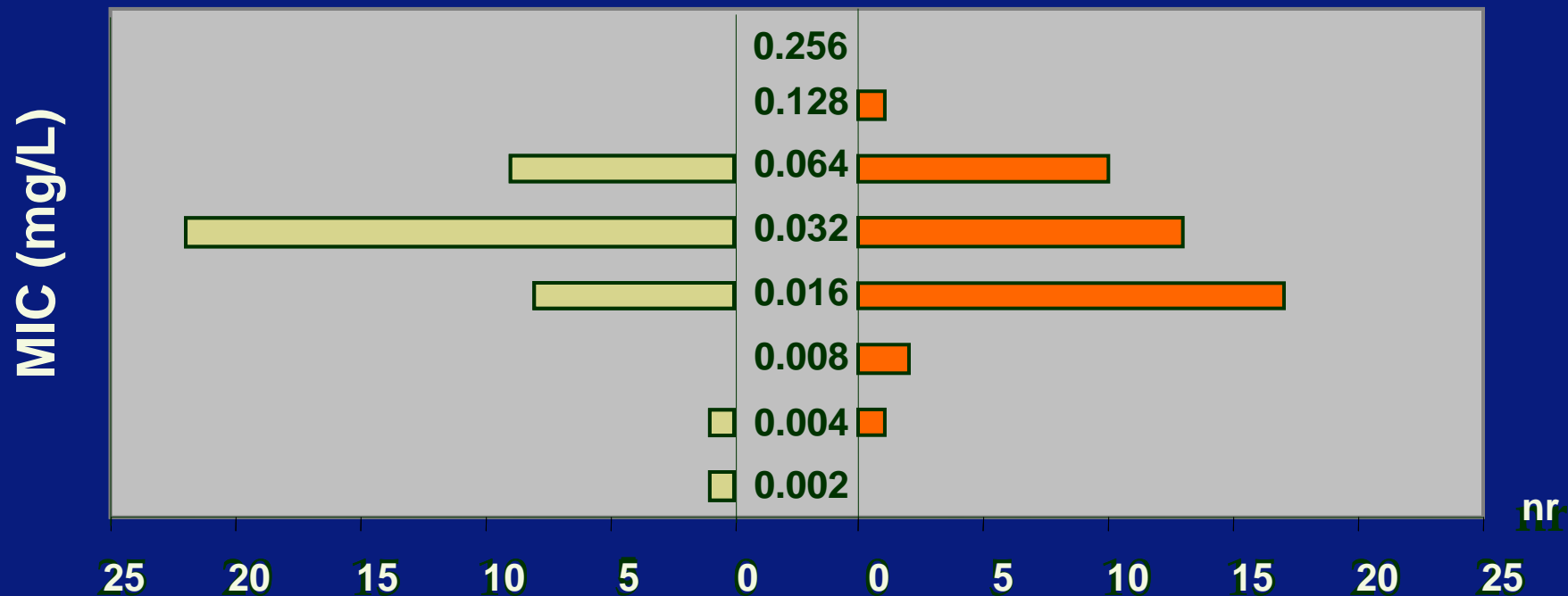


TMC 207 MIC Distribution in Susceptible and Resistant Isolates



41 isolates Susceptible TB

44 isolates MDR TB

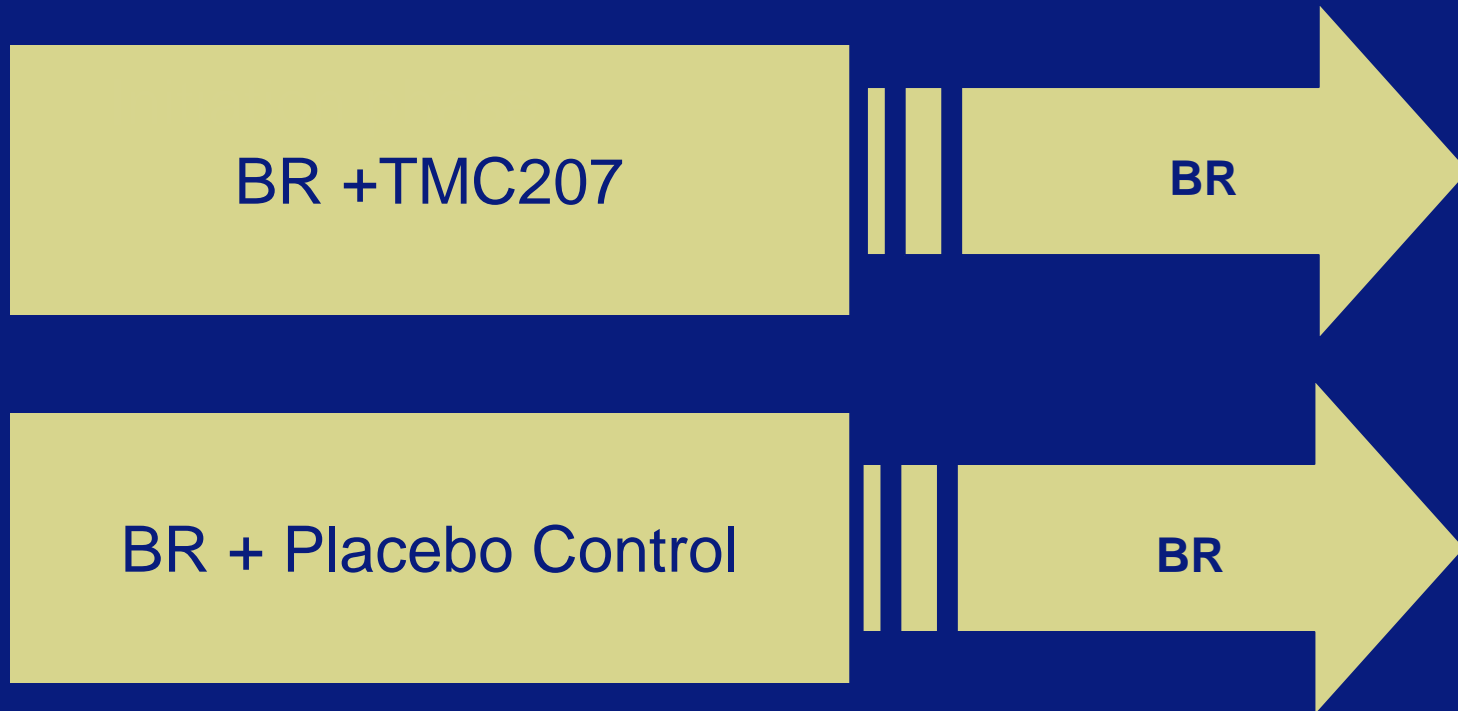


Further developments TMC207

- Need to determine long term efficacy and safety
- Avoid Rifampin drug interaction
- Respond to high unmet medical need: MDR-TB

MDR TB Trial Overview

All patients receive 18-24 mths total treatment



Dose finding 2 months, n=50
Safety & efficacy 6 months, n=150

24 months FU

BR = Background Regimen

TMC207 summary

- New mechanism of action – active against drug susceptible and MDR-TB
- Demonstrated activity of 400mg dose from day 4 in proof-of-concept study
- Dose-finding and long term safety and efficacy study in MDR-TB patients starting Q2/2007

Acknowledgements

- The patients and volunteers who participated in our studies
- Dr. Andreas Diacon, Dr. Ramonde Patientia, Prof. Peter Donald and study team, Stellenbosch University, Cape Town, South Africa.
- Dr. Roxana Rustomjee, Dr. Carl Reddy and study team, Unit for Clinical and Biomedical Tuberculosis Research, Medical Research Council, Durban, South Africa.
- Members of the TMC207 compound development and clinical teams, Tibotec, Inc., Yardley, PA (USA) and Mechelen, Belgium.