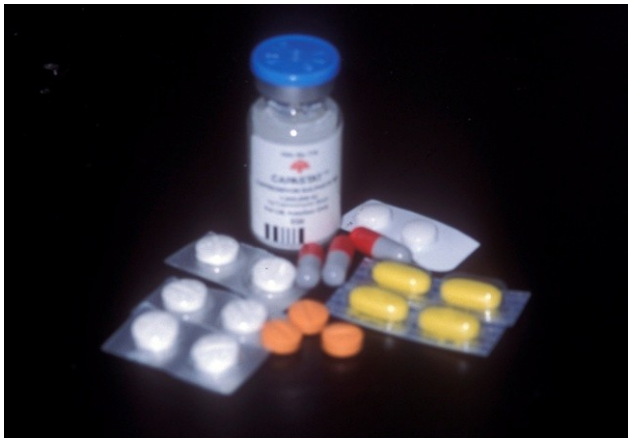
Development and deployment of new TB drugs



Gerry Davies

Reader in Infection Pharmacology

Institutes of Infection and Global Health & Translational Medicine

Malawi-Liverpool-Wellcome Research Unit

UNIVERSITY OF LIVERPOOL

BHIVA Autumn Meeting October 2014

Declarations

Academic co-ordinator of the PreDiCT-TB consortium

Member of WHO Taskforce on Development of New Tuberculosis Drugs

Co-PI on HIRIF trial (NIH)

Steering committee member RIFAQUIN Trial

DSMB Chair RIFATOX trial

Overview

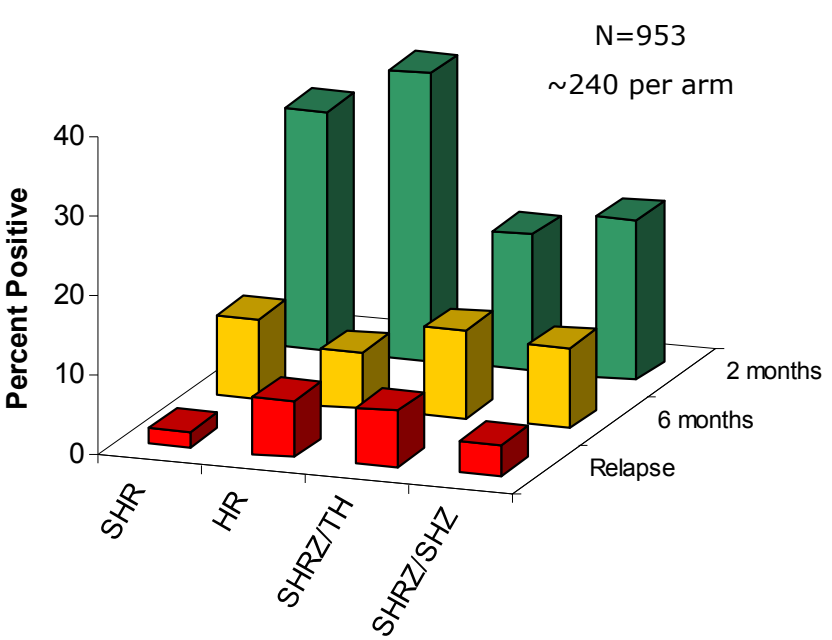
- A changing landscape
- Rifamycin optimisation
- Fluoroquinolones
- Bedaquiline
- Delaminid
- The (near) future

A short history of Short Course Chemotherapy

THE LANCET, NOVEMBER 9, 1974

CONTROLLED CLINICAL TRIAL OF FOUR SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PUMONARY TUBERCULOSIS

SECOND EAST AFRICAN / BRITISH MEDICAL RESEARCH COUNCIL STUDY

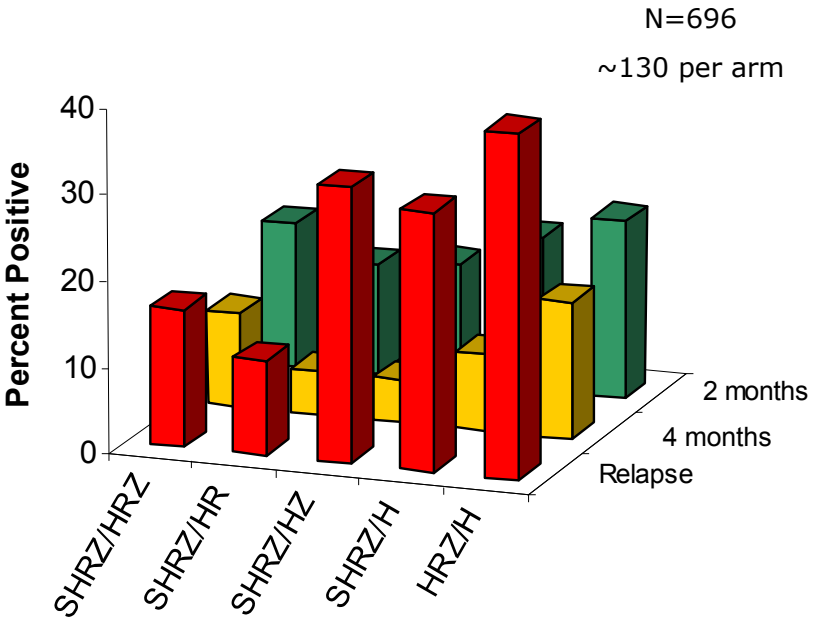


THE LANCET, AUGUST 12, 1978

CONTROLLED CLINICAL TRIAL OF FIVE SHORT-COURSE (4-MONTH) CHEMOTHERAPY REGIMENS IN PULMONARY TUBERCULOSIS

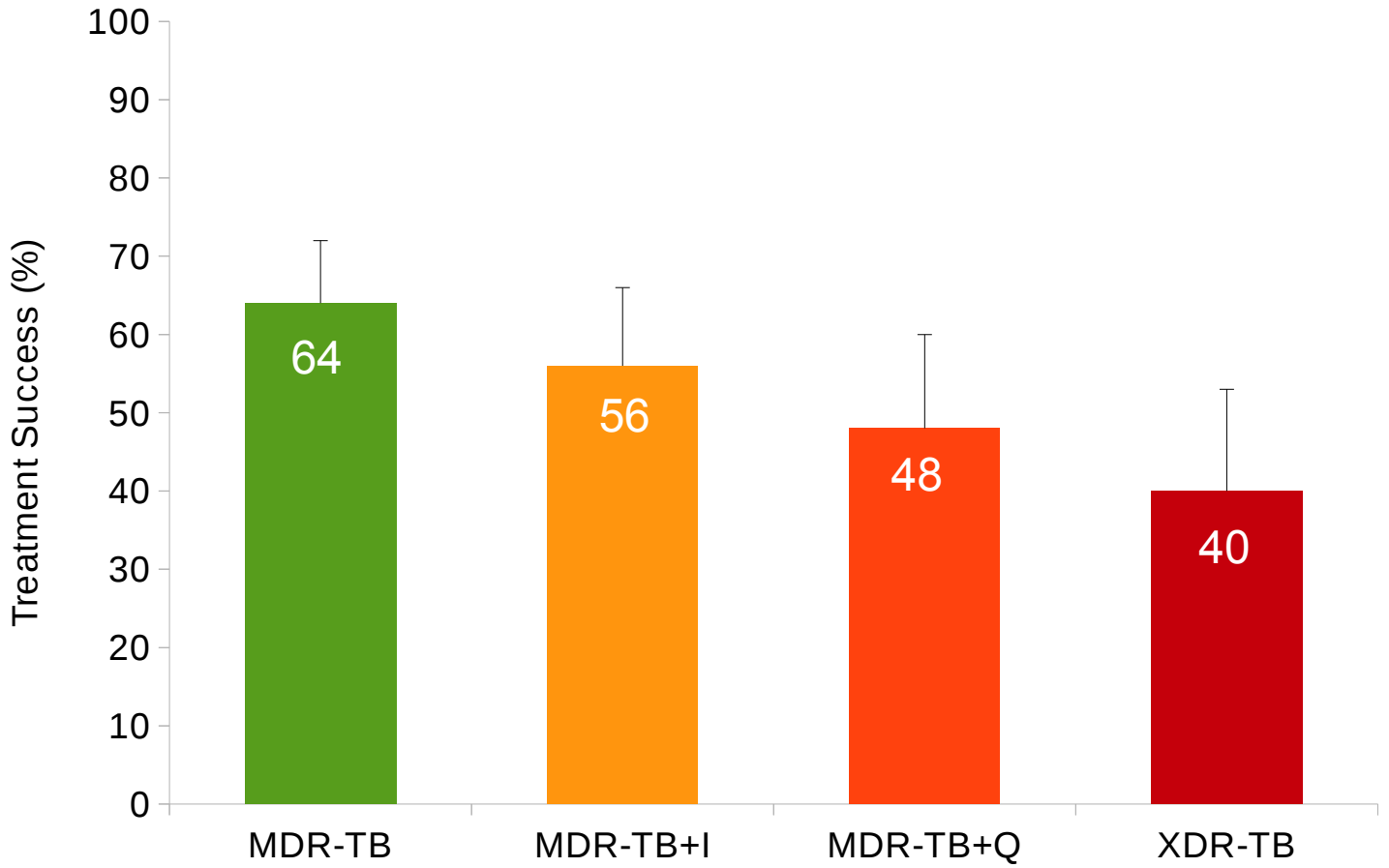
First Report of 4th Study

EAST AFRICAN AND BRITISH MEDICAL RESEARCH COUNCILS



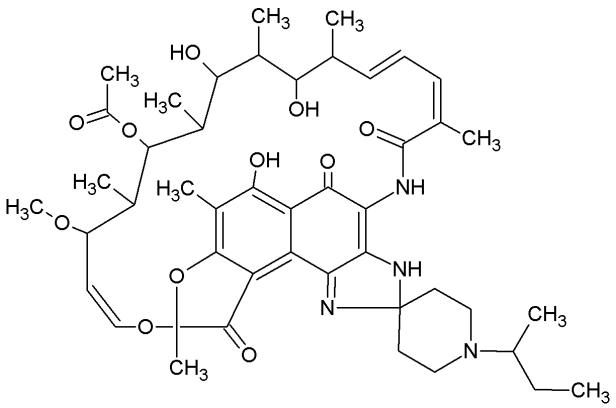
The Challenge of Resistance

Collaborative meta-analysis of 6724 patients on individualised regimens from 26 centres

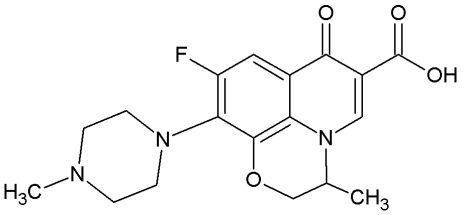


Falzon D Eur Resp J 2013 42 : 156-168

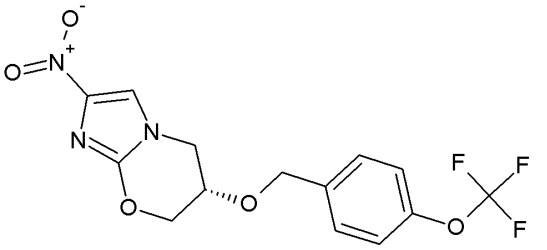
New anti-tuberculosis drugs



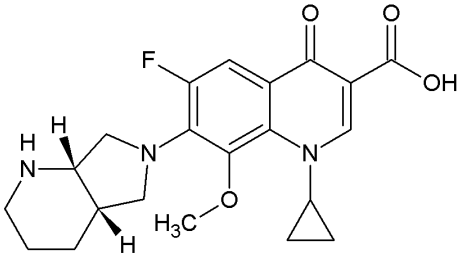
Rifabutin



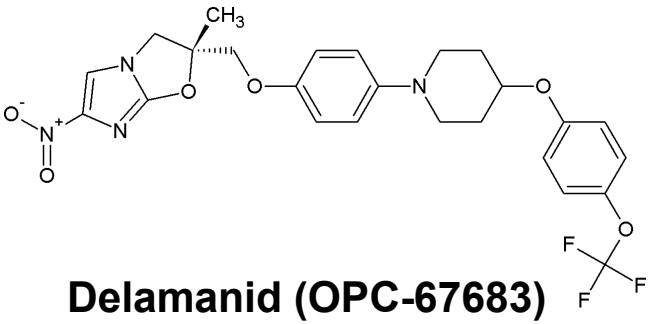
Levo/ofloxacin



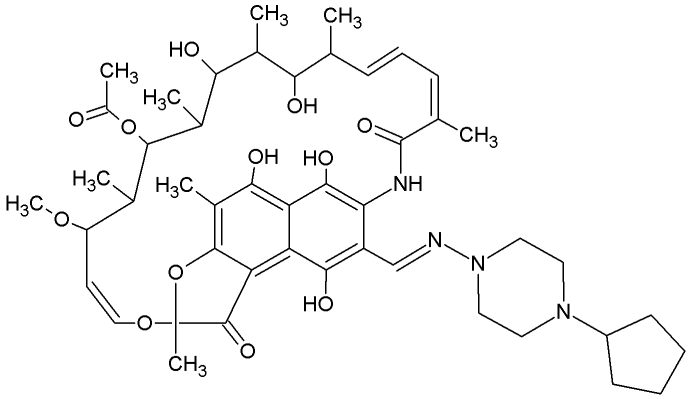
Protomanid (PA-824)



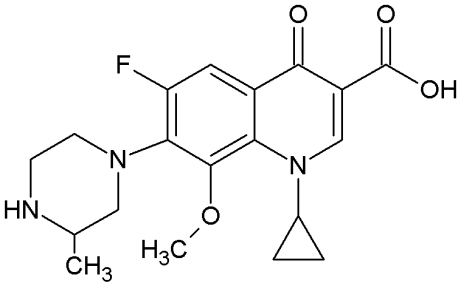
Moxifloxacin



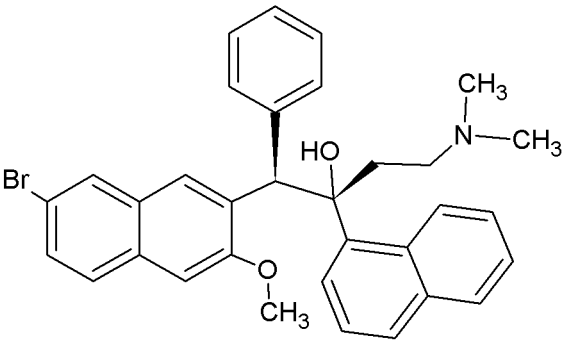
Delamanid (OPC-67683)



Rifapentine

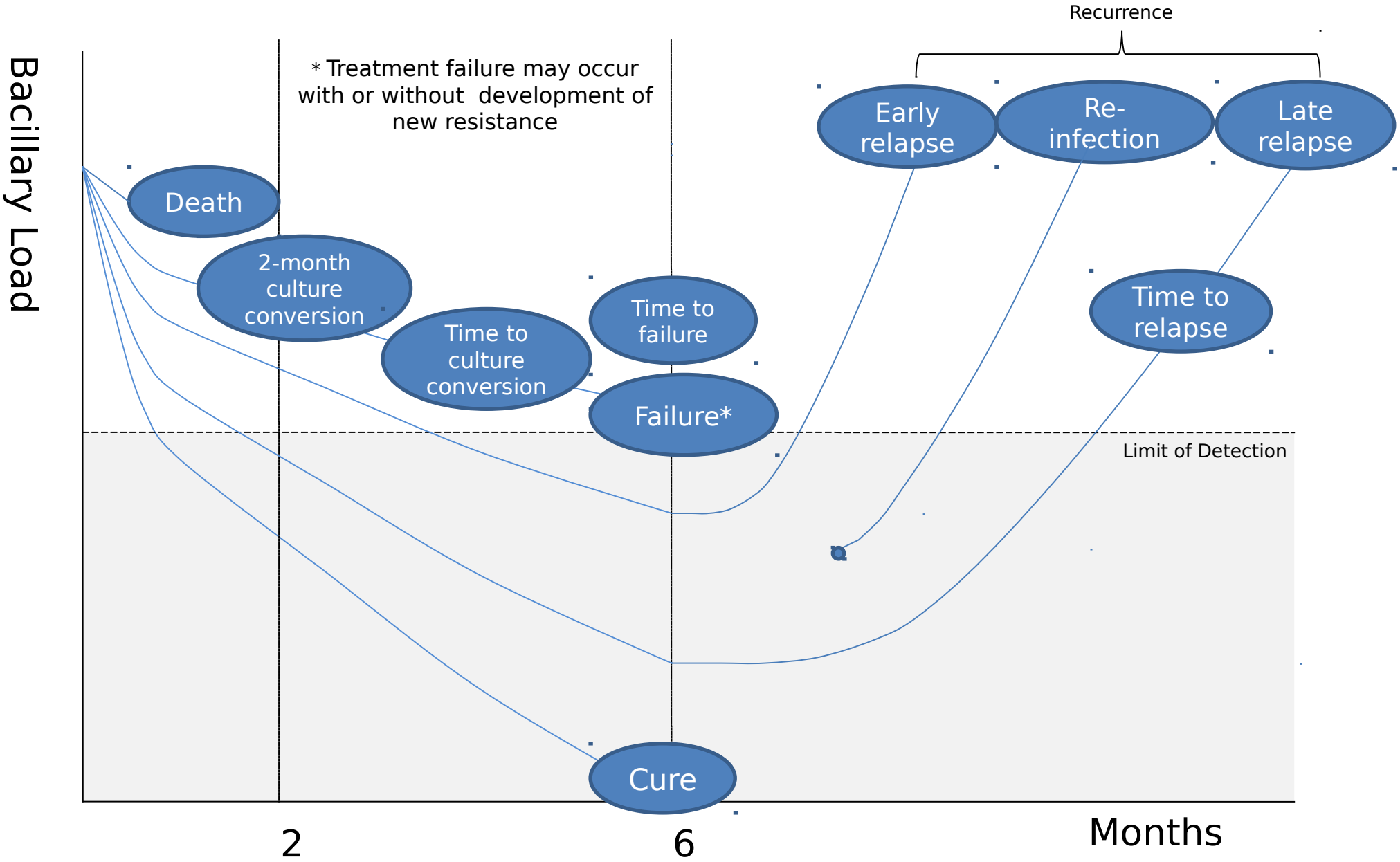


Gatifloxacin



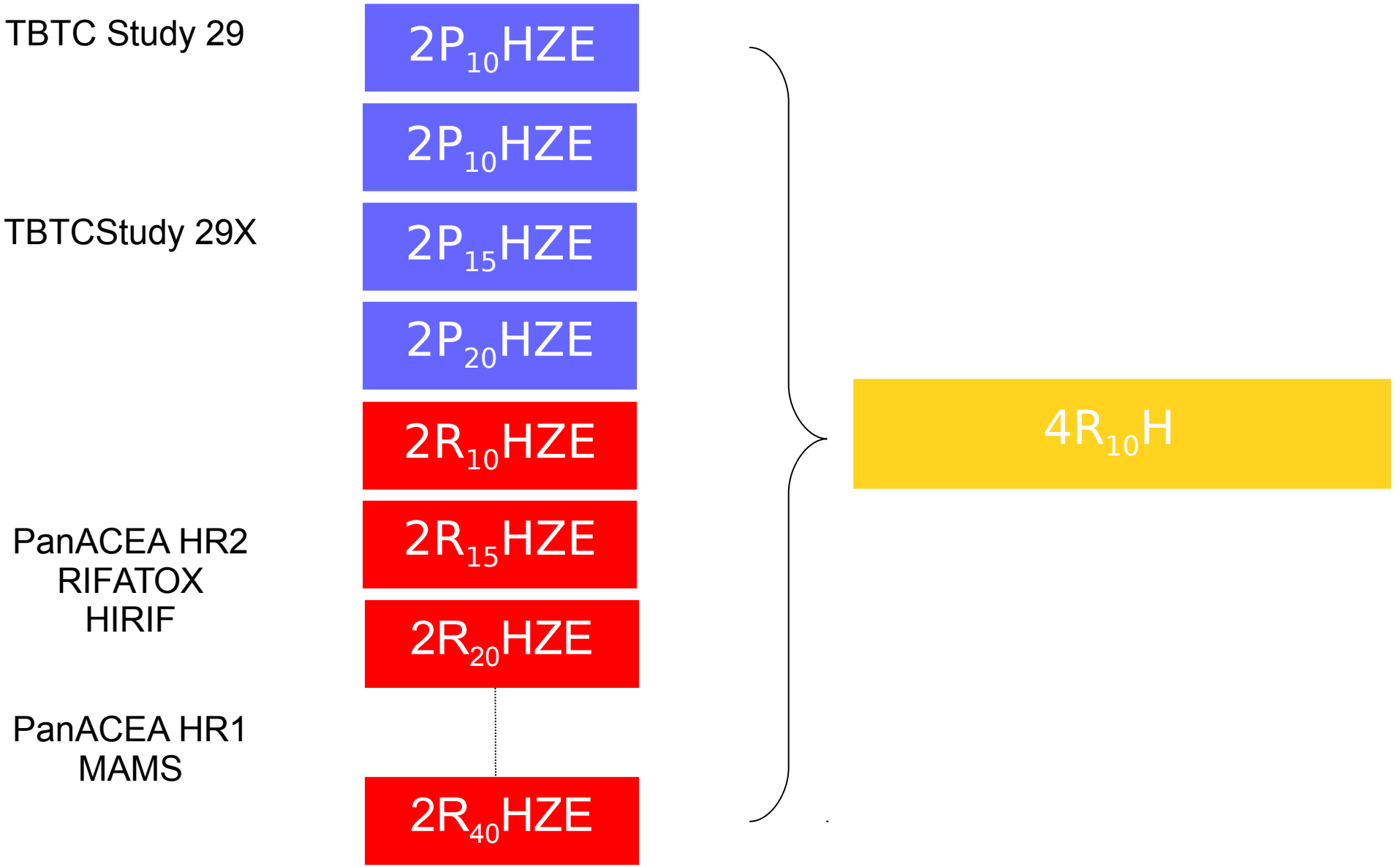
Bedaquiline (TMC-207)

Efficacy endpoints in TB trials

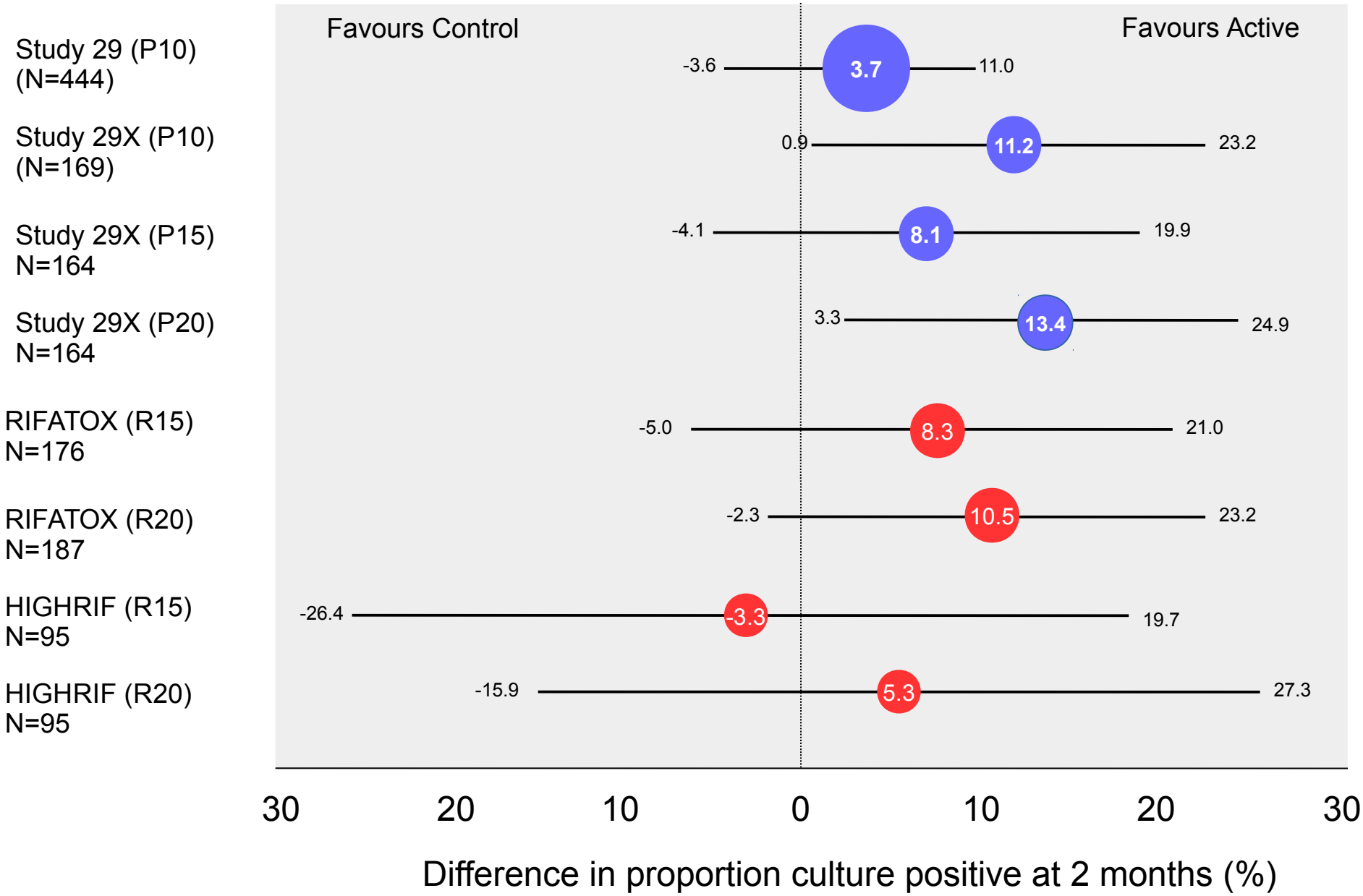


Davies G Tuberculosis 2010 90:171-6

Rifamycins : Phase II trials



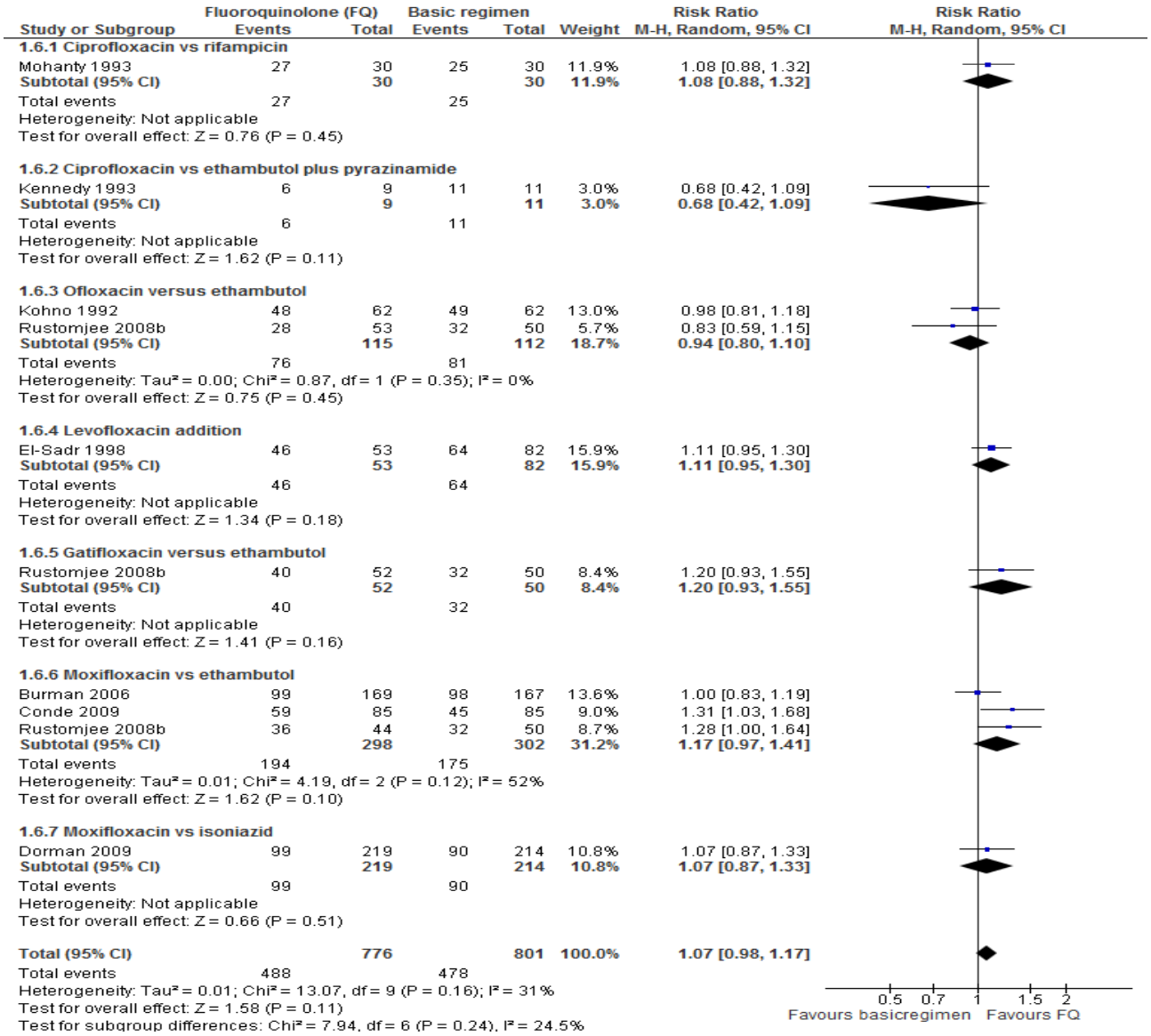
Rifamycins: Phase II Trials



Rifamycins : PK and Safety

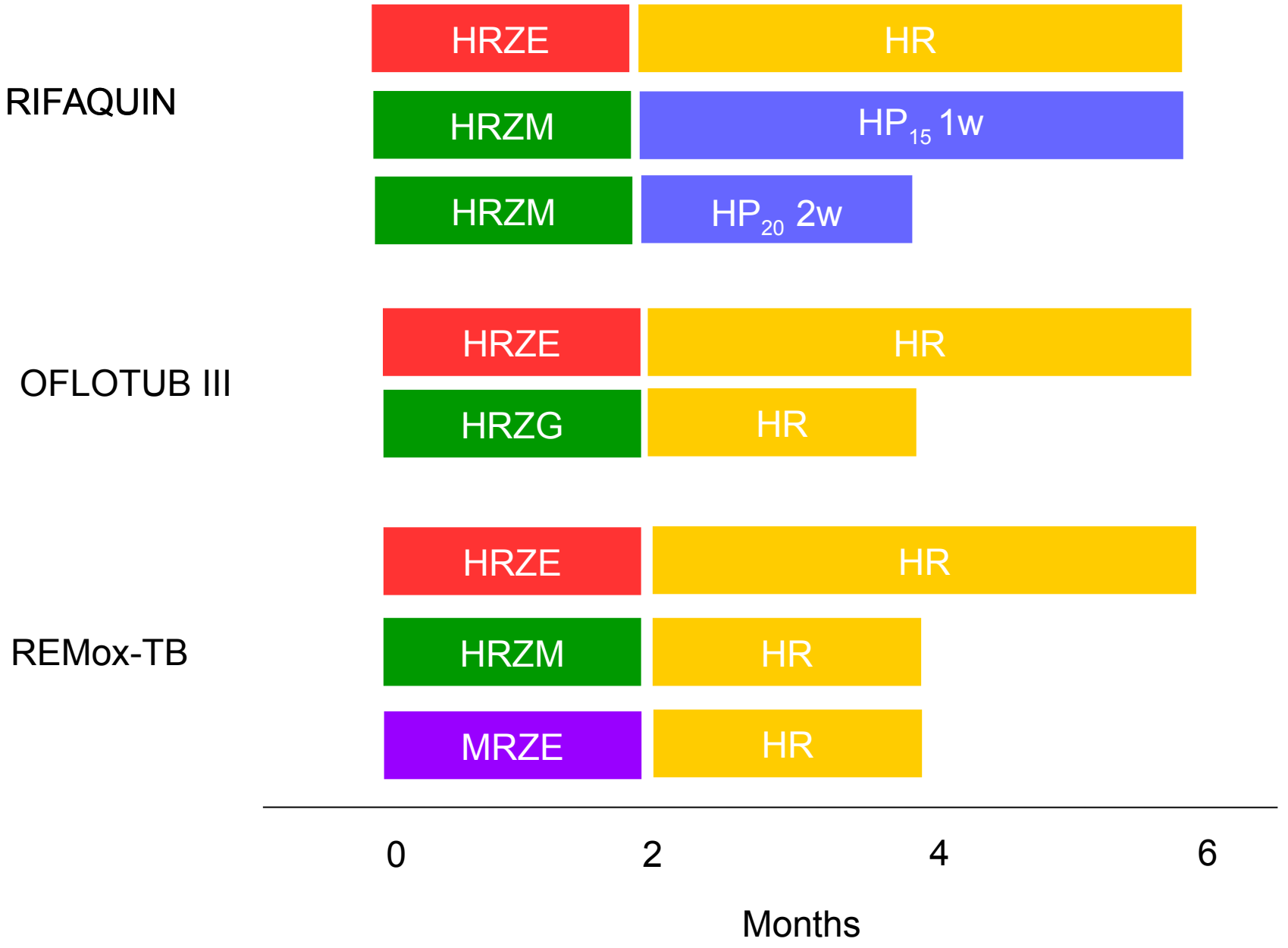
- Saturable and non-linear PK observed for RIF
- Decreasing bioavailability with dose and food effect with RP
- Grade 3 transaminitis/hepatitis 2-4%
- No reports of immune-mediated syndromes
- HR1 MTD Study up to 40 mg/kg
- PanaCEA MAMS Study

Fluoroquinolones : Phase II Trials



Zigansina L, Titarenko A, Davies GR. Cochrane Database of Systematic Reviews update 2013

Fluoroquinolones : Phase III trials



Fluoroquinolones: Phase III Trials

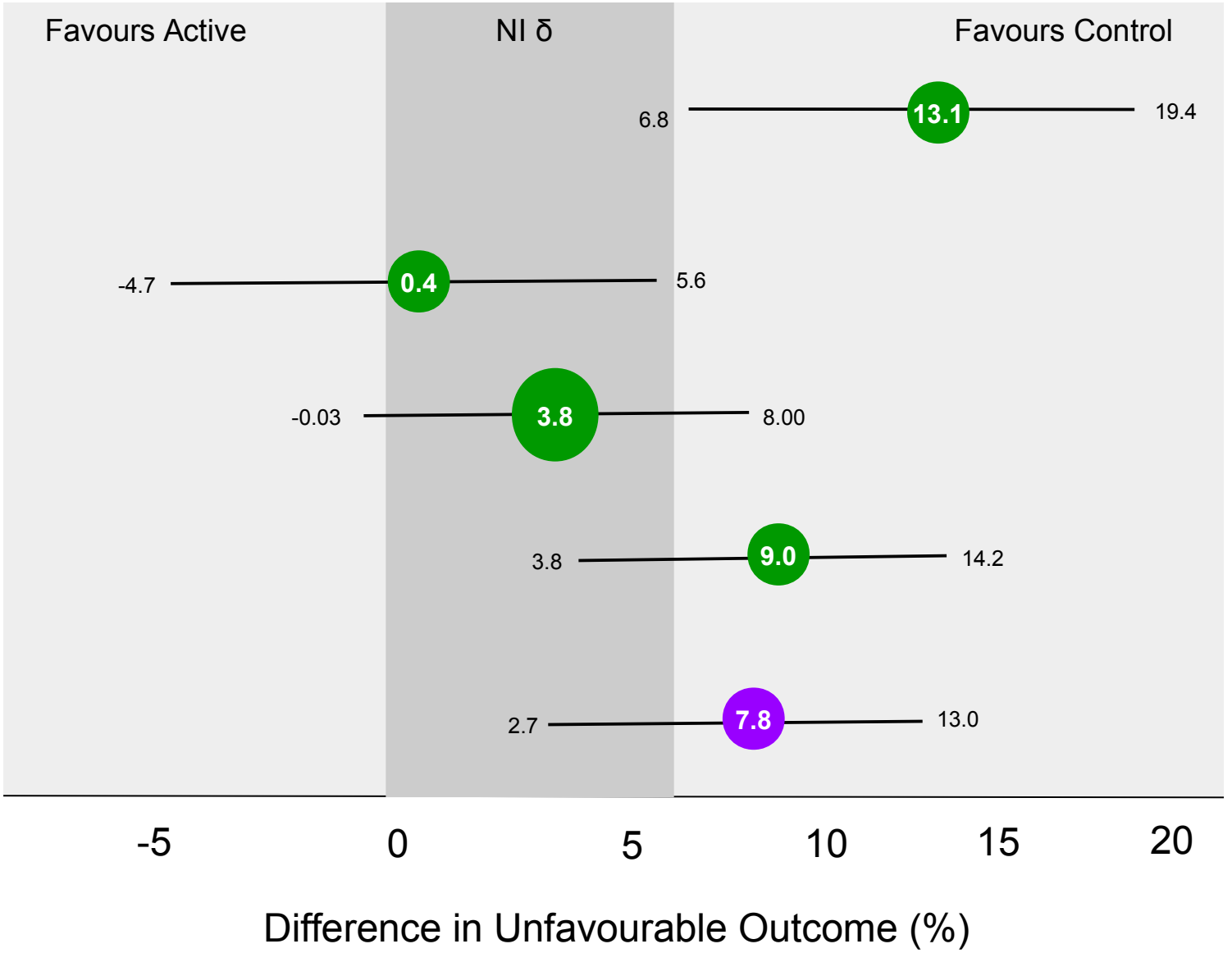
RIFAQUIN 2HRZM/2HP n=593

RIFAQUIN 2HRZM/4HP n=593

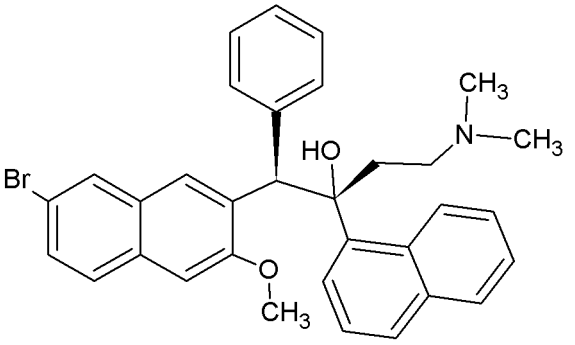
OFLOTUB-III 2HRZG/2HR n=917

REMox 2HRZM/2HR n=524

REMox 2MRZE/2HR n=514



Bedaquiline : pharmacology

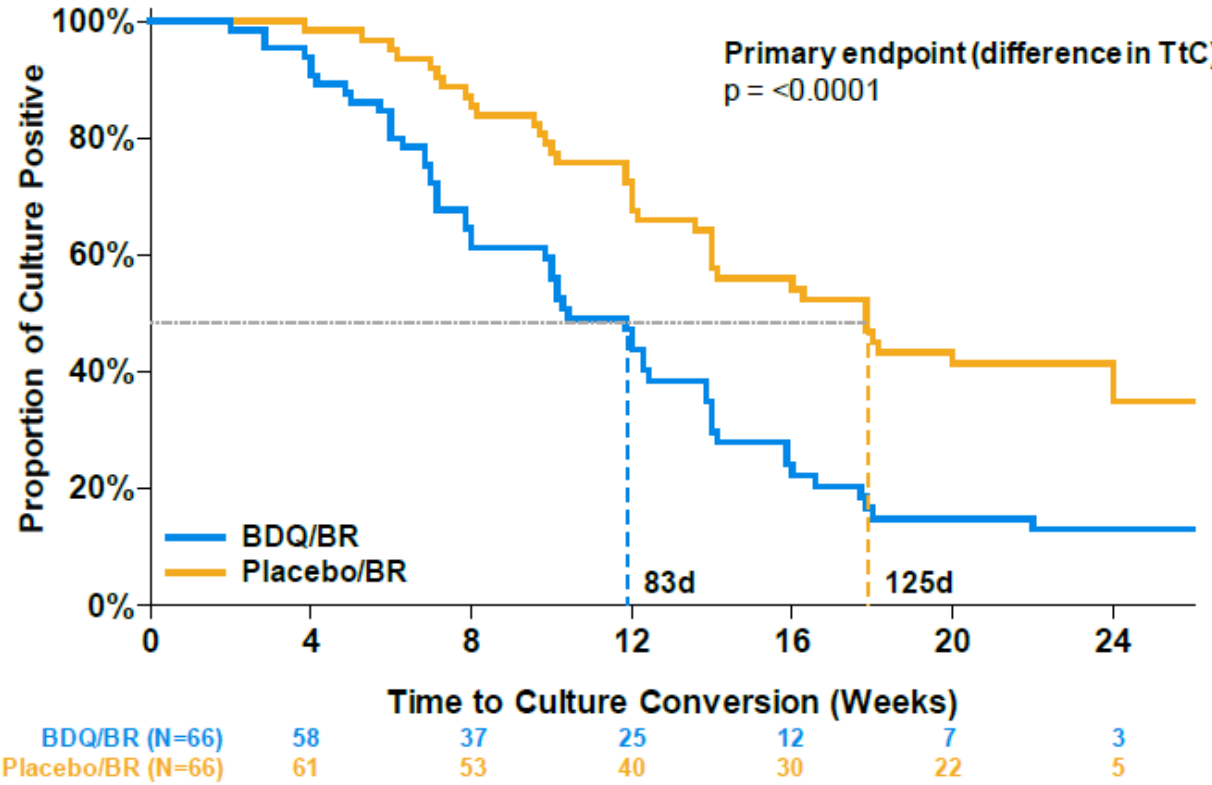


- Target *atpE* subunit of ATP synthase
- Bioavailability 2x with food
- Protein-binding >99%
- Metabolised by CYP3A4, AUC ↓ 50% RIF, ↑ 2-3x RTV
- Inactive monodesmethyl metabolite (M2)
- Complex PK/dosing with loading and terminal $t_{1/2}$ 5.5 months

Andries K 2005 Science 307: 223-7

Bedaquiline : Efficacy

C208 Stage 2:
Time to Culture Conversion (Wk 24 – mITT)



Median time to culture conversion was 12 weeks in the BDQ group and 18 weeks in the placebo group
p-value from Cox proportional model adjusting for strata

FDA NDA 204-384 Briefing package November 2012

Bedaquiline : Safety

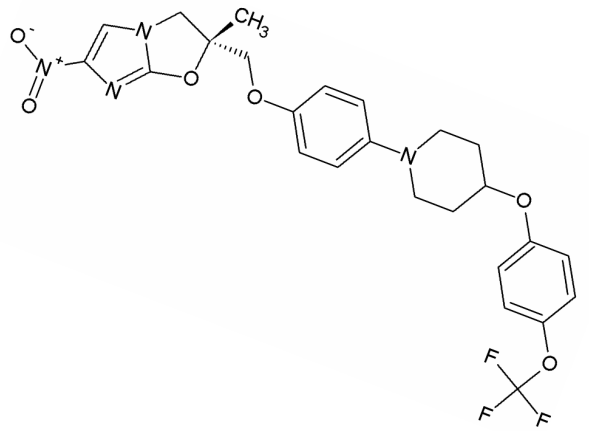
- 12.7% vs 2.5% mortality in C208 trial (p=0.017)
- QTcF prolongation in 26.4% vs 7.7% but no cardiac events
- Conditionally approved with a black-box warning
- WHO guidance recommended informed consent and active pharmacovigilance
- Stronger evidence for early use in MDR-TB then XDR-TB

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis
Interim policy guidance

World Health Organization

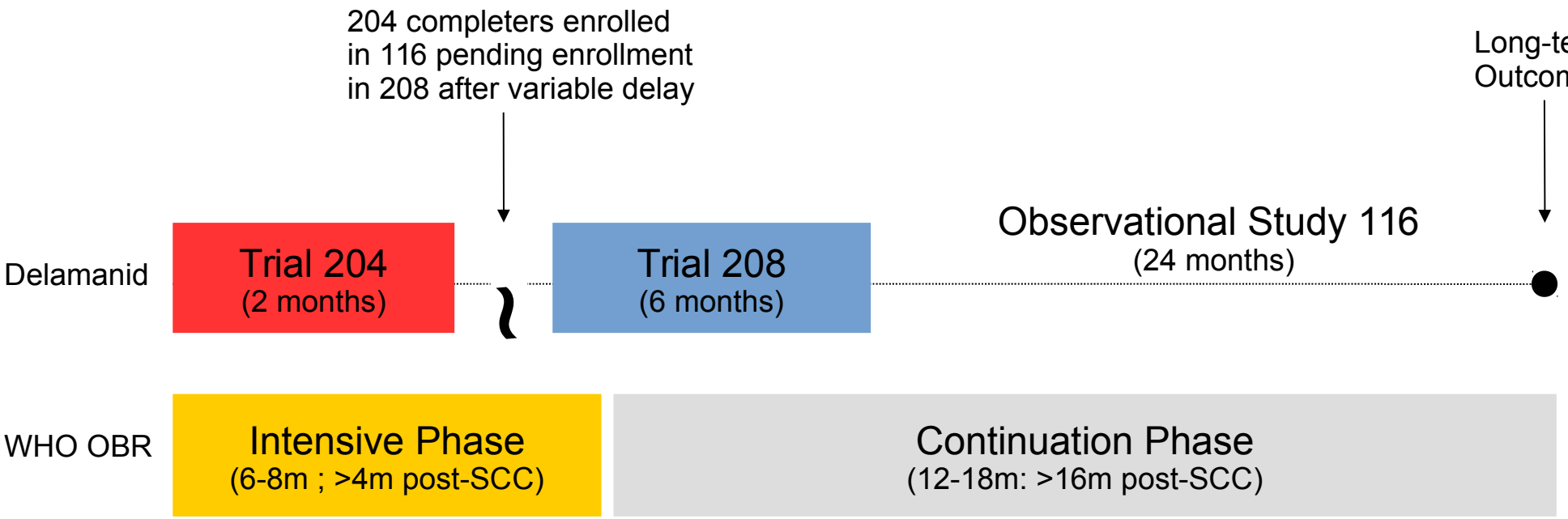
Delamanid : pharmacology

- Target mycolic acid synthesis
- Prodrug substrate for nitroreductases (Rv3547 and F_{420} system)



- Bioavailability 4x with food
- Protein binding >99.5%
- Primary metabolism by albumin amino groups, 8 inactive metabolites
- Some CYP Interaction AUC ↓ 52% RIF, ↑ 20% RTV
- Twice daily dosing with terminal $t_{1/2}$ 32 hours

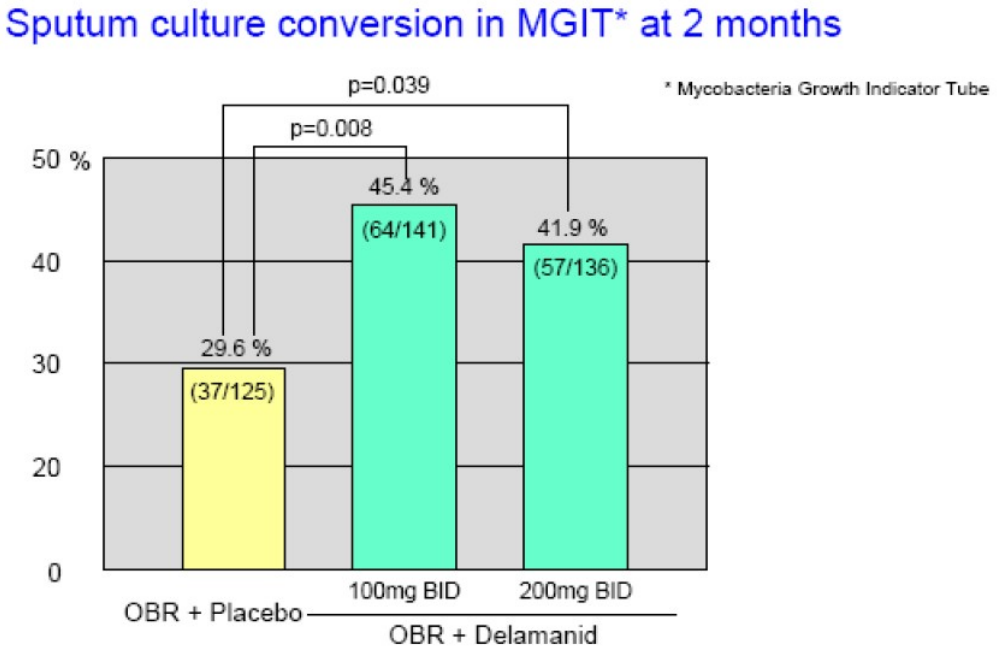
Delamanid : development programme



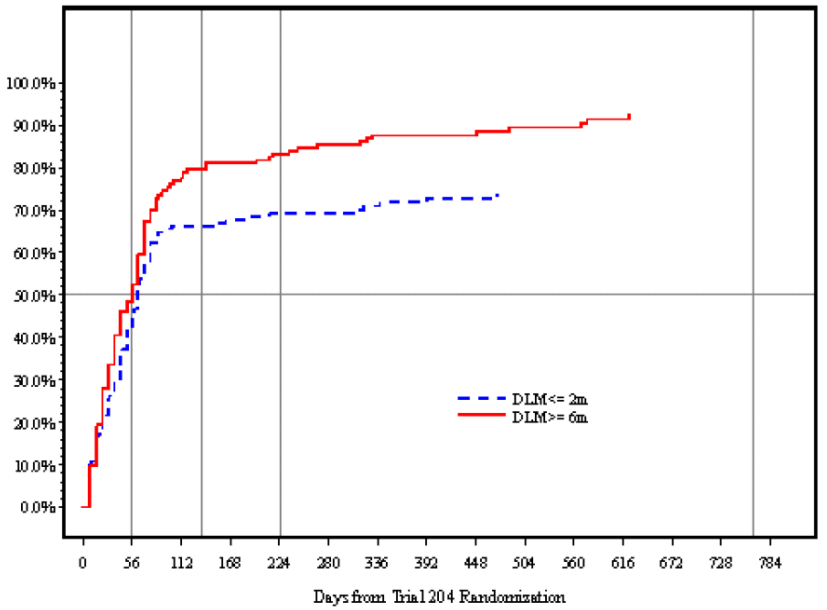
Scripkonoca V Eur Resp J 2013 42 : 1393-400

Delamanid : Efficacy

Trial 204



Trial 208



Mortality 8.3% versus 1% for <2 and >=6m (p<0.001)

EMA Public Assessment Report EMA/CHMP/125521/2013 December 2013

The (Near) Future

- Effective roll-out of novel regimens to NTPs
- Continued efforts to reach an ultra-short regimen for DS-TB (TBTC Study 31)
- Treatment shortening to 9m for MDR-TB (STREAM)
- Completion of Phase III trials for BDQ and DLD (STREAM/ C210, Otsuka 213)
- Evaluation of new drugs in the DS-TB context (NC001-5)
- Promise of Phase III trials of universal regimens (STAND)