Status of TB Drug Pipeline: *Clinical Development*

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Open Forum 4

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Addis Ababa, Ethiopia

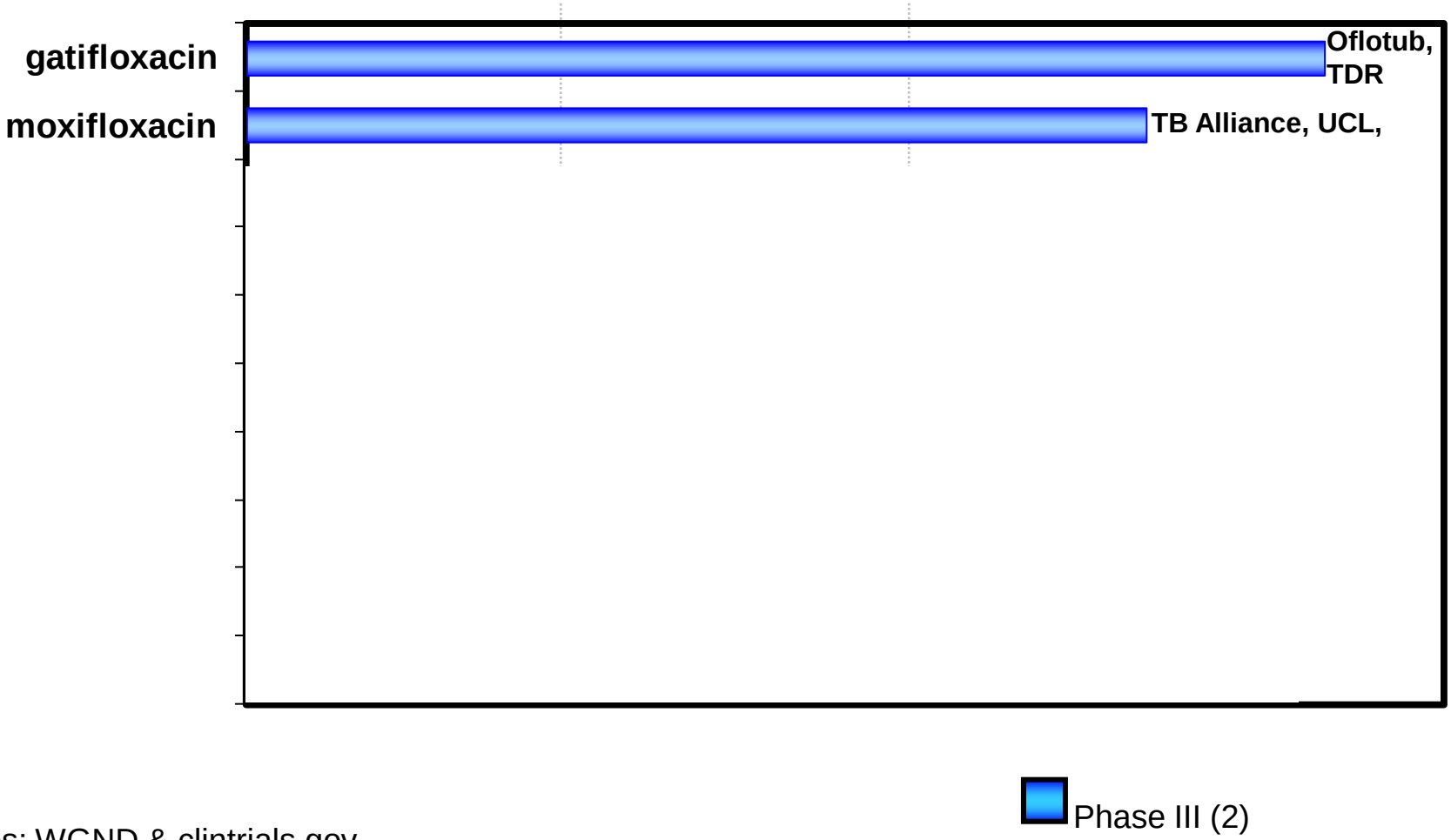
Current TB Therapy and Unmet Needs

Patient Population	Current Therapy	Unmet Needs
Drug-Susceptible DS-TB	4 drugs; ≥6 month therapy (2RHZE + 4RH)	Shorter, simpler therapy
Drug-Resistant M(X)DR-TB	Few drugs (including injectables); ≥18 months; toxicities	Totally oral, shorter, more efficacious and safer therapy
TB/HIV Co-Infection	Drug-drug interactions (DDI) with ARVs	No or low DDI, co-administration with ARVs
Latent TB Infection	6-9 months H	Shorter, safer therapy

* Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)

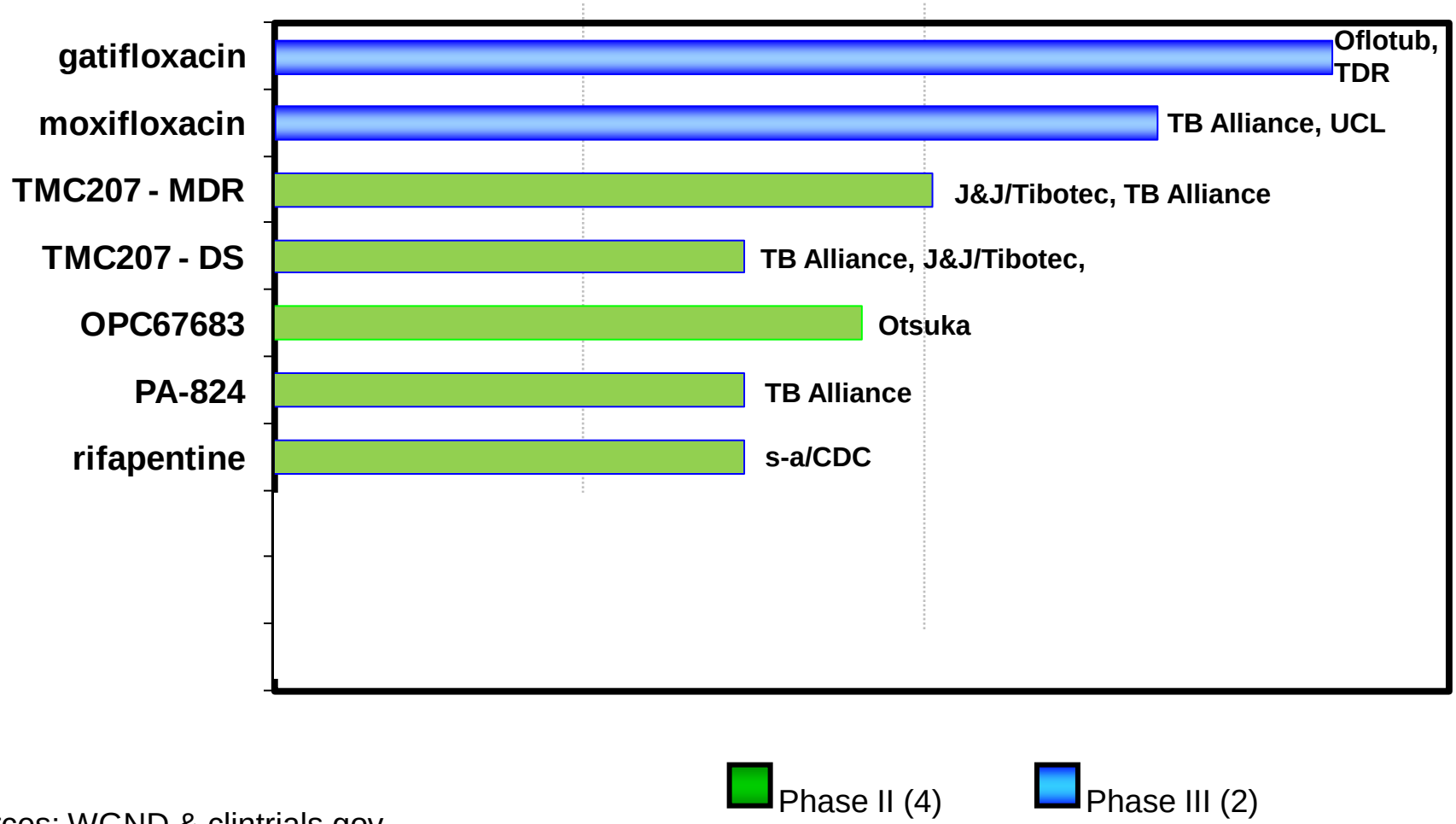
- Need shorter, simpler therapies against both DS and DR-TB
- To accomplish, will need to replace all or most current drugs

TB Drugs in Clinical Development



Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



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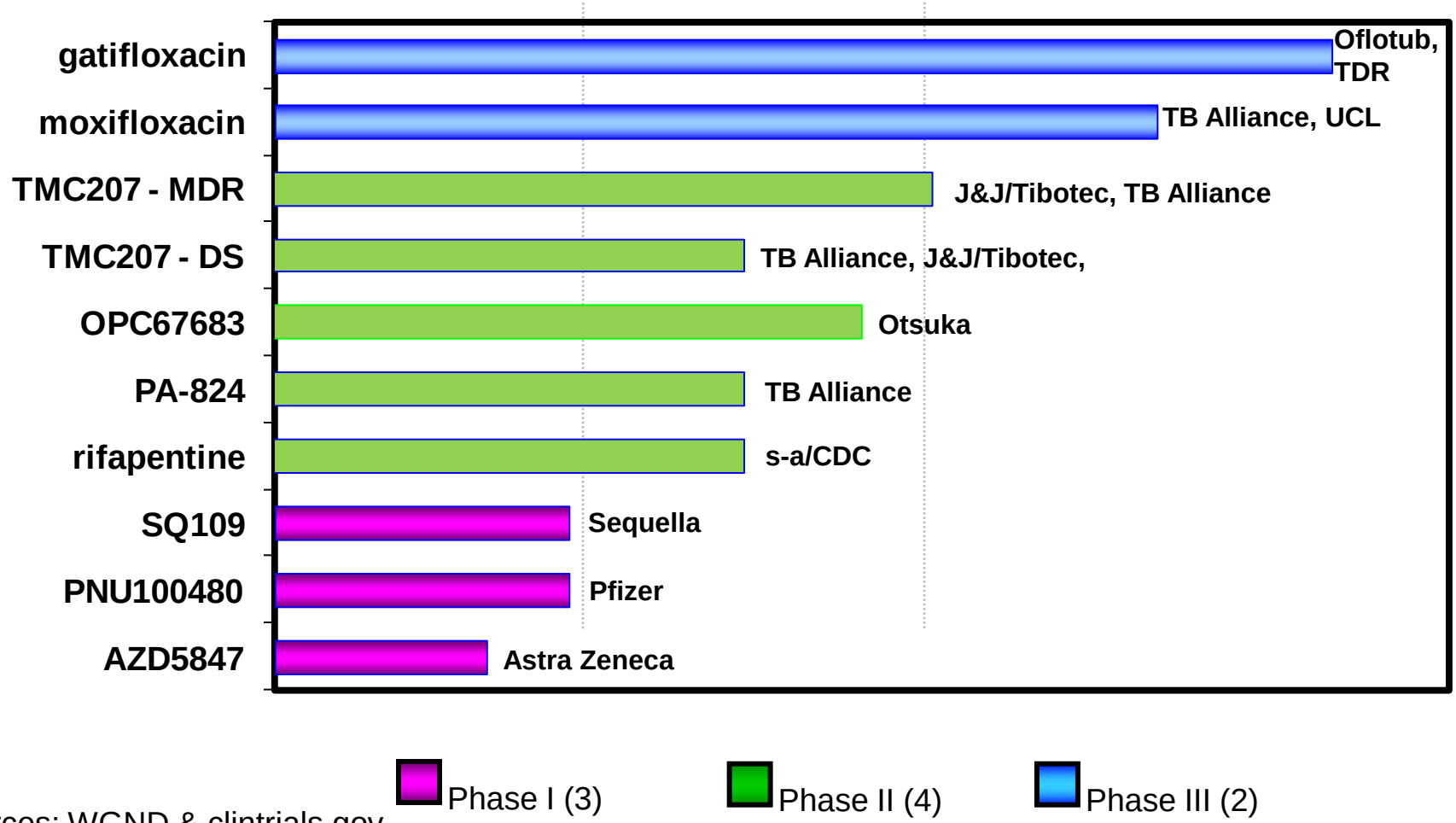

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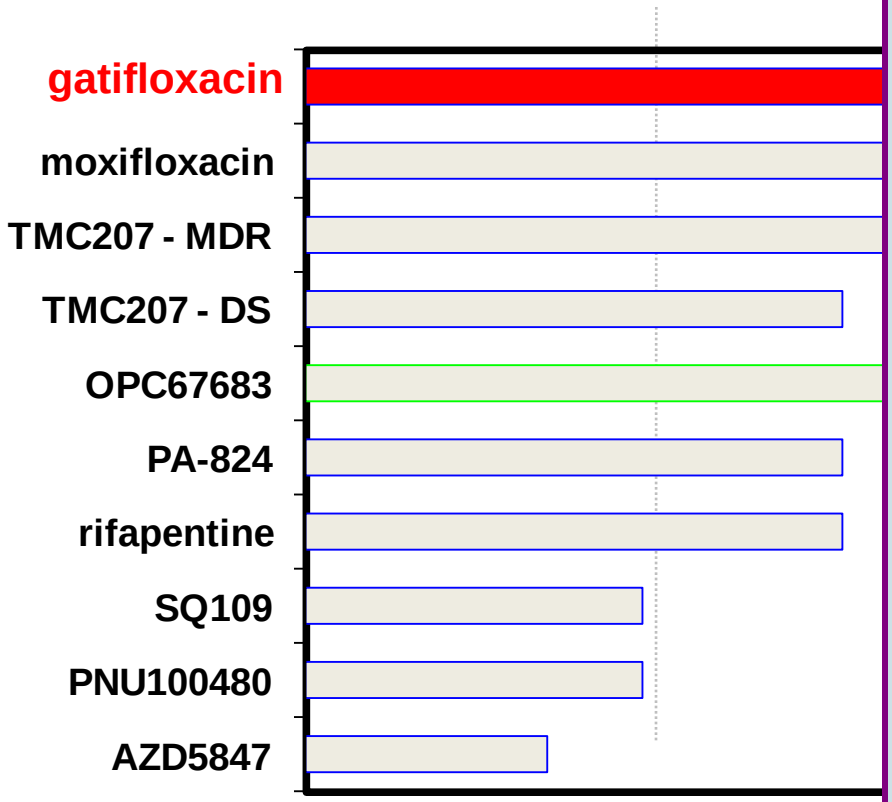


Sponsors:

OFLOTUB Consortium
IRD--C. Lienhardt coordinator
LSHTM, MRC SA, KEMRI, NTPs Benin, Senegal, Guinea, European Commission, WHO/TDR, Inst. of Tropical Med (B)
Lupin Pharma

Drug class:

Flouroquinolone

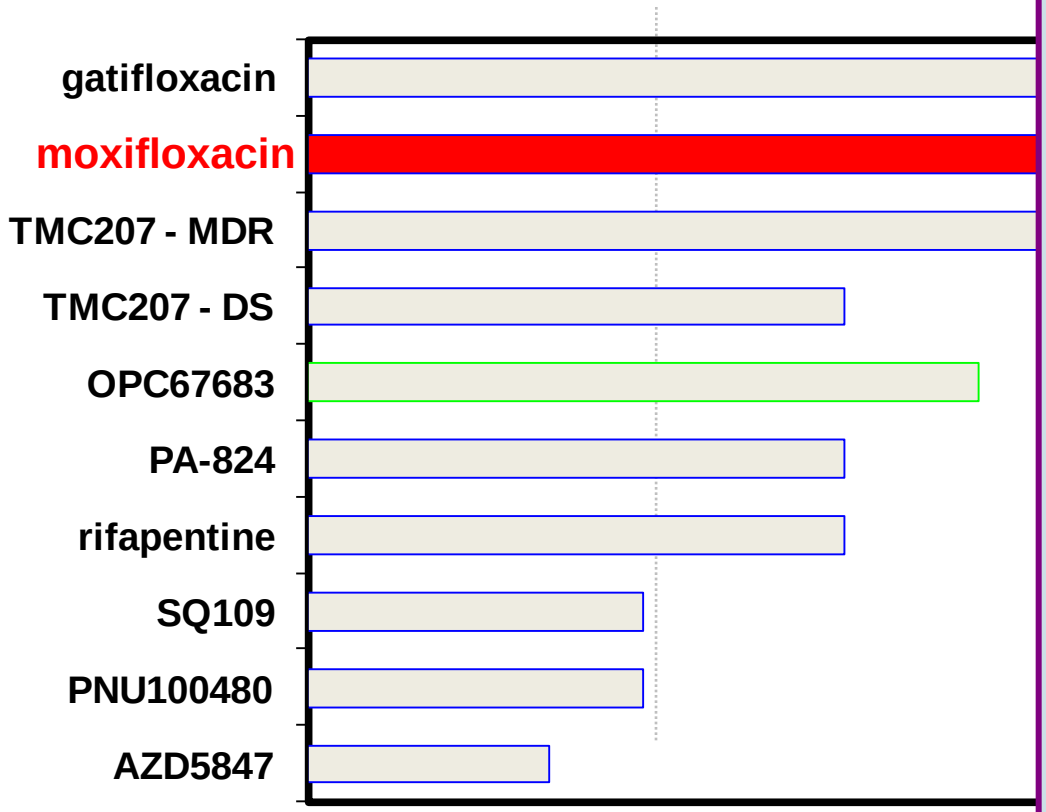
Most advanced Ph III program
1st trial ↓ RX to 4 mo; Follow-up=2 yrs
1 EP: % failure + relapse
Enrollment = 1,836
Completed
Data not yet available

Sites:

Benin, Guinea, Kenya, Senegal, S. Africa

Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



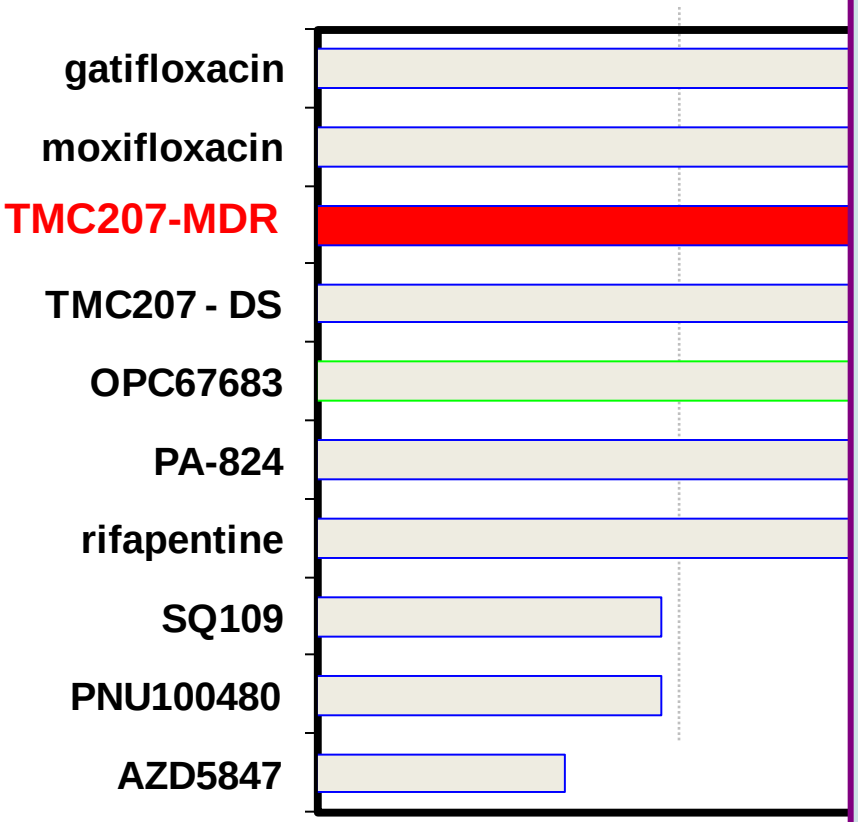
Sponsor: UCL & TB Alliance supported by EDCTP & Bayer

Drug class:
Flouroquinolone

REMox TB (Ph III)
Largest registration trial ever for TB
↓ RX to 4 months
2 experimental arms:
H◂M, E◂M
1 EP: %fail+relapse @ 12 months post Rx
Enrolled > 600
Target = 2,400

Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



Sponsor: J&J/Tibotec

Drug class: diarylquinoline

Study C208 (Ph II)

Stage 1: OBR+TMC 400 mg qd (2wks)
→200 mg 3X/wk (6wks)
(n = 47 completed Stage I)

Results:
Culture conversion after 8 wks →
48 vs 8% (TMC+OBR vs pbo+OBR)

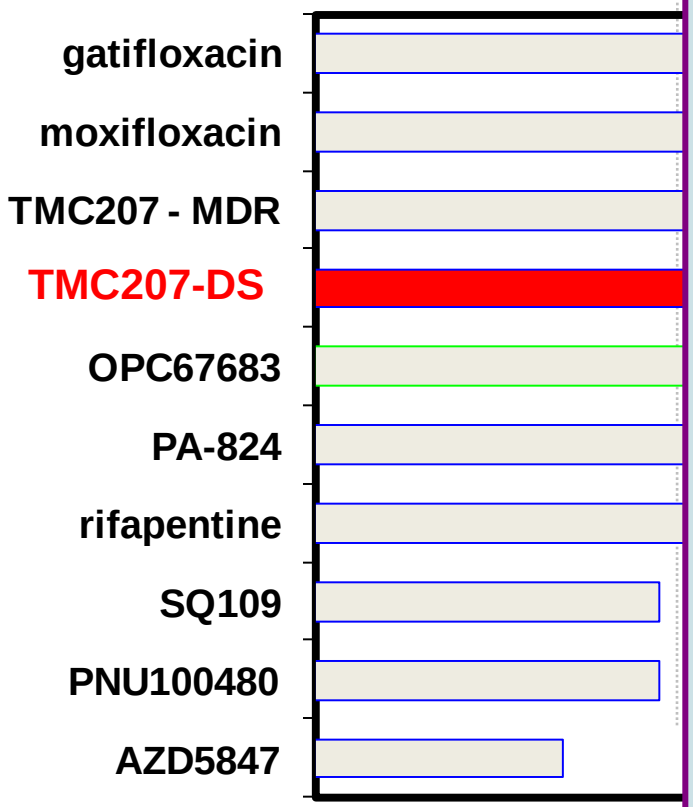
Stage 2: OBR+TMC 400 mg qd (2wks)
→200 mg 3X/wk (22wks)
(n = 150 in stage 2)
2 yr. f/u; safety/PK + relapse

6-mo results from Stage 2 available soon

Ongoing (C209):
Open label study with TMC + OBR
N=225 pts; Rx duration=6 mo
F/U: 19 mo on OBR

Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



Sponsor: TB Alliance

Drug class: diarylquinoline

DDI study completed:

Compared the effects of 2 CYP3A4 inducers R and P on plasma conc of TMC in healthy subjects
Results: both R and P cause ~50% reduction

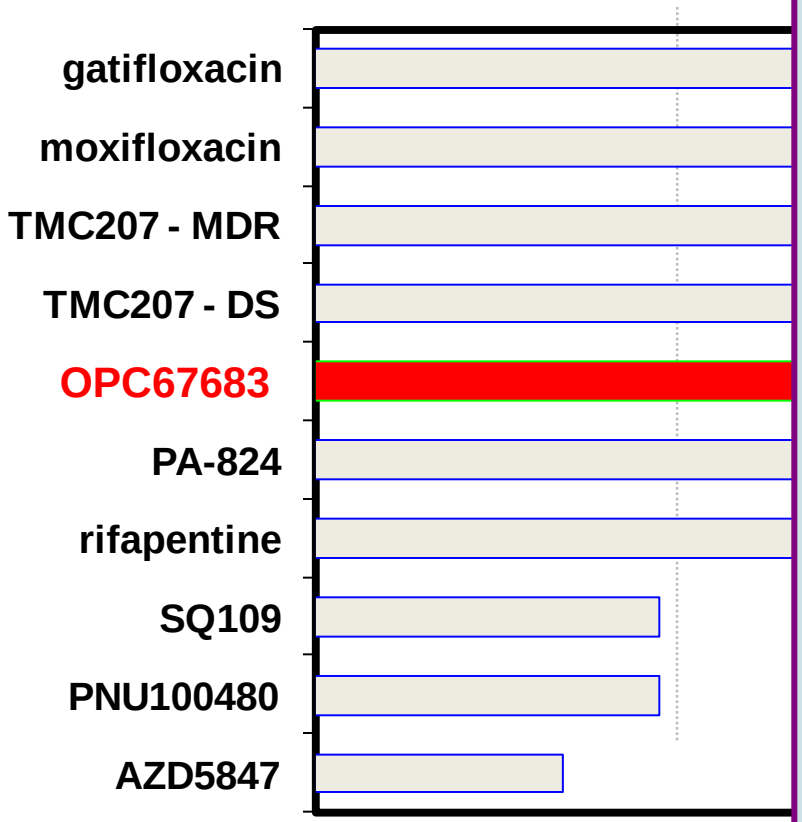
Phase II 14-day EBA study initiated:

In patients with newly diagnosed, smear +, drug sensitive pulmonary TB
Given doses of TMC to achieve Cav (Days 2-14) of ~ 500, 1000, 1500 & 2000 ng/mL
Enrollment is completed
Data anticipated in 4Q 2010

A phase II 14-day combo EBA study is being planned

Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



Sponsor: Otsuka

Drug class: Nitro-dihydro-imidazooxazole

Phase I SD & MD studies completed

Two EBA studies completed

Ph II dose ranging study:

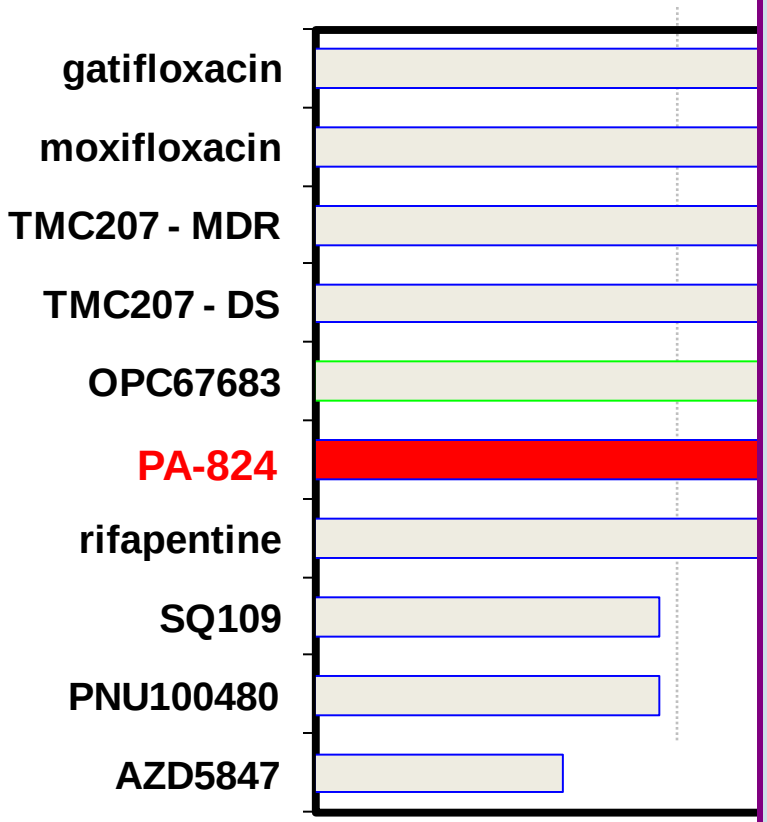
430 MDR pts enrolled & Rxd for 8 wks with Pbo or OPC 100/200 mg BID + OBR
1 EP = Sputum conversion
Results not yet available

Ongoing:

Open-label dose escalation trial to assess The S/T/PK & Efficacy in MDR patients
250-400 mg BID + OBR
N=30
Recruiting in Latvia and Lithuania

Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



Sources: WGND & clintrials.gov

Sponsor: TB Alliance

Drug class: Nitroimidazooxazine

Several Phase I studies completed

Key results:
Well tolerated & PK c/w 1X/day or less freq dosing
No significant food effect at anticipated clinical dose
Not a significant inhibitor/inducer of CYP3A4

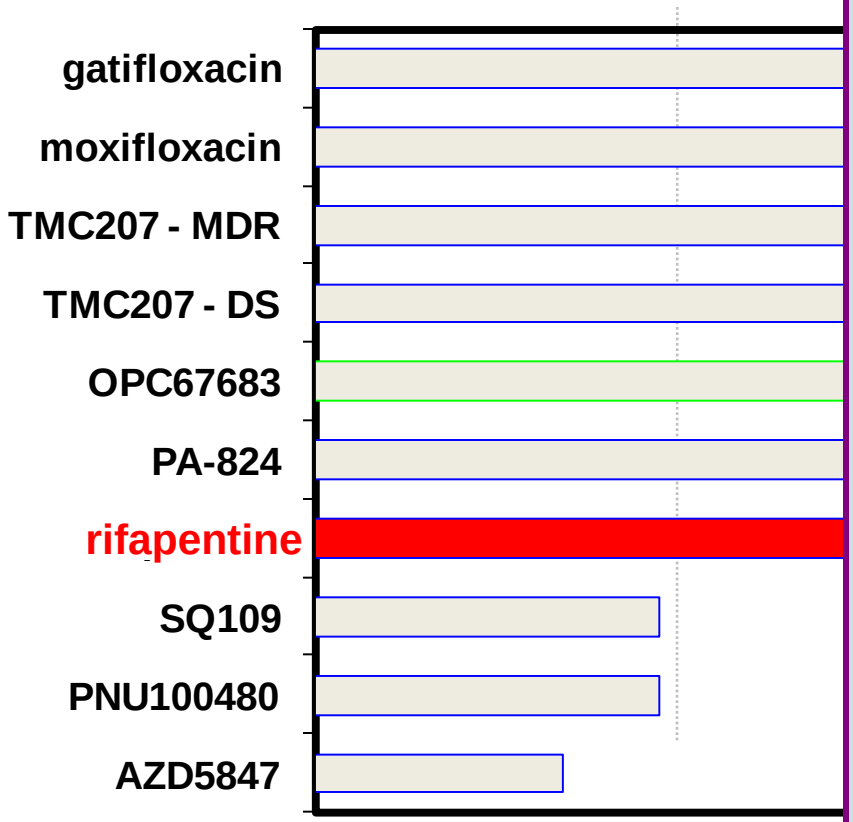
Phase II:
Two 14-day EBA studies in patients with newly diagnosed, smear +, drug sensitive pulmonary TB

First study showed equivalent efficacy of all doses (200, 600,1000,1200 mg/d) evaluated.

Second study evaluated 50, 100, 150 & 200mg/d
Preliminary data analysis revealed evidence of dose-dependent efficacy

A phase II 14-day combo EBA study is being planned

TB Drugs in Clinical Development



Sponsor: CDC & sanofi-aventis

Drug class: Rifamycin

TBTC S29B:

In healthy subjects:
Determine S/T of ↑ doses (5, 10, 15 & 20 m/k/d) as well as effects on induction of metabolizing enzymes
N=36 (M+F)

TBTC S29:

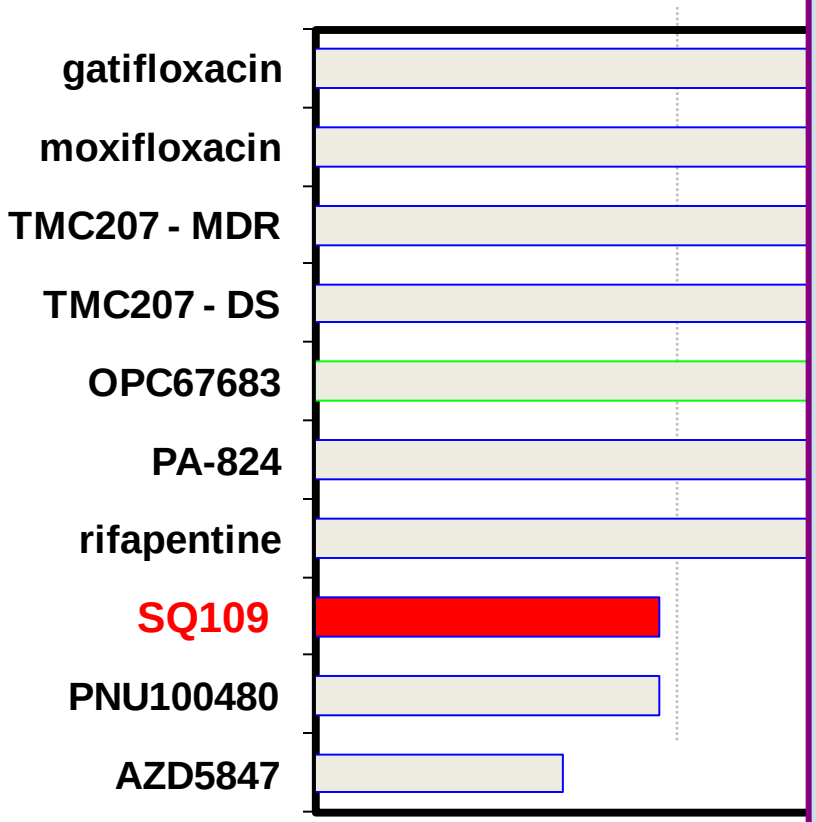
RHZE vs PHZE in patients with pulmonary TB
Both R & P at 10m/k/d
N=480 (M+F)
1 EP = culture conversion after 8 wks (40 doses)

TBTC S26 (LTBI):

Open label study comparing effectiveness of weekly P/H for 3 mos to daily H for 9 mos
In PPD high risk reactors with no active TB
N=8000 (M+F, > 2yr old)

Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



Sponsor: Sequella supported by NIH

Drug class: Ethylenediamines

Phase I:

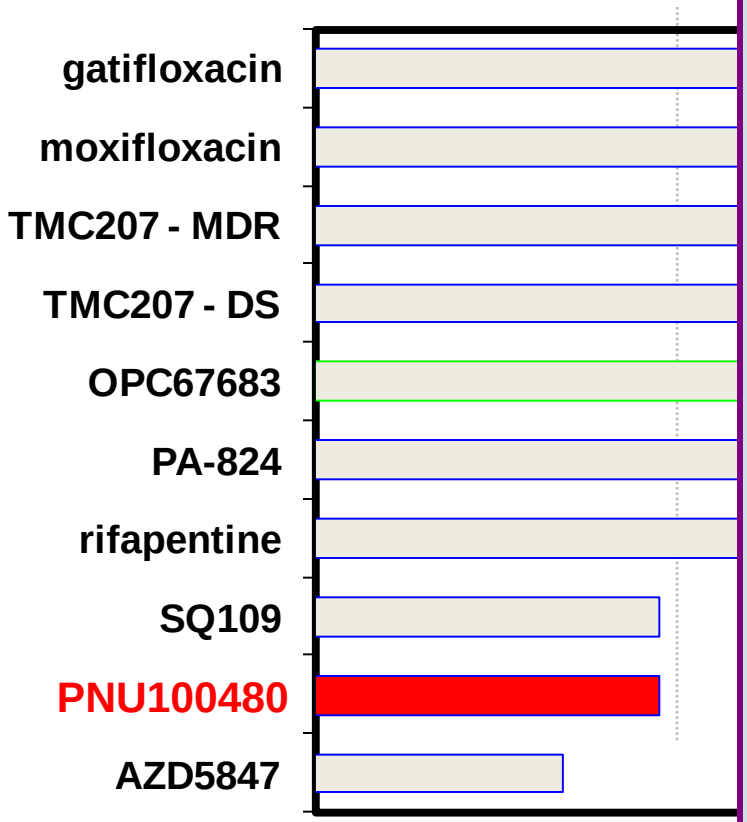
Single ↑ dose study completed
N=62 (M+F)
Doses up to 300 mg well tolerated
61 hr. half-life

Multiple dose study completed
75 and 150 mg for up to 14 days
N=30 (M +F)
Well tolerated and PK data indicated
Steady state was reached by day 7

Based on the data, plan to evaluate 300mg/d for 14 days in healthy subjects

Sources: WGND & clintrials.gov

TB Drugs in Clinical Development



Sponsor: Pfizer

Drug Class: oxazolidinone

A Linezolid derivative with 2 active metabolites

Compared to LZD:

↓MIC50 and ↑MPS IC50
Superior safety margin & bactericidal activity
Earlier sterilization in the mouse model

Phase I:

SD and MD studies in healthy subjects completed
Food effect as well as whole blood bactericidal activity assessed
Data not yet published

Next study likely to be a Phase II EBA study in patients with pulmonary TB

Sources: WGND & clintrials.gov

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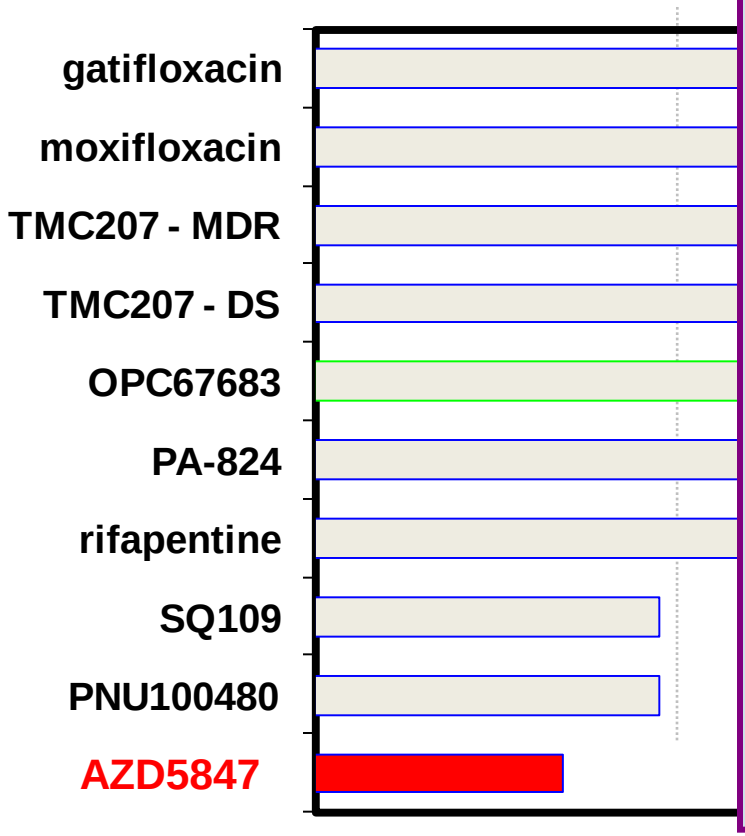

Sponsor: AstraZeneca

Drug Class: oxazolidinone

Phase I:

Single dose study in healthy subjects completed
Food effect also assessed
Data not yet published

Multiple dose study in healthy subjects enrolling
Daily dosing up to 14 days
N=60 (M+F)

Next study likely to be a Phase II EBA study in patients with pulmonary TB

Sources: WGND & clintrials.gov

Summary

- Great need for new drugs to address the challenges and unmet needs in TB therapy
- Need for a stronger and more robust global TB drug pipeline
  - Resurgence in TB drug R&D
- Need a new approach to the clinical development of novel anti-TB drug regimens
  - Will be reviewed in the next session

Thank you