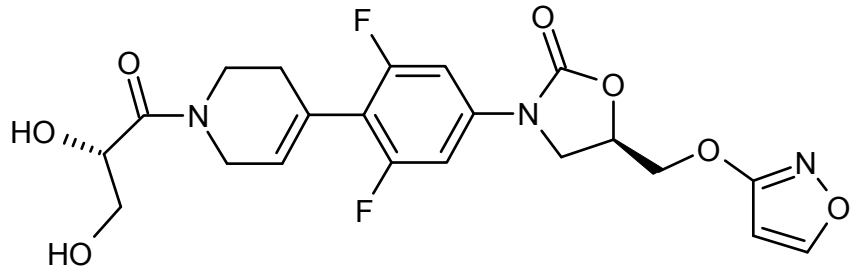
AZD5847

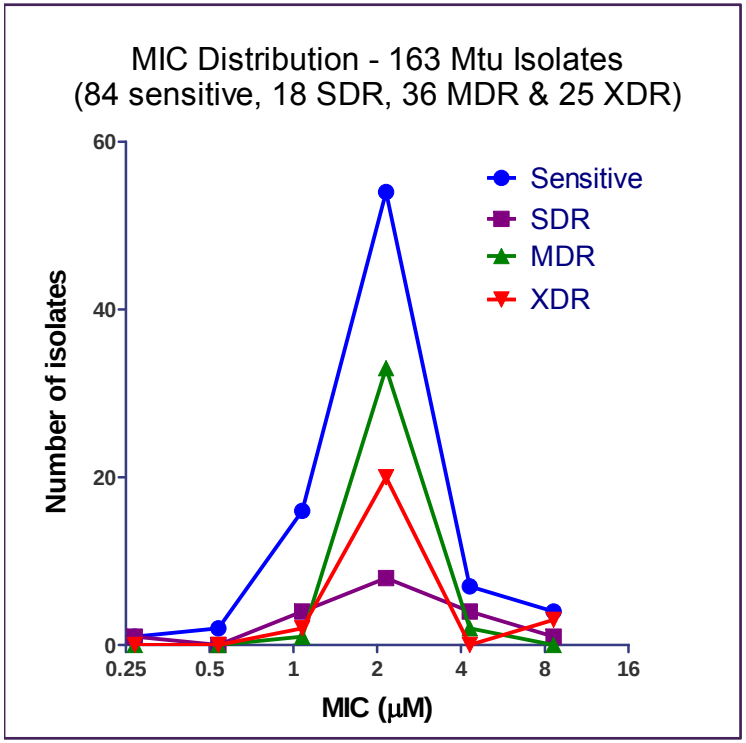


Phase 1 completed in healthy volunteers

- Bactericidal vs. multiple physiological states of TB bacteria: an uncommon attribute among TB drugs
- Well tolerated at predicted therapeutic dose in healthy volunteers
- Hematologic toxicities, a key risk seen at exposures above the predicted therapeutic dose

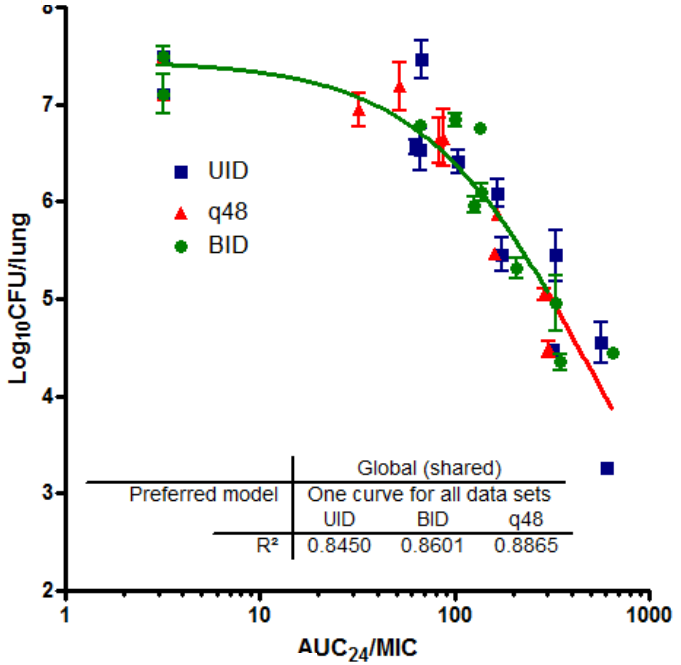
Risk versus benefit is the key question

Key Pre-clinical Data

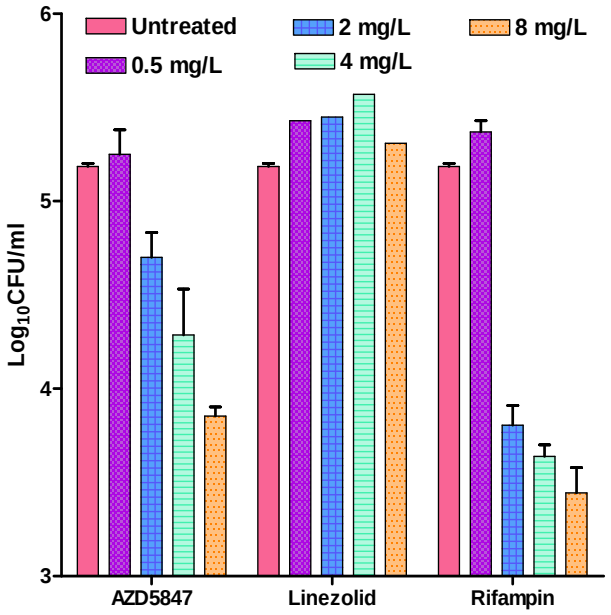


Excellent intracellular and in vivo efficacy vs TB

Efficacy in the Mice Model of TB

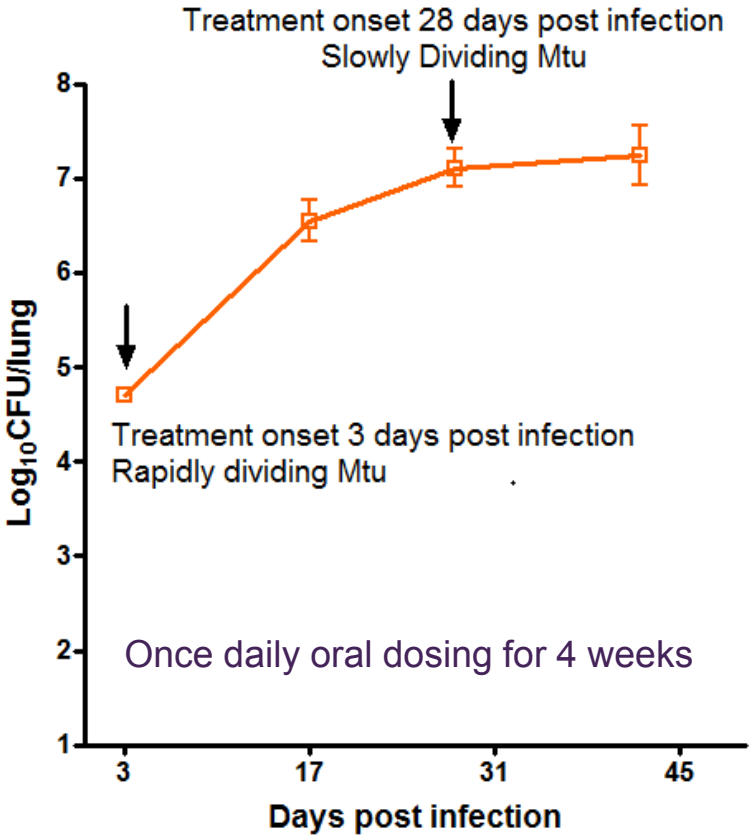


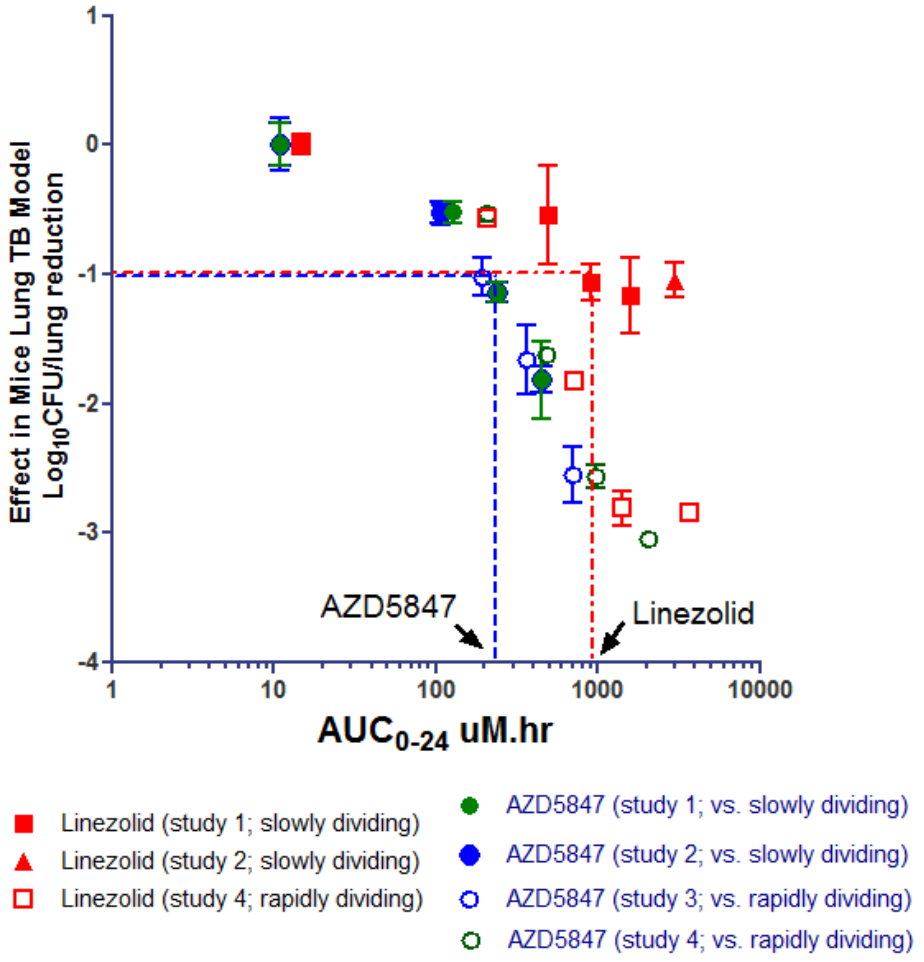
Efficacy in the Macrophage Model of TB



AZD5847 retains PKPD index vs. rapidly dividing and slowly dividing Mtu in mouse lung TB model

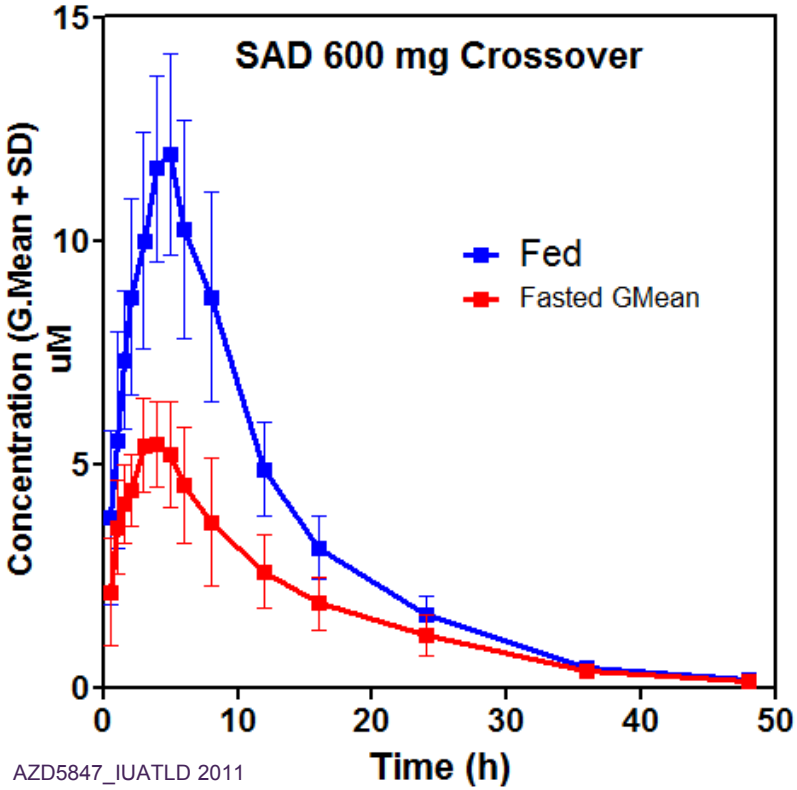
- AZD5847 and linezolid are equally effective versus rapidly dividing Mtu in mouse lung TB model
- But, AZD5847 has superior activity versus **slowly dividing** Mtu, that is key to achieving sputum sterilization.

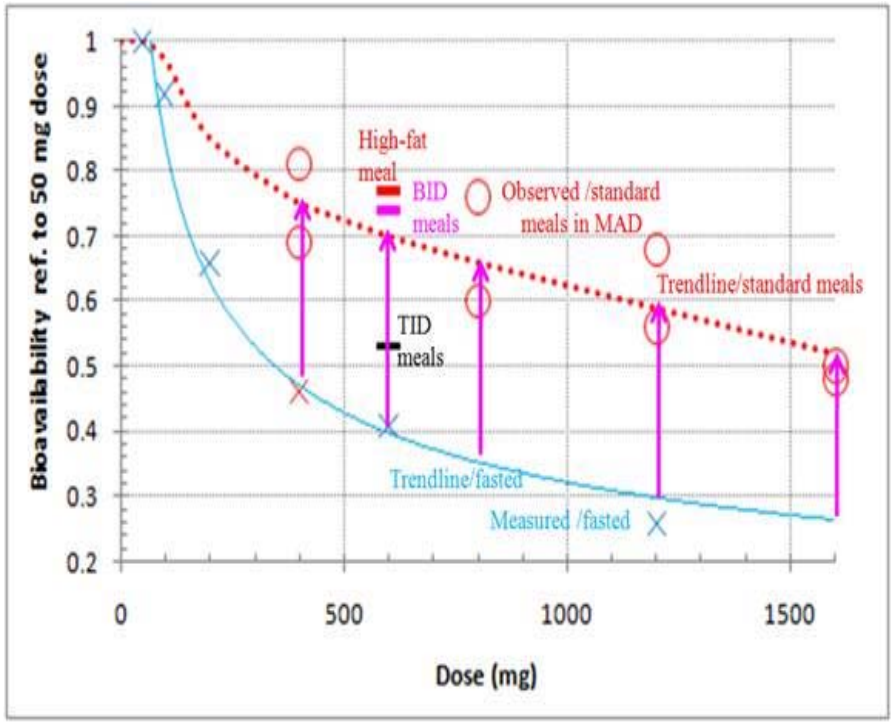




Key Clinical Data: Phase 1

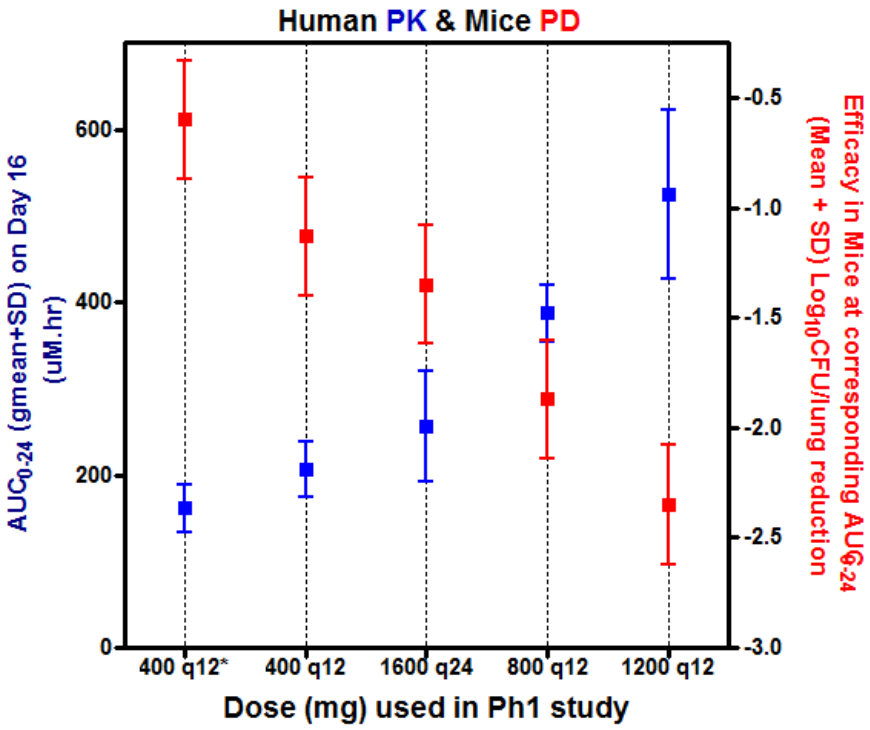
- The maximum dose administered was 1200mg PO q12h x 14 days
  - Maximum gmean daily AUC: 524.6 µM.hr (fAUC 104.9 µM.hr)
  - Maximum gmean Cmax: 31.8 µM (fCmax 6.4 uM)
- Bioavailability decreases with increasing dose, but largely compensated if taken after meals





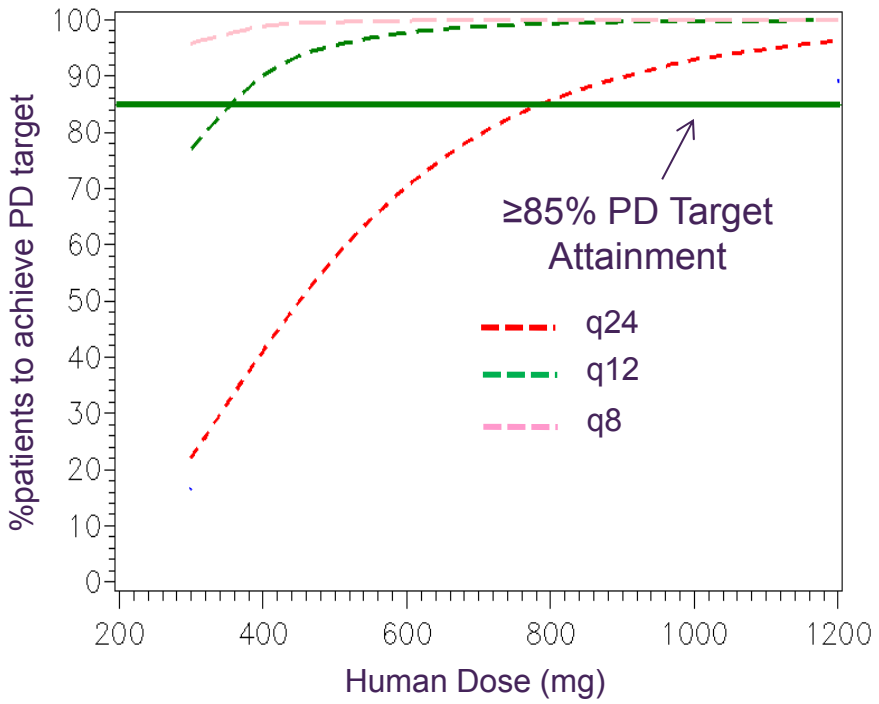
Key Clinical Data

Exposures in Phase 1 correspond to efficacious level in the mouse model



Modelling of Ph1 Data for Likely Attainment of Preclinical PD Target

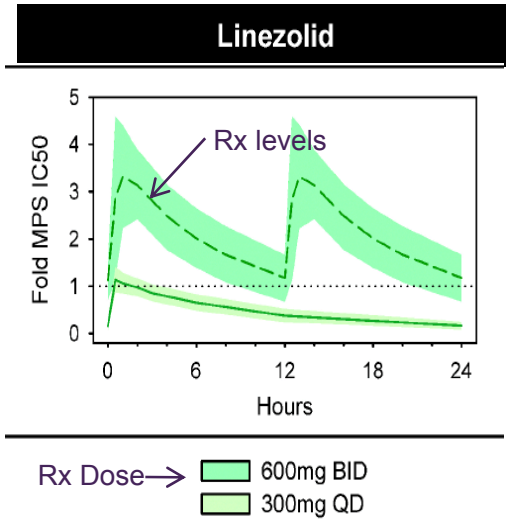
- Inter-subject PK variability and the MIC distribution for *M. tuberculosis* are taken into account
- Monte-Carlo simulation is used to calculate target attainment in ≥85% patients



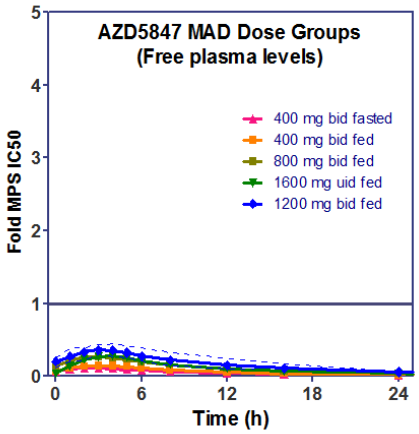
800 mg qd / 400 mg q12 likely to give efficacy

Key Safety Data: **M**itochondrial **P**rotein **S**ynthesis inhibition

- For linezolid, the linkage to myelotoxicity, lactic acidosis and neuropathy may be MPS inhibition[1,2,3]
- At the approved dosage (600mg PO q12h), linezolid plasma levels are above the *in vitro* IC_{50} for MPS during the entire dosing interval, which may explain its toxicity upon use >14 days[4]
- AZD5847 offers an increased margin vs. in vitro MPS. Longer term studies will be required to determine the clinical significance of this observation.



AZD5847: Phase 1 data



1. Garrabou, G., Soriano, A., et al.. (2007). Antimicrob. Agents Chemother. 51, 962-967.
2. Nagiec, E. E.; Swaney, S. M.; et al.. (2005) Antimicrob. Agents Chemother. 49, 3896-3902.
3. McKee, E. E.; Ferguson, M.; et al.. (2006) Antimicrob. Agents Chemother. 50, 2042-2049.
4. Wallis R. S. et al.. (2011) Antimicrob Agents Chemother. 55(2):567-74.

Salient Features

Mechanism of action

- AZD5847 targets bacterial protein synthesis
- Bactericidal vs. clinical *M. tuberculosis* (Mtu) isolates (susceptible, MDR- and XDR-isolates)
- AZD5847 demonstrates activity vs. extracellular, intracellular, rapidly dividing and slowly dividing Mtu in mouse model of tuberculosis

PK/PD

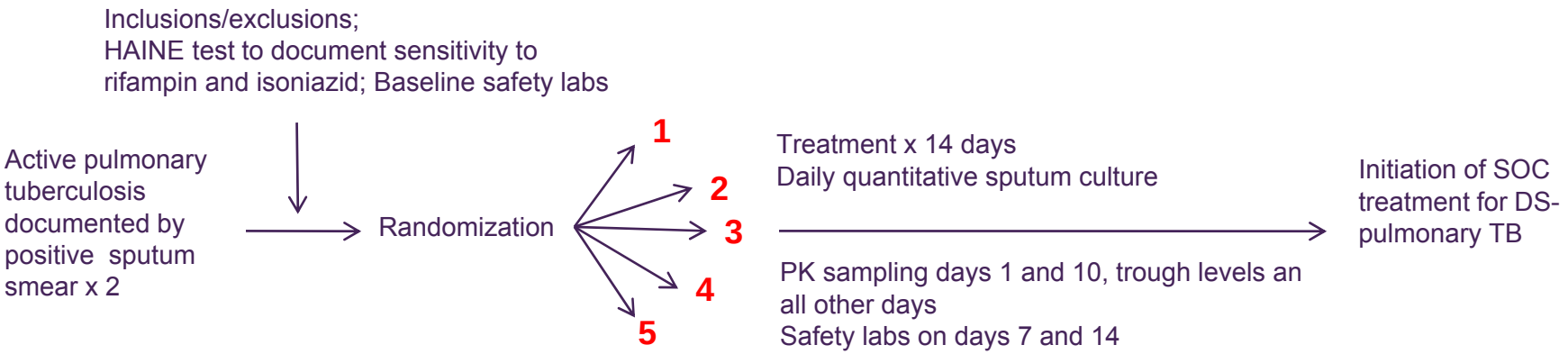
- Efficacy in the mouse lung TB model is linked to AUC/MIC
- AZD5847 is not an inducer or inhibitor of major CYPs
- Human PK data show that food enhances bioavailability such that therapeutic exposure levels predicted from PK/PD modeling have been achieved.

Safety

- AZD5847 generally well tolerated over 14 days in healthy volunteers
- Reversible changes in WBC and reticulocyte counts seen at exposure > predicted therapeutic
- Improved *in vitro* margin vs. inhibition of mitochondrial protein synthesis for AZD5847 vs. linezolid
- Inhibits human Monoamine oxidase A *in vitro*

Phase 2a: (Supported by NIAID)

Study to be conducted in South Africa
Principal Investigators:
Andreas Diacon, Cape town, S. Africa; Henry Boom, Case Western Reserve, Cleveland, USA



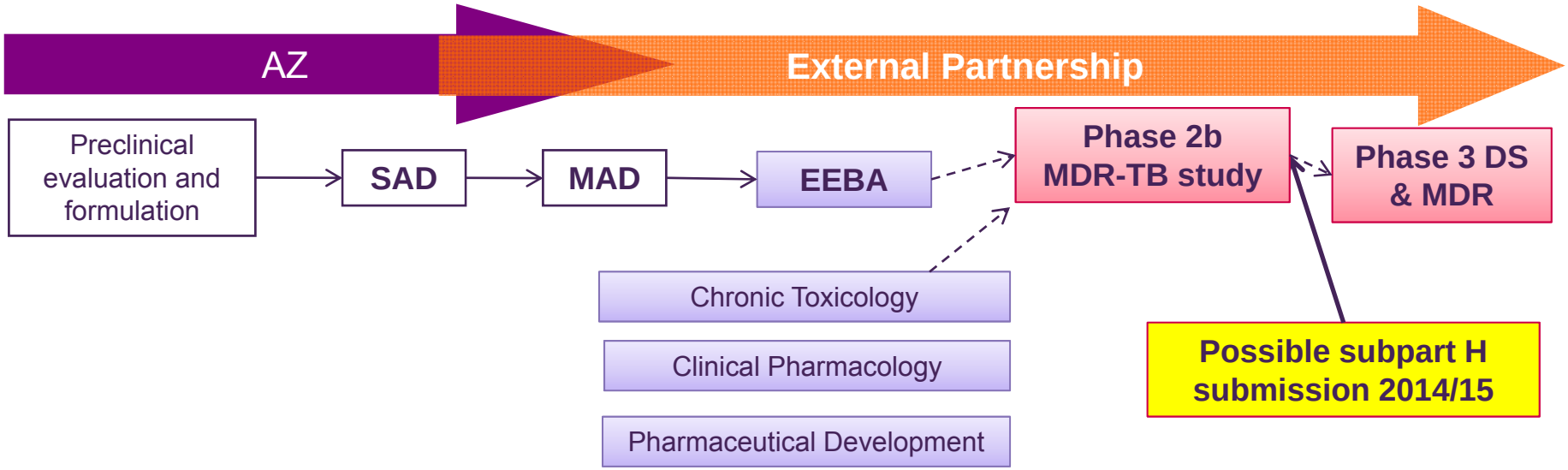
Treatment groups with Diol

1. **AZD5847 500mg qd**
2. **AZD5847 500mg bid**
3. **AZD5847 1200mg qd**
4. **AZD5847 800mg bid**
5. **Rifafour 1 tab PO qd**

AZD5847 Dosing regimens	Cmax range (µM)	Total Daily AUC range (µM.hr)
500 mg, QD	9.5-11	131 -146
500 mg, BID	12-15	250 - 304
1200 mg, QD	17-21	228 - 288
800 mg, BID	17-21	352 - 430

Current Development Strategy for AZD5847

Next step: Phase 2a EEBA study via NIAID support



Line of sight (Clinical Plan & Partnerships)

Platform of evidence	• Bactericidality, activity against resistant TB, and efficacy in mouse models of TB • Effective against intra- and extracellular TB • Confidence in oxazolidinone class as effective clinical anti-TB agents • Predicted therapeutic range covered in GLP toxicology in rats and dogs	**Pre-clinical: AZ**
POP	• Demonstrated from Phase1 Single and multiple (14 days) day dosing studies (max dose 1200mg PO q12h x 14 days) - tolerated exposures in healthy volunteers exceeded predicted efficacious exposures, as predicted by preclinical PD models • Food (irrespective of type of food) enhanced bioavailability.	**Ph1: AZ**

POC	• Ph2a planned with NIAID to demonstrate bactericidal activity of AZD5847, following 14-day monotherapy in DS TB patients. Bactericidal activity and acceptable tolerability profile will enable progression to Ph2b
	• Adequate oral bioavailability in tablet (needs to be established)
	• Ph2b objective (to be partnered): Objective -Superiority over placebo in combination with background regimen in MDR-TB patients.
	  • Faster rate of sputum negativity achieved in MDR patients in the AZD5847 arm
	  • Higher percentage of patients achieve sputum negativity in the AZD5847 arm
		Ph2a: NIAID
		Ph2b: seeking partners

DFL	• Subpart H approval from FDA based on Ph2b outcome • AZD5847 as part of novel combination(s) for achieving sputum sterilization and reduce duration of treatment in comparison to SOC.	**Ph3: seeking partners**
Vision	*A safe, effective antituberculosis agent with options for novel combinations treating drug-sensitive and drug-resistant TB patients, including HIV co-infected patients, and offering a public health benefit from reduced infectivity.*	