

AZD5847

Oxazolidinone for the treatment of Tuberculosis

Scott Butler

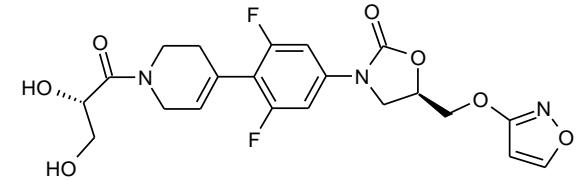
Infection Innovative Medicines Group
AstraZeneca R&D, Boston



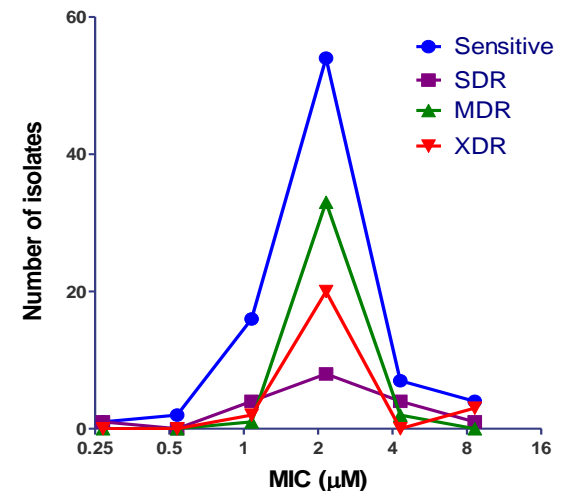
Key Features of AZD5847

Product Concept: Oxazolidinone suitable for use in combination therapies to treat DS and/or MDR/XDR tuberculosis (+HIV co-infected)

- AZD5847 binds 50S ribosomal subunit and blocks initiation of protein synthesis
- Bactericidal against *M. tuberculosis*: susceptible, MDR- and XDR-TB isolates
- AZD5847 is active against extracellular, intracellular, rapidly dividing, and slowly dividing mycobacteria in mouse models
- In vitro data suggests low DDI risk with likely combination drugs (including antiretrovirals)
- Generally safe and well tolerated over 14 days (volunteers and patients)



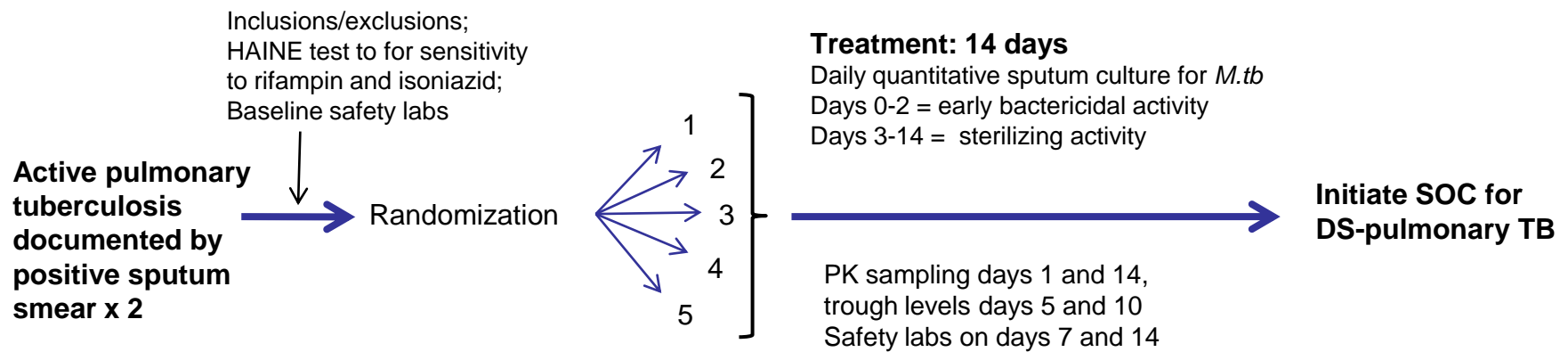
MIC distribution – 163 TB isolates
(84 sensitive, 18 SDR, 36 MDR & 25 XDR)



Phase 2a: EBA Study (Sponsored by NIAID)

Short duration (14 days) monotherapy with AZD5847 in patients with drug sensitive TB

- Ongoing in South Africa (TASK, Andreas Diacon)



Treatment groups (total enrollment ~75: **15 per arm**)

1. AZD5847 500mg qd
2. AZD5847 500mg bid
3. AZD5847 1200mg qd
4. AZD5847 800mg bid
5. Rifafour 1 tab PO qd (weight based)

Endpoint: Rate of change in sputum colony forming unit (CFU) counts (bactericidal activity) during the entire 14 days of study drug administration (EBA0-14)

Phase 2a: EBA Study Status

- **As of September 25:**
 - 57 patients enrolled
 - 36 have completed the protocol
 - Generally very well tolerated
 - Last patient expected to complete follow up in December
- **Final study report expected ~April 2014**

From September monthly report:

Characteristics	Study Drug Arm					Total N=48
	Rifabutin (EHRZ) n=10	AZD5847 500 mg qd n=10	AZD5847 500 mg bid n=9	AZD5847 1200 mg qd n=10	AZD5847 800 mg bid n=9	
<u>Demographic:</u>						
Age (yrs), median (IQR)	41 (27)	26 (21)	29 (9)	36 (11)	35 (8)	35 (19)
Male, n (%)	7 (70)	9 (90)	6 (67)	7 (70)	8 (89)	37 (77)
<u>Clinical:</u>						
Body weight (kg), median (IQR)	45 (6)	52 (8)	47 (20)	54 (10)	56 (7)	51 (13)
BMI (kg/m ²), median (IQR)	17 (4)	19 (2)	17 (5)	20 (3)	20 (3)	19 (4)
<u>Laboratory</u>						
Hemoglobin (gm/dL), median (IQR)	12 (2)	12 (4)	12 (3)	12 (1)	12 (1)	12 (2)
WBC (10 ³ cells/mm ³), median (IQR)	13 (5)	10 (7)	9 (2)	9 (2)	8 (3)	9 (4)

BMI = Body Mass Index, weight was measured in kilograms (kg) and height in meters (m).
WBC = White-blood-cell count; IQR = Interquartile Range.

90 Day Chronic Toxicology - Mouse

- Study Sponsored by DMID, NIAID
- In life completed

Treatment Level (mg/kg)	Dose Conc. (mg/ml)	# Animals		No. Undosed Females for Mating	No. TK Satellite Animals
		Day 91	Day 182		
0	0	10 M/10 F	6 M/6 F	16F	3 M/3 F
50	5	10 M/10 F	---	16F	9 M/9 F
250	25	10 M/10 F	---	16F	9 M/9 F
1000	100	10 M/10 F	10 M/10 F	16F	9 M/9 F
Total No. Animals		40 M/40 F	16 M/16 F	64 F	30 M/30 F

- Overall, AZD 5847 was well tolerated in male and female CD-1 mice after repeat oral gavage administration of 50, 250, or 1000 mg/kg for 90 days
- Draft Histopathology report due 14 Oct 2013.
- Draft final report due 31 Jan 2014.

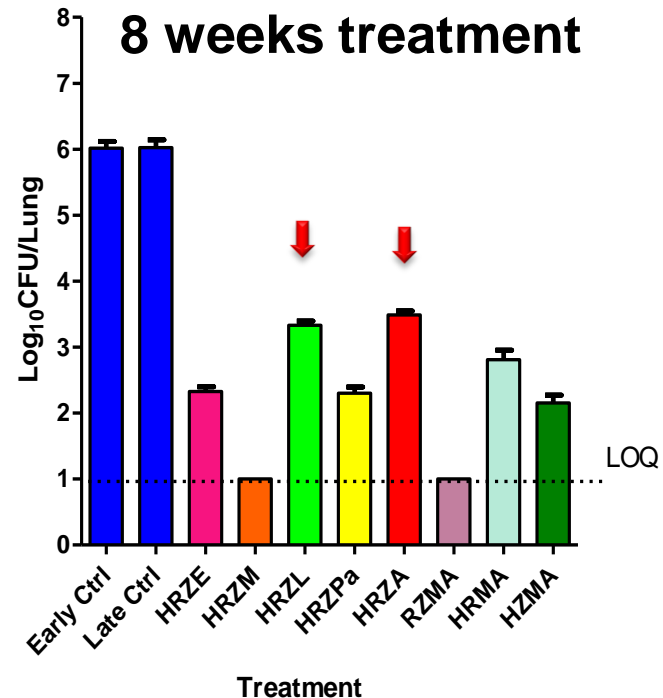
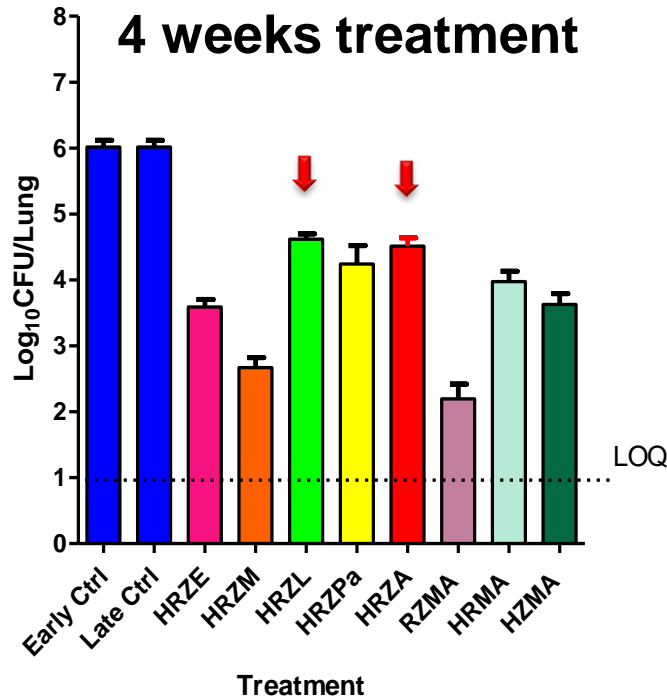
90 Day Chronic Toxicology - Dog

- Study Sponsored by DMID, NIAID
- In life study is ongoing

Treatment Level (mg/kg)	Dose Conc. (mg/ml)	No. Animals Sacrificed	
		Day 91	Day 182
0	0	3 M/3 F	3 M/3 F
5	2.5	3 M/3 F	---
20	10	3 M/3 F	---
60	30	3 M/3 F	3 M/3 F
Total No. Animals		12 M/12 F	6 M/6 F

- To date, AZD 5847 has been well tolerated in male and female beagle dogs after repeat oral capsule administration of 5, 20, or 60 mg/kg for 90 days
- Main necropsy scheduled for 18 Sept 2013
- Draft final report due 30 Apr 2014.

AZD5847 and Linezolid show similar efficacy in combination with SOC

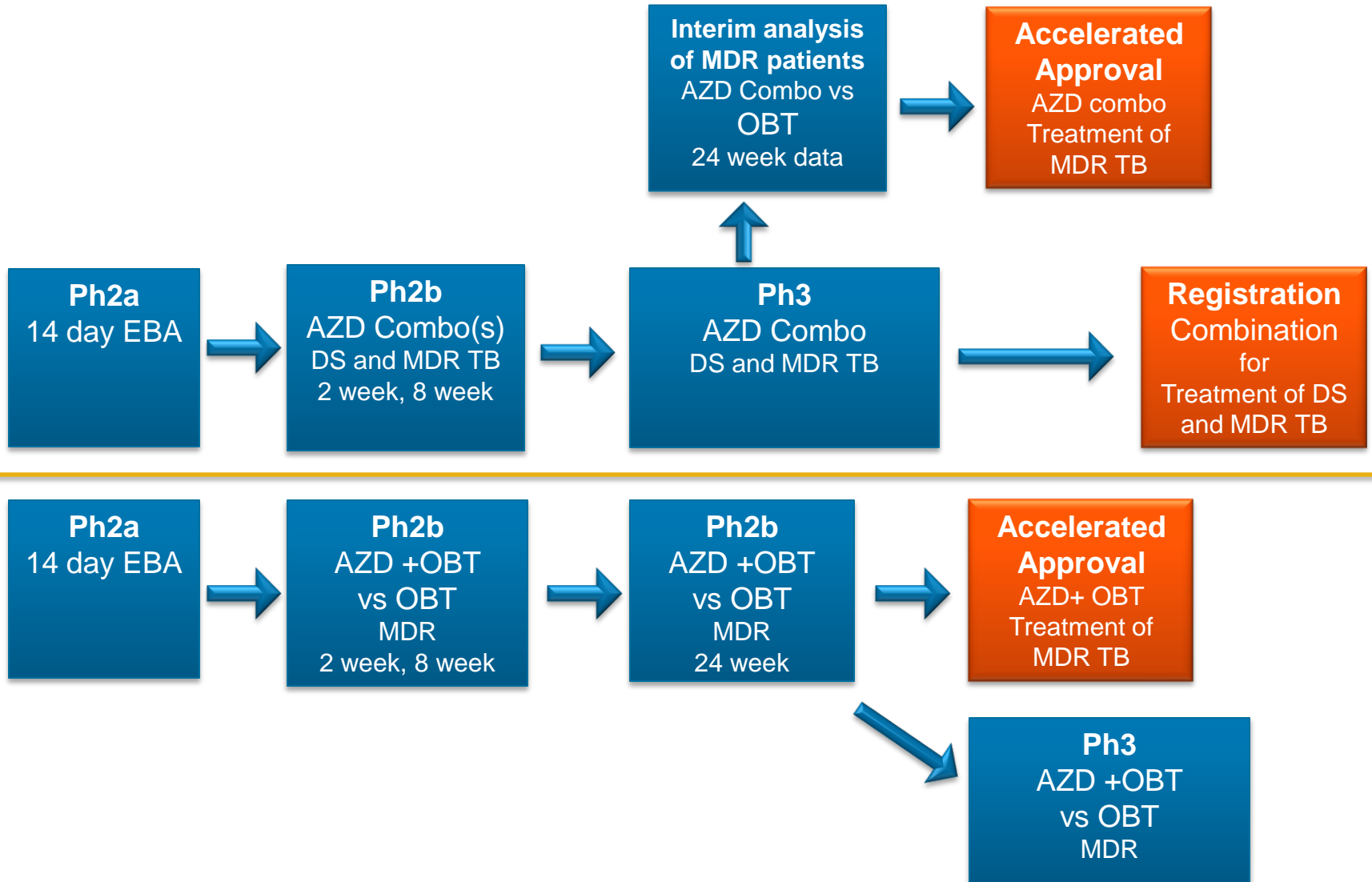


- New novel combination studies ongoing in mouse chronic infection and relapse model (E. Nuernberger, sponsored by Global Alliance for TB)

Looking Toward Phase 2b Studies

- **Pharmaceutical Development**
 - DMID sponsored formulation development and manufacture of capsules to support Ph2b studies
- **Understanding potential Drug-Drug Interactions**
 - AZD5847 is a substrate of P-gp/BCRP and acid metabolite is a substrate of OATP1B1/1B3
 - AZD5847 inhibits OATP1B1 (IC_{50} 33 μ M)
 - In vitro studies on UGT1A1 and several transporters, including OATP1B1, OAT1, OAT3, OCT2, BCRP, and others
 - Confirm the proposed major route of elimination through hepatic metabolism by human 14 C ADME

Development Pathways



Summary

- **Oxazolidinones offer a promising (clinically validated) addition to future combination regimens**
 - MDR/XDR treatment or simplified/reduced duration SOC
- **AZD5847 has potential to differentiate among oxazolidinones:**
 - Active against slowly dividing *M. tuberculosis*
 - Active against intracellular *M. tuberculosis*
 - Potential for improved safety profile
- **AZD5847 is generally safe and well tolerated at predicted efficacious doses**
- **Phase 2a trial to finish clinical phase in December 2013**
 - Final study report ~April 2014
- **Work ongoing to position AZD5847 for Phase 2b by mid 2014**
 - With safety coverage for up to 90 days treatment