New Anti-Tuberculosis Drugs

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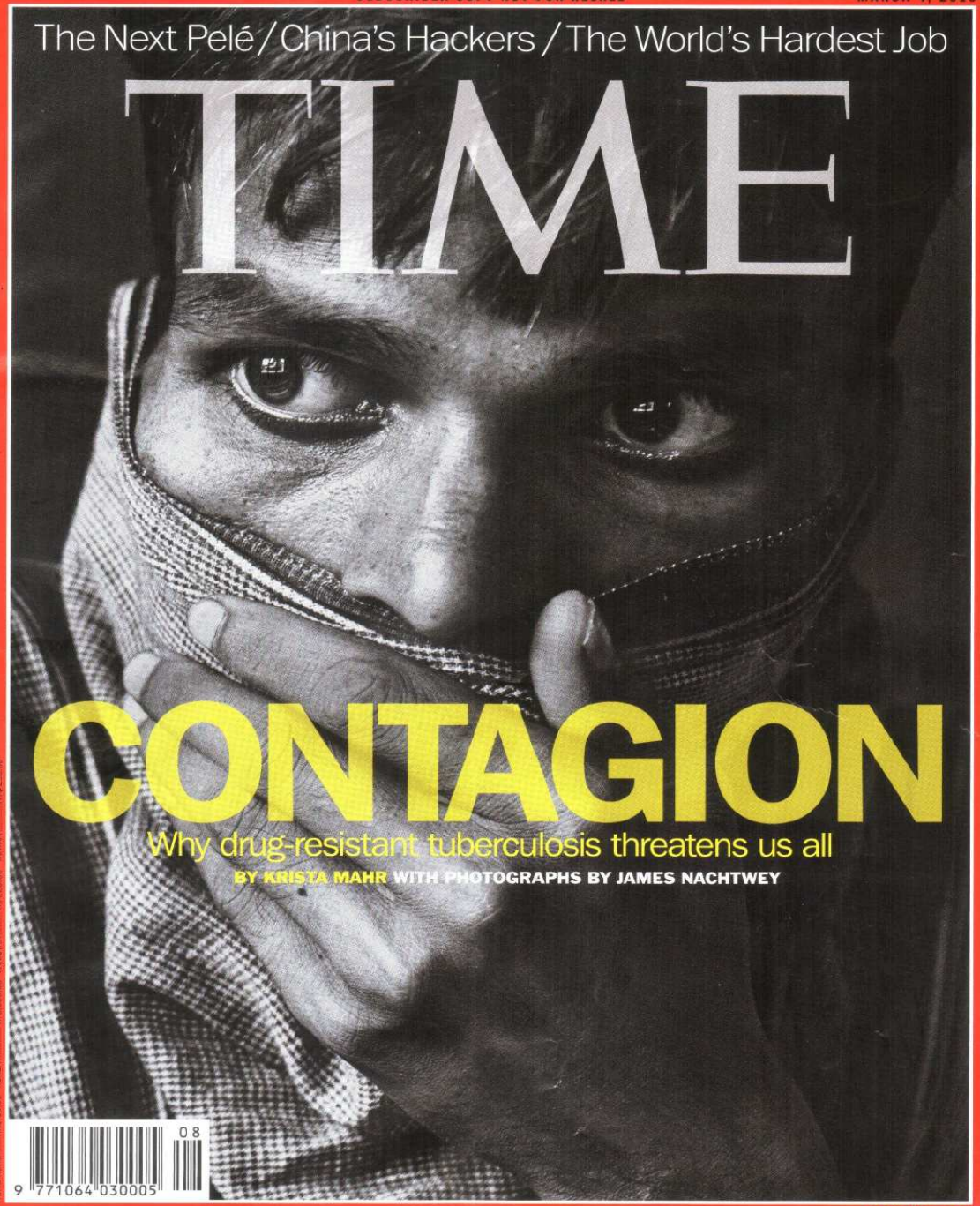
TIME



CONTAGION

Why drug-resistant tuberculosis threatens us all

BY KRISTA MAHR WITH PHOTOGRAPHS BY JAMES NACHTWEY

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Classification of Drug Resistant Tuberculosis

- Primary or Initial drug resistant
- Secondary or Acquired drug resistant
- Drug resistant (DR)
  - Mono-drug resistant
  - Poly-drug resistant
- Multi-drug drug resistant (MDR)
- Extensively drug resistant (XDR)
- Totally drug resistant (TDR)

First Line Drugs

- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol
- Streptomycin

Second Line Drugs (6 classes)

* **Aminoglycosides** : Kanamycin, Amikacin
* **Fluoroquinolones** : Levofloxacin, Moxifloxacin
* **Cyclic polypeptide** : Capreomycin
* **Serine analog** : Cycloserine,Terazidine
* **Thioamide** : Ethionamide, Prothionamide

- **Salicylic acid derivatives** : PAS
- **Oxazolidinone** : Linezolid
- **Clofazimine**

Diagnosis of DR/MDR/XDR-TB

- Clinical signs and symptoms are not specific
- Chest X-ray is not specific
- Diagnosis of DR/MDR/XDR is based on result of drug susceptibility test
- Standard susceptibility test take time of 8-12 weeks to get result
- Rapid DST is recommended by WHO but is only for INH and RMP

Principle of MDR-TB Treatment

- Number of drug used to treatment MDR : at least 4 drugs that are likely to sensitive
- Duration of using aminoglycoside injection : 6 months and 4 months after culture negative
- Duration of treatment : 18 months after culture negative
- Any case with known MDR from DST , treatment must be changed to MDR regimen
- Surgical intervention should be considered in every MDR/XDR-TB patients

Proposed Treatment Regimen

- **Kanamycin or Amikacin for 6 months**
  because less likely to resist
- **Levofloxacin is the recommended**
  fluoroquinolone (listed in the essential drug list)
- **Ethionamide**
- **Cycloserine**
- **PAS**

Current Tuberculosis Treatment ?

- **Standard treatment is short course six months regimen**
- **Too long to patient. Patient usually lost from treatment after few months when symptoms improve**
- **Too many drugs mean difficult to swallow**
- **Too many drugs mean more adverse drug reactions**

Treatment of MDR/XDR-TB ?

- Use injection drug for more than 6 months
- Treatment is more than 20 months
- Treatment composes of 4 – 5 toxic second line drugs
- Almost all of patients experienced with some kinds of adverse drug reactions
- Availability of second line drugs
- Treatment success is less than 80 %

What do we need for TB treatment?

- New drugs for shortening duration of treatment both susceptible and resistant TB.
- Less number of drug to use for treatment of both susceptible and resistant TB.
- New drug should have
  - Bacteriocidal, sterilizing activity against *M.tuberculosis*
  - Favorable PK/PD
  - Less toxic
- New drug should not every expensive so that every patient can access to drug

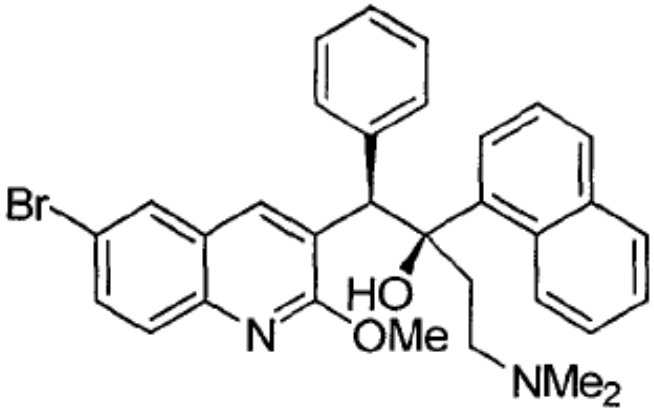
New Drugs for MDR/XDR-TB Treatment ?

- **Bedaquiline (TMC 207)**
- **Delamanid (OPC 68673)**
- **Oxazolidinone**
  - **Linezolid**
  - **Sutezolid (PNU 100480)**
  - **AZD 58473**
- **Ethambutol derivative**
- **PA 824**

Bedaquiline : New anti-TB drug

2.1.2. Structural Formula

R207910



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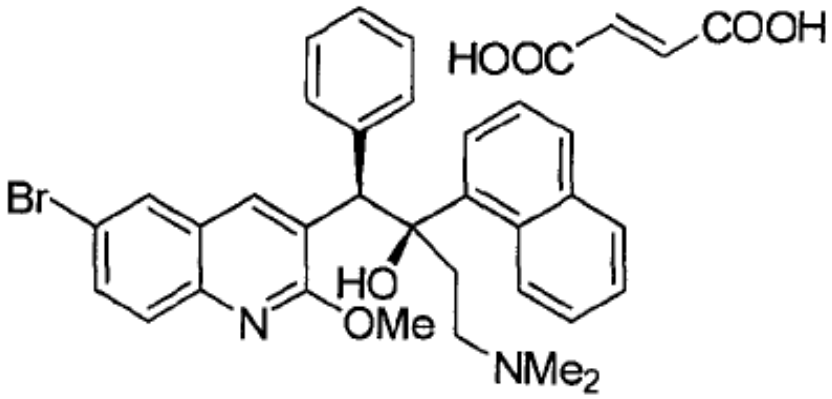


Bedaquiline : New anti-TB drug

Table 7: In Vitro Activity of TMC207 Against *M. tuberculosis* Preclinical Isolates

Organism	MTB Resistance Subtype	N	TMC207 MIC (µg/mL)			
			MIC Range	MIC_{50}	MIC_{90}	MIC_{95}
M. tuberculosis	All	109	≤ 0.008 - 0.12	0.03	0.06	0.06
	DS-TB	65	≤ 0.008 - 0.12	0.03	0.06	0.06
	MDR-TB	44	≤ 0.008 - 0.12	0.03	0.06	0.06

N = number of strains

Bedaquiline : New anti-TB drug

Table 31: Mean (±SD) Observed Pharmacokinetic Parameters of TMC207 and M2 at Weeks 2 and 24 in TMC207- C208 Stage 2

		Results C208 Stage 2	
		TMC207	**M2**
Week 2 (n = 26)[a]	C_{min} (ng/mL)	728 ± 257	332 ± 122
	C_{max} (ng/mL)	2763 ± 1185	467 ± 157
	$C_{ss,avg}$ (ng/mL)	1371 ± 529	383 ± 130
Week 24 (n = 17)[b]	C_{min} (ng/mL)	356 ± 170	120 ± 57
	C_{max} (ng/mL)	1267 ± 435	178 ± 71
	$C_{ss,avg}$ (ng/mL)	584 ± 197	152 ± 53

C_{min} = minimum plasma concentration, C_{max} = maximum plasma concentration, $C_{ss,avg}$ = average plasma concentration over the dosing interval

[a] n = 30 for C_{min}, n = 29 for C_{max}

[b] n = 18 for C_{min}, n = 19 for C_{max}

Bedaquiline : New anti-TB drug

Table 8: In Vitro Activity of TMC207 Against Other Mycobacterial Species

Mycobacterial Organism	N	TMC207 MIC (µg/mL)	
		MIC Range	Median
M. bovis	1	-	0.003
M. avium/M. intracellulare (MAC)	7	0.007 - 0.010	0.010
M. kansasii	1	-	0.003
M. marinum	1	-	0.003
M. fortuitum	5	0.007 - 0.010	0.010
M. abscessus	1	-	0.250
M. smegmatis	7	0.003 - 0.010	0.007
M. ulcerans	1	-	0.500

N = number of strains

Source: data published by Andries et al., Science 2005[14]

Bedaquiline : New anti-TB drug

Table 9: In Vitro Activity of TMC207 Against Non-Mycobacterial Isolates

Non-Mycobacterial Organisms	N	TMC207 MIC (µg/mL)	
		MIC Range	Median
Corynebacterium jeikeium	1	-	4
Corynebacterium urealyticum	1	-	4
Helicobacter pylori	20	2 - > 4	4
Nocardia asteroides	1	-	> 16
Nocardia farcinica	1	-	> 16
Escherichia coli	1	-	> 32
Haemophilus influenzae	1	-	> 32
Streptococcus pneumoniae	10	16 – > 32	> 32
Staphylococcus aureus	1	-	> 32

N = number of strains

Source: data published by Andries et al., Science 2005[14]

Bedaquiline : New anti-TB drug

Table 10: Bacterial Counts and Proportion of Mice With Negative Cultures in the Lungs After Treatment

Group[a]	Bacterial Count (Log_{10} CFU) (Mean ± SD)			% of Mice Culture Negative at 2 Months
	Day 0	1 Month	2 Months	
Untreated	7.2 ± 0.5			
TMC207		4.1 ± 1.8	2.3 ± 0.7	22
PZA		6.2 ± 0.3	6.4 ± 0.9	0
TMC207 + PZA		1.6 ± 1.6	0	100
RMP + INH + PZA		3.9 ± 0.7	2.2 ± 0.6	0

TMC207 25 mg/kg; RMP 10 mg/kg; INH 25 mg/kg; PZA 150 mg/kg

SD = standard deviation

[a] In each treatment group, 10 mice were sacrificed after 1 month of treatment, and 10 were sacrificed after 2 months of treatment. Monotherapy with PZA alone did not completely prevent mortality, and 7 out of the 20 mice treated with this drug died from TB between Days 8 and 22.

Bedaquiline : New anti-TB drug

Table 13: Proportion of Mice With Positive Culture of Lung or Spleen at the End of Treatment and 3 Months After Treatment Completion (Relapse)

Regimen	At the End of Treatment				3 Months After the End of Treatment[a]			
	Month 2	Month 3	Month 4	Month 6	Month 2 (+ 3)	Month 3 (+ 3)	Month 4 (+ 3)	Month 6 (+ 3)
2 (RHZ) + 4 (RH)	ND	ND	ND	0/10 (0%)	ND	ND	ND	5/30 (17%)[b]
2 (RMZ) + 2 (RM)	ND	5/9 (56%)	0/8 (0%)	NA	ND	16/19 (84%)	8/19 (42%)	NA
2 (JR) + 2 (JR)	1/6 (17%)	1/7 (14%)	0/7 (0%)	NA	10/18 (56%)	5/18 (28%)	2/15 (13%)	NA
2 (JHZ) + 2 (JH)	0/9 (0%)	0/9 (0%)	0/8 (0%)	NA	13/19 (68%)	13/18 (72%)	5/17 (29%)	NA
2 (JRHZ) + 2 (JRH)	0/9 (0%)	0/9 (0%)	0/9 (0%)	NA	12/18 (67%)	7/20 (35%)	1/17 (6%)	NA

J = TMC207; M = MXF; R = RMP; H = INH; Z = PZA

ND = not done, NA = not applicable

[a] Month 2 (+ 3), Month 3 (+ 3), Month 4 (+ 3) and Month 6 (+ 3) indicate that the mice were killed 3 months after completing 2, 3, 4, and 6 months of treatment.

[b] Positive culture means lung or/and spleen is/are positive.

Bedaquiline : New anti-TB drug

Table 14: Bactericidal Activity of TMC207 in Combination With Second-line Drugs in the Established Infection Murine TB Model

Regimens[a]	Mean Log CFU Counts ± SD			
	Spleen at 1 Month	Spleen at 2 Months (Proportion of Mice Negative Cultures/Total No. of Mice)	Lungs at 1 Month	Lungs at 2 Months (Proportion of Mice Negative Cultures/Total No. of Mice)
Untreated	6.5 ± 0.2	-	5.9 ± 0.5	-
J	2.6 ± 1.3	1.2 ± 0.5 (0/8)	2.9 ± 0.9	0.2 ± 0.3 (6/8)
RHZ	4.5 ± 0.3	1.9 ± 0.5 (1/10)	3.7 ± 0.4	1.0 ± 0.5 (0/10)
RHZJ	1.9 ± 0.31	0.1 ± 0.2 (4/10)	1.8 ± 0.4	0 ± 0 (10/10)
AEMZ	3.2 ± 0.5	1.6 ± 0.4 (1/10)	2.9 ± 0.2	0.1 ± 0.1 (5/10)
AEZ	4.0 ± 0.3	2.8 ± 0.3 (0/10)	3.7 ± 0.2	1.2 ± 0.3 (0/10)
AMZ	3.6 ± 0.2	1.9 ± 0.5 (0/10)	3.4 ± 0.3	0.8 ± 0.6 (0/10)
AEZJ	1.2 ± 0.2	0.1 ± 0.1 (7/9)	0.2 ± 0.3	0 ± 0 (9/9)
AMZJ	1.2 ± 0.2	0 ± 0 (8/8)	0.2 ± 0.3	0 ± 0 (8/8)
AEMZJ	1.2 ± 0.3	0 ± 0 (8/8)	0.5 ± 0.4	0 ± 0 (8/8)

J = TMC207; M = MXF; R = RMP; H = INH; Z = PZA; A = AMK; E = ETH; M = MXF

SD = standard deviation

[a] Drugs were administered 5 times/week: RMP 10 mg/kg; TMC207 25 mg/kg; INH 25 mg/kg; PZA 150 mg/kg; AMK150 mg/kg; ETH 50 mg/kg; MXF 100 mg/kg

Bedaquiline (TMC 207)

- **Bedaquiline is 100 mg per tablet**
- **Cmax is 3-5 µg/ml. (MIC of *M.tuberculosis* is 0.03-0.3 µg/ml for both susceptible and resistant strains).**
- **Half life is 5-7 days, Time to Cmax is 5 hours.**
- **Dosage is 4 tablets (400 mg.) once daily for 14 days and then 2 tablets (200 mg.) three times per week for 22 weeks.**
- **Taking with meal will enhance absorption.**
- **No data of using in hepatic or renal impairment patients.**

Bedaquiline (TMC 207)

- **Two patients had SAE (death) but not related to study drug (hepatoma and hemoptysis).**
- **No adverse drug reaction related to Bedaquiline. All adverse drug reactions were related to back ground regimen drugs and tuberculosis.**
- **Slightly prolonged QT interval in ECG was observed in some patients but no clinical significance**

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

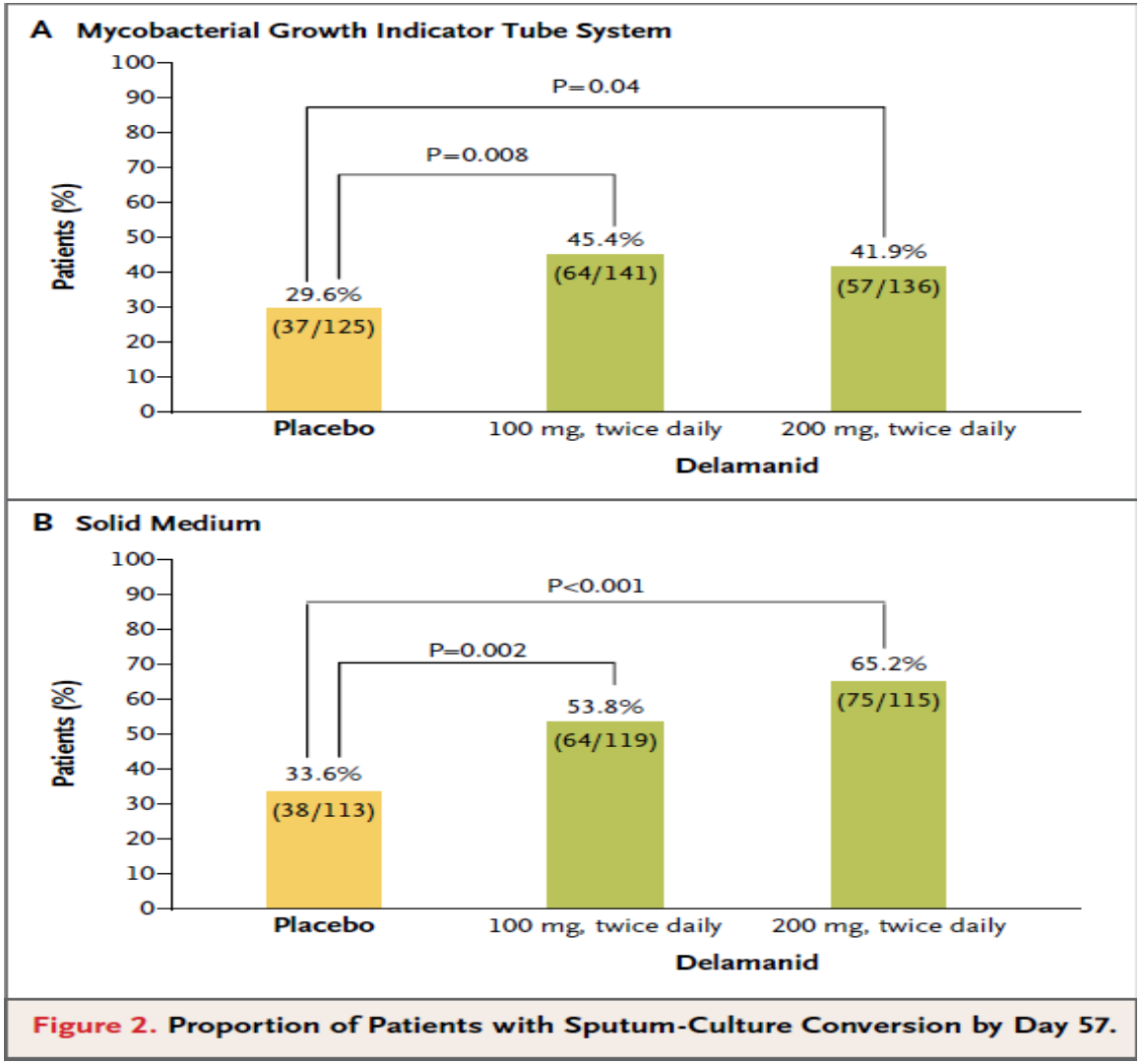


Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

N Engl J Med 2012;366:21510-60

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

RESULTS

Among patients who received a background drug regimen plus 100 mg of delamanid twice daily, 45.4% had sputum-culture conversion in liquid broth at 2 months, as compared with 29.6% of patients who received a background drug regimen plus placebo (P=0.008). Likewise, as compared with the placebo group, the group that received the background drug regimen plus 200 mg of delamanid twice daily had a higher proportion of patients with sputum-culture conversion (41.9%, P=0.04). The findings were similar with assessment of sputum-culture conversion in solid medium. Most adverse events were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QT prolongation on electrocardiography were observed, QT prolongation was reported significantly more frequently in the groups that received delamanid.

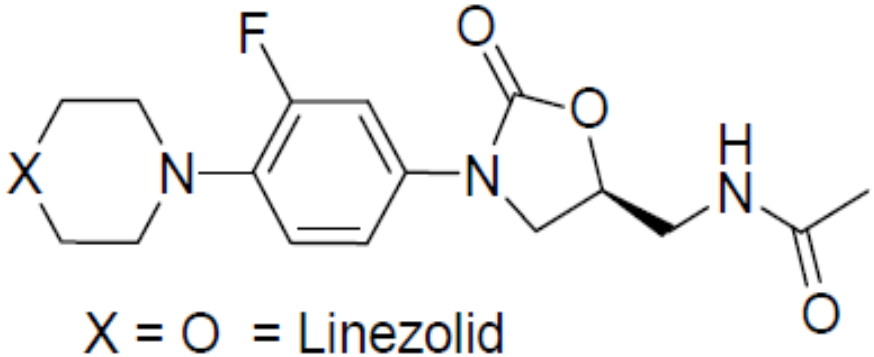
CONCLUSIONS

Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. This finding suggests that delamanid could enhance treatment options for multidrug-resistant tuberculosis. (Funded by Otsuka Pharmaceutical Development and Commercialization; ClinicalTrials.gov number, NCT00685360.)

N Engl J Med 2012;366:21510-60

Sutezolid (PNU 100480)

PNU-100480 (Oxazolidinone)



X = O = Linezolid
X = S = PNU-100480
X = S(O) = PNU-101603
X = $S(O)_2$ = PNU-101244

Susceptibility of Clinical *Mycobacterium tuberculosis* Isolates to a Potentially Less Toxic Derivate of Linezolid, PNU-100480[▽]

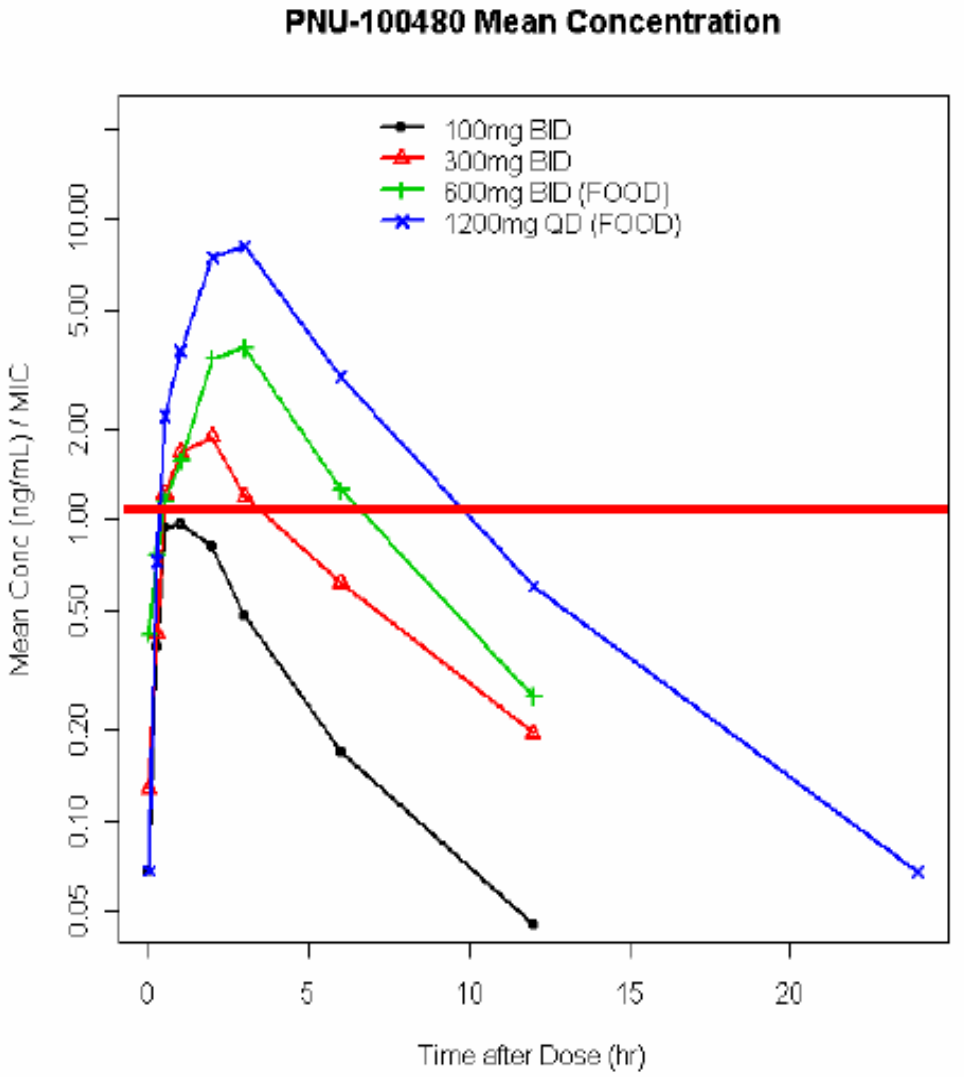
TABLE 1. MICs of linezolid and PNU-100480 and susceptibility to INH, rifampin, ethambutol, and streptomycin for 23 isolates of *Mycobacterium tuberculosis*

Isolate no.	Resistance/susceptibility profile[a] for:				MIC (mg/liter) of:	
	Isoniazid	Rifampin	Ethambutol	Streptomycin	Linezolid	PNU-100480
1	R	R	R	R	≤0.25	≤0.0625
2	R	R	S	R	≤0.25	0.125
3	R	R	R	R	≤0.25	≤0.0625
4	R	R	R	R	≤0.25	0.25
5	R	R	S	R	0.5	0.25
6	R	R	R	R	0.5	0.125
7	R	R	S	R	0.5	0.125
8	R	R	S	R	1	0.125
9	R	R	R	R	1	0.25
10	R	R	R	R	1	0.25
11	S	R	R	R	>1	0.5
12	S	S	S	R	1	0.125
13	R	R	R	S	≤0.25	0.125
14	R	R	R	S	≤0.25	0.125
15	R	R	S	S	0.5	0.25
16	R	R	R	S	0.5	0.125
17	R	R	S	S	0.5	≤0.0625
18	R	S	R	S	0.5	0.25
19	S	S	S	S	0.5	0.25
20	S	S	S	S	1	0.25
21	S	S	S	S	1	0.5
22	S	S	S	S	1	0.25
23	S	S	S	S	1	0.25

[a] R, resistant; S, susceptible.

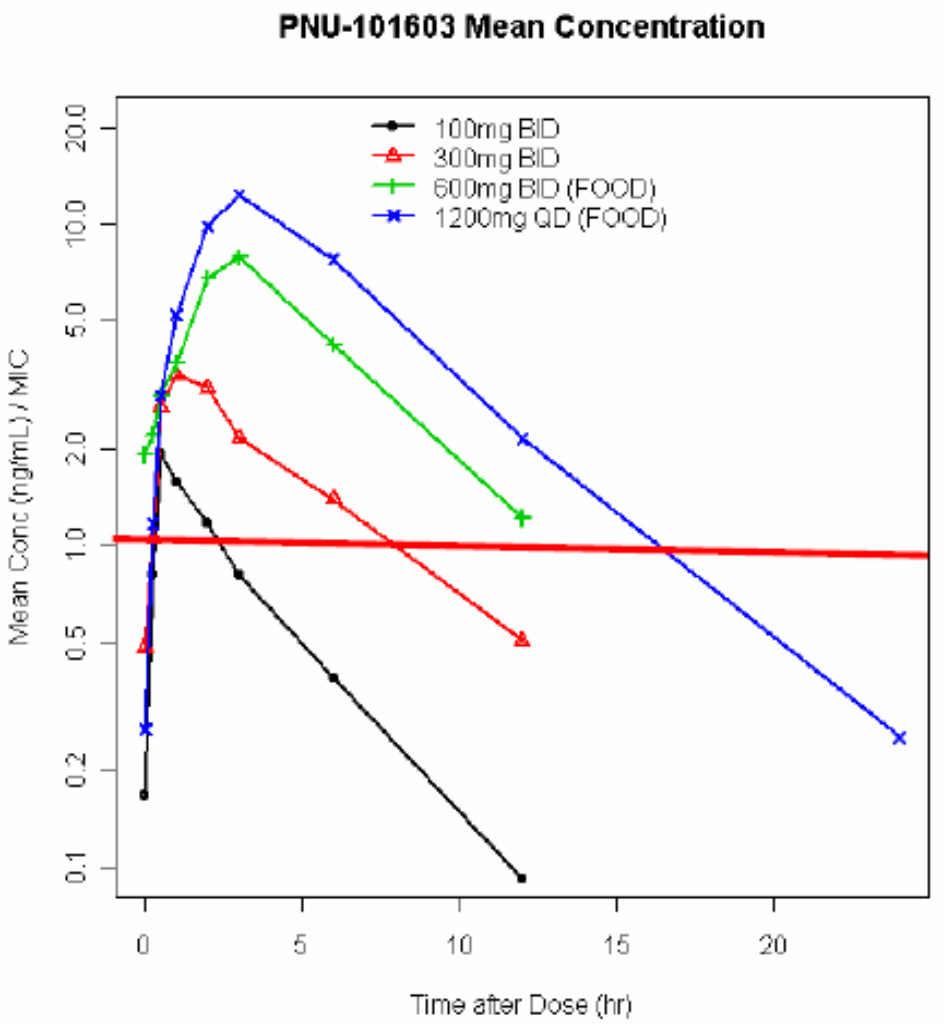
Antimicrob Agents Chemother 2011;55:1287-89

Sutezolid (PNU 100480)



- T_{max} – 1-2 hrs (Fasting)
- Slight shift in Tmax with food (1.5 to 3 hours)
- Fast Turnover in Humans
- Terminal $T_{1/2}$ – 4-8.4 hrs
- Concentration above MIC for ~ 6hrs at doses > 600mg

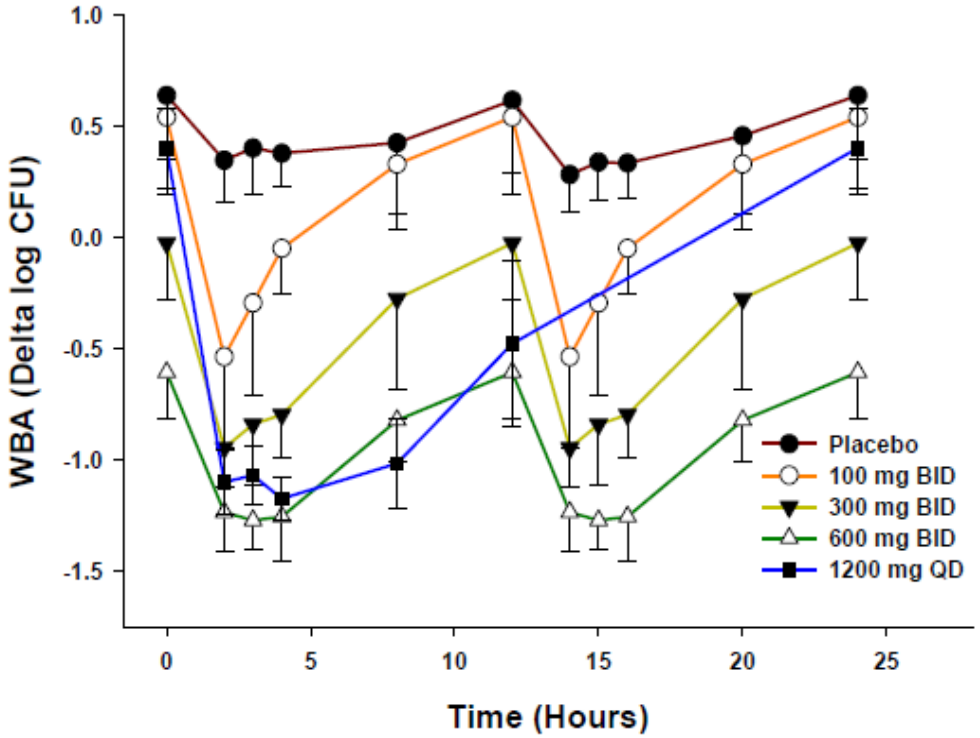
Sutezolid (PNU 100480)



- Exposure of major metabolite is 5-7 times of parent
- Combined exposures of the active analytes increased approximately proportionally

Sutezolid (PNU 100480)

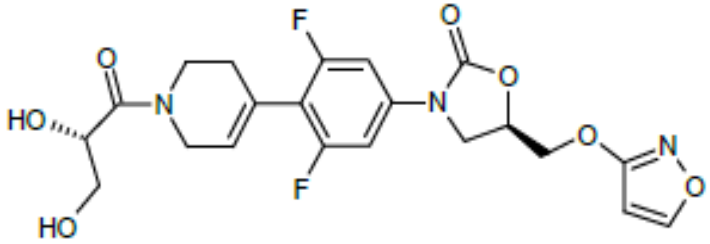
Observed Mean Bacterial Killing (WBA)



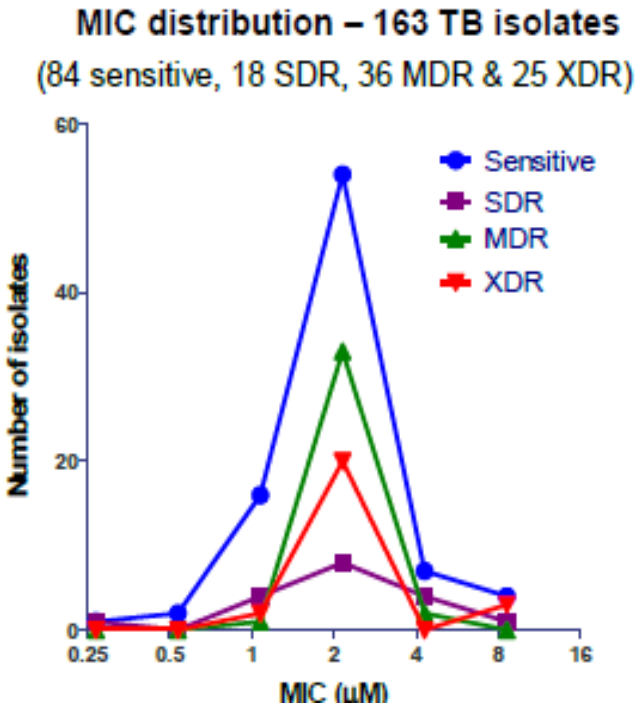
- Increasing dose resulted in increased net killing
- Maximal mean WBA activity observed is -1.1 Log in SAD **(-0.37 log/day)**

AZD 5847 : An oxazoidinone for TB treatment

Product Concept: Suitable for incorporation into novel combination therapies to treat DS and/or MDR/XDR tuberculosis (+HIV co-infected)



AZD5847



AZD 5847 : An oxazoidinone for TB treatment

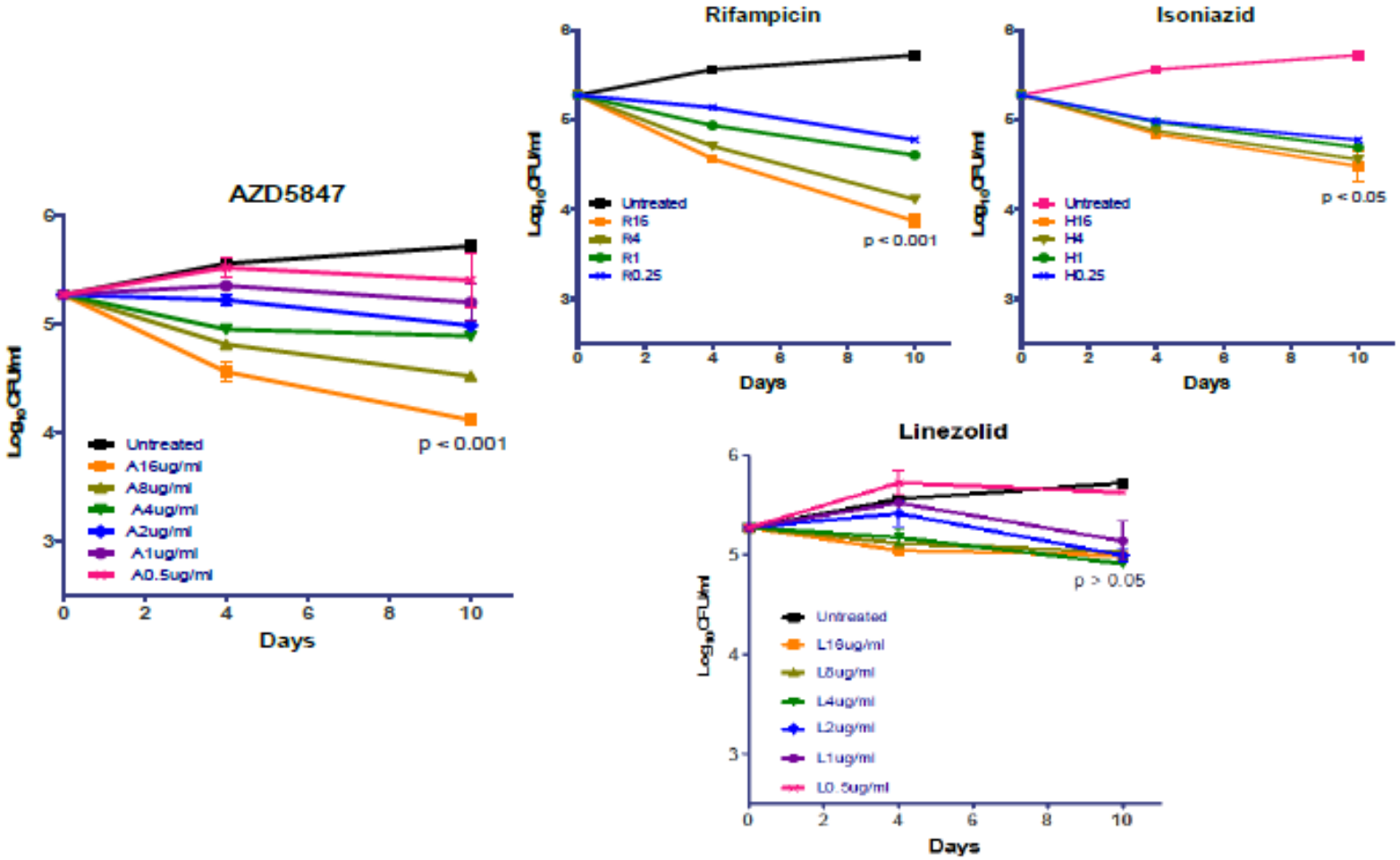
AZD5847 Ph1 Clinical safety summary

AZD5847 was generally well tolerated over 14 days in healthy volunteers at doses predicted to drive efficacy in humans

- n=42 single-dose (SAD) subjects; n=45 multiple-dose (MAD) subjects
- Maximum administered dose 2400mg per day x 14 days
  - Predicted therapeutic dose 400mg BID / 800mg QD
- No SAEs; 3 DAEs: pustular rash, self limited rectal bleed, migraine/scotoma
- Most common AE: Dose-related nausea, reduced by dosing with food
- Decreased WBC counts (5/9 volunteers 2400mg/day) and increased reticulocyte counts (1600-2400mg/day) were observed
- Transient myalgias noted for 3/9 volunteers who received 2400mg/day (no CPK elevation)
- No clinically significant ECG findings

AZD5847 is bactericidal against intracellular Mtu

- **Bone marrow derived macrophage model:** AZD5847and rifampicin are effective against intracellular Mtu, whereas isoniazid and linezolid are weakly active



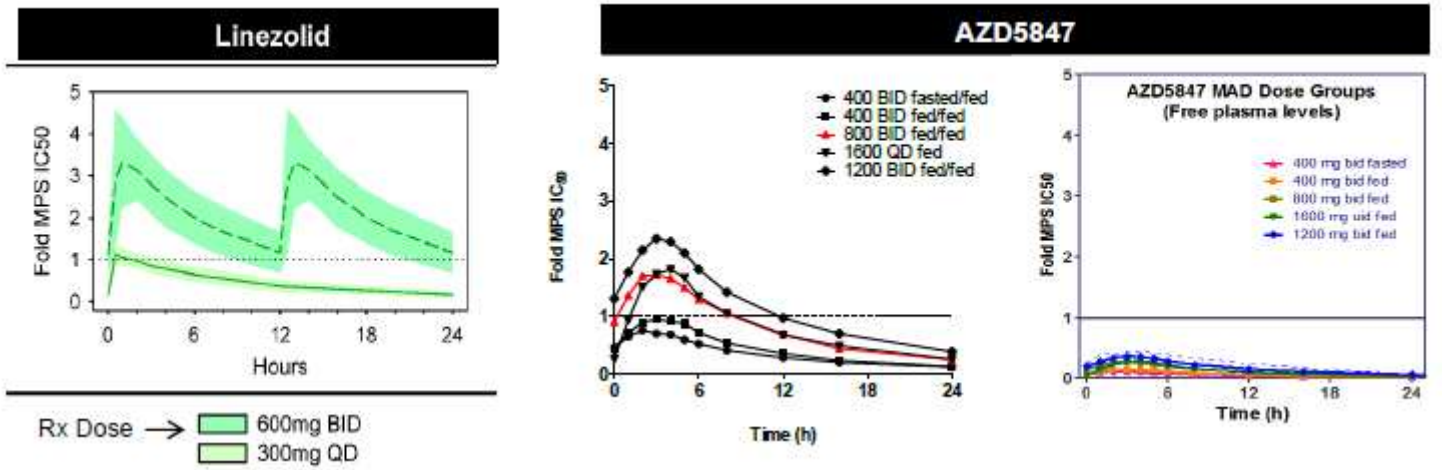
AZD 5847 : An oxazoidinone for TB treatment

Summary

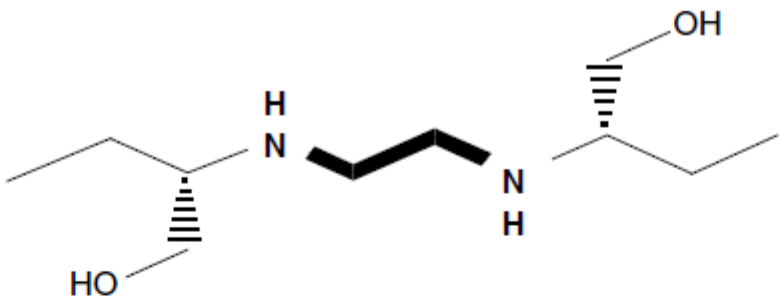
- Oxazolidinones offer a promising (clinically validated) addition to future novel combination regimens (MDR/XDR treatment or simplification/reduced duration)
- AZD5847 has potential to differentiate in the clinic:
  - Active against slowly dividing mTB
  - Active against intracellular TB
  - Has reduced potency against human mitochondrial protein synthesis
- AZD5847 is safe and well tolerated at predicted efficacious doses
- Phase 2a trial to start October/November 2012

AstraZeneca

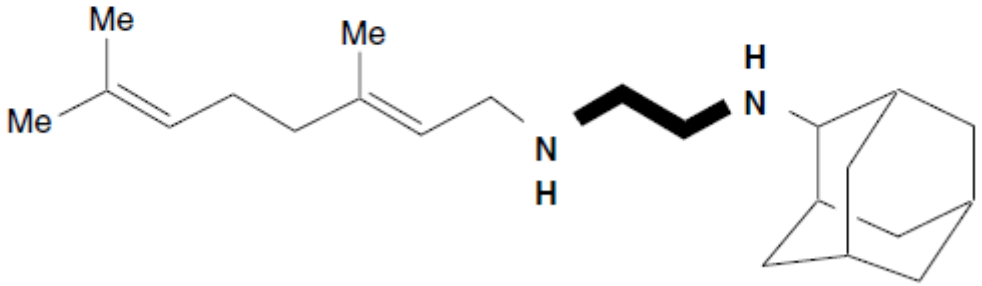
AZD 5847 : An oxazoidinone for TB treatment



Pharmacodynamics and pharmacokinetics of SQ109, a new diamine-based antitubercular drug



EMB



SQ109

Figure 1 Chemical structures of EMB and SQ109.

British j Pharm 2005;144:80-7

Pharmacodynamics and pharmacokinetics of SQ109, a new diamine-based antitubercular drug

Table 1 CFU counts in organ homogenates after 28-day oral administration of SQ109, EMB and INH to mice inoculated with *M. tuberculosis* H37Rv

Treatment (daily dose)[a]	*Log_{10} CFU/organ (mean ± s.d.)* *Lung*	*Spleen*
Untreated	7.05 ± 0.13	6.58 ± 0.18
INH (25 mg kg^{-1})	4.24 ± 0.12*	4.22 ± 0.05*
EMB (100 mg kg^{-1})**	5.38 ± 0.19*	5.13 ± 0.12*
SQ109 (0.1 mg kg^{-1})	6.69 ± 0.13**	6.06 ± 0.17***
SQ109 (10 mg kg^{-1})**	5.45 ± 0.16*	5.36 ± 0.20*
SQ109 (25 mg kg^{-1})**	5.18 ± 0.15*	5.14 ± 0.14*

[a]Treatment was started 20 days after the mice ($n = 8$ per group) received inoculation.
*Statistically significant difference from the untreated group, $P < 0.01$.
**$P = 0.052$, compared to the untreated group.
***$P = 0.032$, compared to the untreated group.

British j Pharm 2005;144:80-7

Pharmacodynamics and pharmacokinetics of SQ109, a new diamine-based antitubercular drug

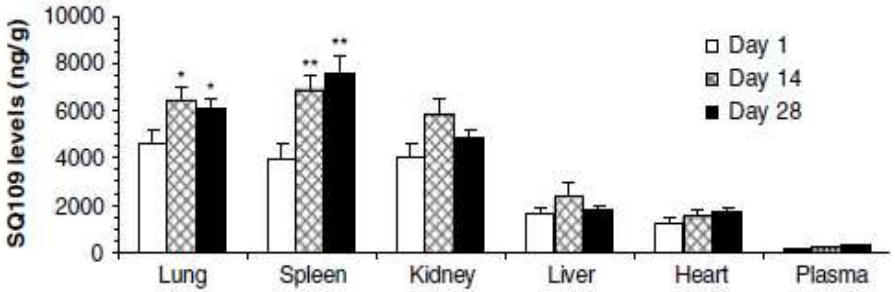


Figure 3 SQ109 concentrations (mean ± s.d.) in the lung, spleen, kidney, liver, heart and plasma at 1 h after oral administration of the compound to mice (10 mg kg^{-1} day^{-1}). Groups of 4–5 mice were killed on days 1, 14 and 28 during the 28-day dosing period. SQ109 concentrations in the lung, spleen and kidney were significantly higher than those in liver, heart and plasma ($P<0.001$). Statistically significant SQ109 accumulation in lungs and spleen was found on days 14 and 28 *versus* day 1: $*P<0.05$; $**P<0.01$.

Table 2 Compartmental analysis of pharmacokinetic parameters (mean ± s.e.m.) of SQ109 in mice

Route	*i.v.*	*p.o.*
Dose (mg kg^{-1})	3	25
$AUC_{0\rightarrow\infty}$ (ng h^{-1} ml^{-1})	792 ± 369	254 ± 184
$t_{1/2\alpha}$ (h)[a]	0.07 ± 0.051	
$t_{1/2\beta}$ (h)[b]	0.43 ± 0.35	
$t_{1/2el}$ (h)[c]	3.5 ± 6.6	5.2 ± 1.1
C_{max} (ng ml^{-1})	1038 ± 93	135 ± 10
T_{max} (h)		0.31 ± 0.06
CL (ml kg^{-1} h^{-1})	3788 ± 1768	
Vd_{ss} (ml kg^{-1})	11826 ± 14878	
Bioavailability (%)		4

[a]Half-life of the distribution phase.
[b]Half-life of the initial elimination phase.
[c]Half-life of the terminal elimination phase.

British j Pharm 2005;144:80-7

Chest Disease Institute