Emerging resistance to novel TB drugs: Insights from mouse models

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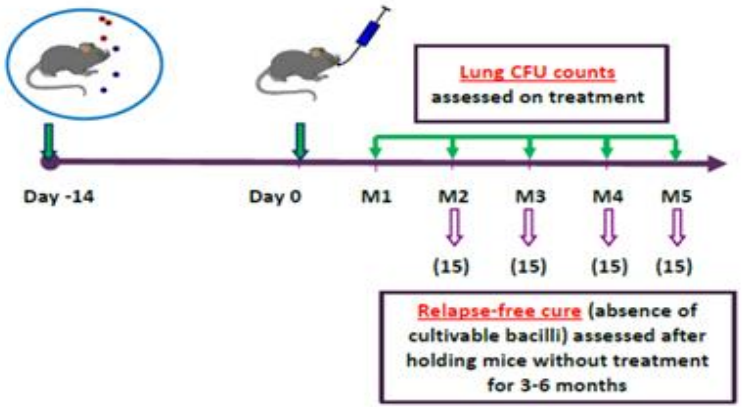
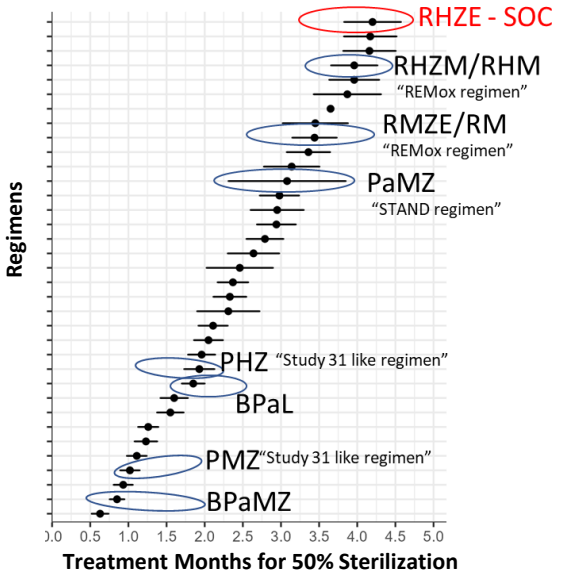
BALB/c relapsing mouse model (RMM)

Scheme for relapsing mouse model (RMM)



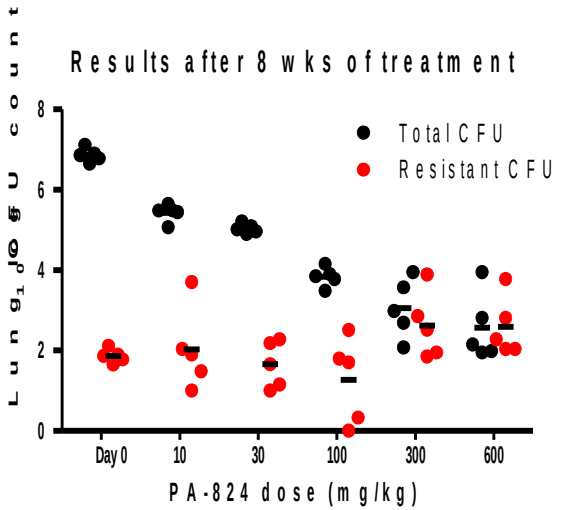
BALB/c RMM: Ranking of regimens*

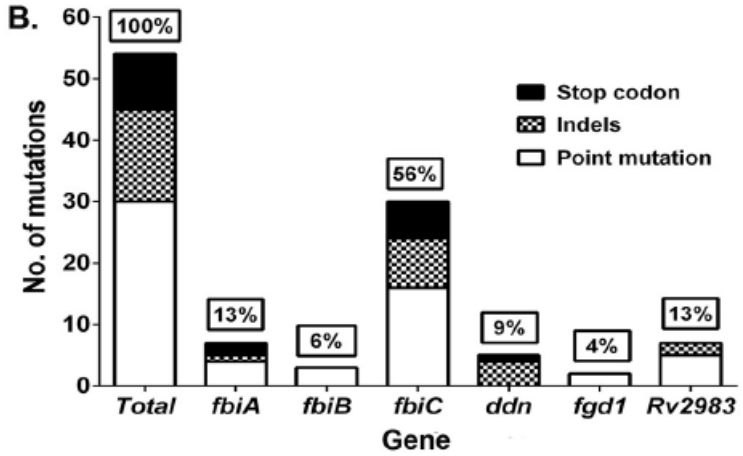


- BALB/c RMM has proven useful for rank-ordering novel TB regimens according to sterilizing activity

*based on data derived from multiple study sources

Dose-dependent selection of pretomanid-resistant mutants in BALB/c mice





- Mice are useful to study exposure-response relationships for selective amplification of resistance and predict mutations likely to lead to resistance
- In the case of pretomanid, diverse mutations in ≥1 of the following 6 genes: *ddn*, *fgd*, *fbiA*, *fbiB*, *fbiC*, *fbiD (Rv2983)* were identified

Rifat et al, AAC (2021); 65: e01948-20

Addition of pretomanid to BDQ-containing combinations suppresses selection of BDQ-resistant mutants

TABLE 2 Lung CFU counts during treatment against *M. tuberculosis* H37Rv WT and *pncA* mutant and proportion of mice relapsing after treatment completion in experiment 2

Regimen	Mean lung $\log_{10}$ CFU count[a] (±SD)				Proportion of mice relapsing after treatment for[b]:				
	D−14	D0	M1	M2	1 mo	1.5 mo	2 mo	3 mo	4 mo
WT									
Untreated	4.06 ± 0.05	7.90 ± 0.16							
BL			4.87 ± 0.16	2.69 ± 0.30			$15/15^{7}$	$15/15^{5}$	$14/15^{5}$
BPaL			3.29 ± 0.09	0.68 ± 0.24			7/15	0/15	0/15
BMZ			1.29 ± 0.19		15/15	6/15	1/15		
BPaMZ			1.05 ± 0.18		14/15	0/15	0/15		
pncA mutant									
Untreated	4.36 ± 0.17	8.09 ± 0.08							
BMZ			4.06 ± 0.23	1.24 ± 0.17			$15/15^{3}$	$7/20^{3}$	
BPaMZ			4.22 ± 0.23	1.61 ± 0.32			$15/15^{1}$	0/20	

[a]Time points are shown as days (D−14 or D0) or months (M1 or M2) of treatment. 1 mo indicates that the mice were held for 3 additional months after completing 1 month of treatment.
[b]Superscript numbers represent the number of mice with isolates resistant to 0.125 mg/liter BDQ.

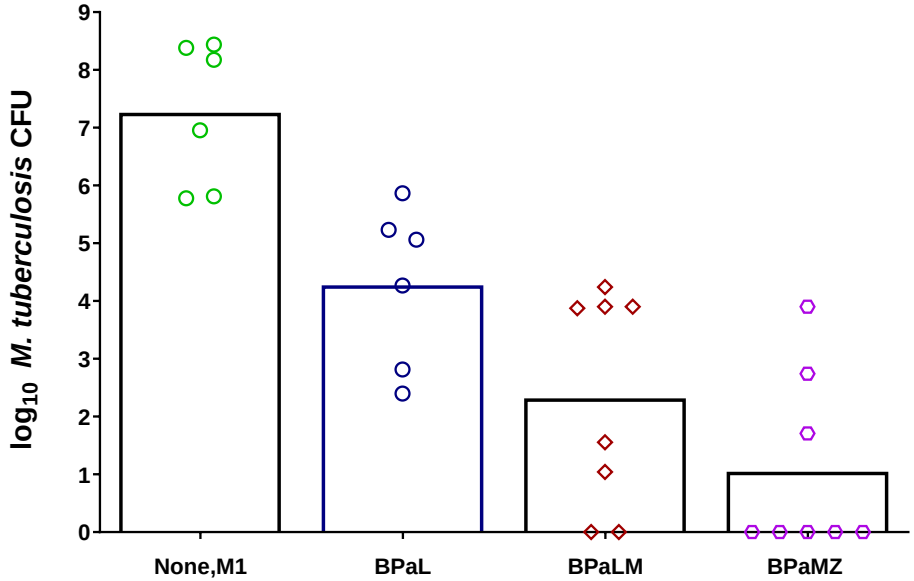
Mouse no.	Sequence[a] *Rv0678*	*pepQ*
BL-4	g73t (G25C)	
BL-6	WT	t68c (M23T)
BL-7	WT	WT
BL-11	t128c (L43P)	
BL-14	g457c (A153P)	WT
BL-6	g320t (R107C)$^{1/2}$, WT$^{1/2}$	
BL-8	g73t (G25C)$^{2/2}$	
BL-9	g457c (A153P)$^{2/2}$	
BL-12	g74a (G25D)$^{1/2}$, g197a(G66E)$^{1/2}$	
BL-14	c286t(R96W)$^{1/2}$, WT$^{1/2}$	

Mouse no.	Sequence[a] *Rv0678*	*pepQ*
BMZ-1	g362a (G120E)$^{2/2}$	
BMZ-11	a436 insertion (146 codon shift)$^{2/2}$	
BMZ-12	WT$^{2/2}$	g812 insertion (271-codon shift)$^{2/2}$
BPaMZ-15	a202g (S68G)$^{2/2}$	
BMZ-1	WT	WT
BMZ-9	G deletion at nt 168 (56-codon shift)$^{2/2}$	
BMZ-13	t407c (L136P)$^{2/2}$	

- Mice can be used to evaluate the susceptibility of regimens to emergence of resistance (i.e., ability of companion drugs to prevent selection)
- In this case, neither L nor M could completely prevent the selective amplification of BDQ-resistant mutants in relapsing mice, but adding Pa to BL or BM was more effective
- BDQ resistance was attributable to *rv0678*, *pepQ* mutations

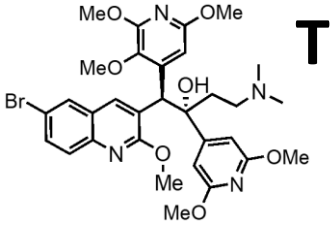
Xu et al, AAC (2019); 63: e00021-19

Addition of M to BPaL restricts selection of BDQ-resistant mutants in C3HeB/FeJ (“Kramnik”) mice



For BPaL vs. BPaLM, there were 3/6 vs. 0/8 mice with ≥0.1% CFU resistant to BDQ (range, 0.11 to 0.51%).

After an additional 2 weeks of treatment, no growth was observed on BDQ plates, suggesting both regimens can eradicate BDQ-resistant mutants if given for long enough.



TBAJ-876, a next-generation diarylquinoline

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(1) reduced cardiovascular liability (eg, hERG inhibition)
(2) larger pre-clinical safety margin

Improved physicochemical properties and PK
(1) better aqueous solubility
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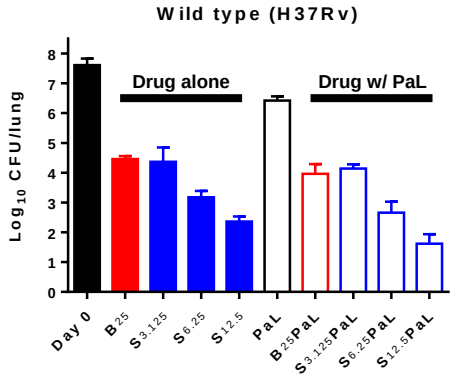
(1) superior efficacy in murine TB models
(2) superior potency against *Rv0678* variant*
(* IS6110 insertion at aa16/nt49)

Now in Phase 2b trial (NC-009)

Potency and safety parameters

	BDQ	TBAJ-876
MIC v. *Mtb* H37Rv (μg/ml)	0.03	0.006
MIC v. Rv0678 variant (μg/ml)	0.25	0.025
hERG IC_{50} (μM)	0.37	>30
28-Day Rat NOAEL (mg/kg/day)	6	40
Safety Margin Rat (Male)	0.2	15

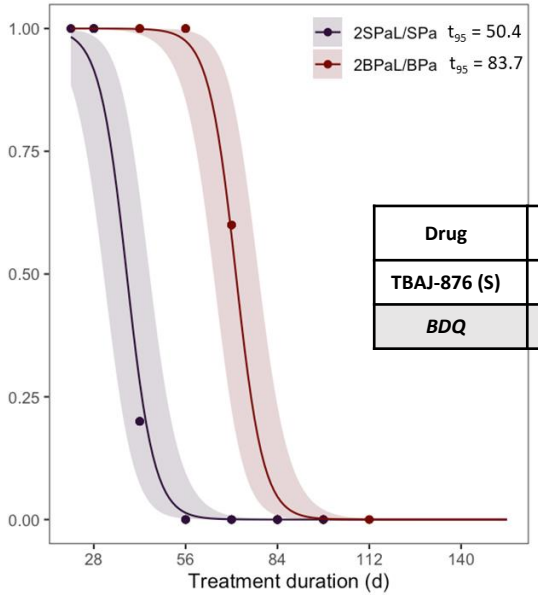
In vivo potency of TBAJ-876 (S) vs. BDQ (B)



C. Cooper et al, World Microbe Forum 2021
Almeida et al, AAC 2021

TBAJ-876 dose-response in combination with PaL in BALB/c RMM

TBAJ-876 6.25 mg/kg replacing B 25 mg/kg



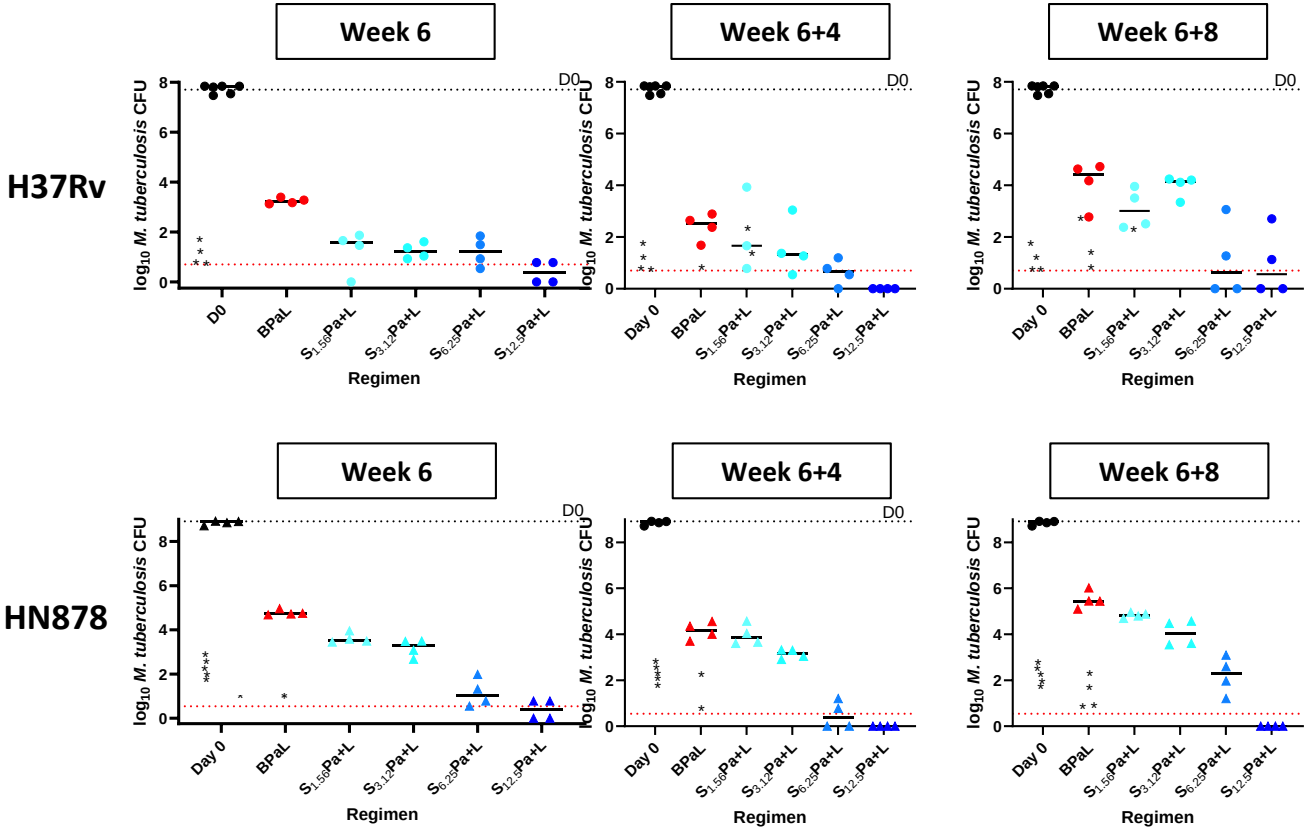
Drug	Dose (mg/kg)	$AUC_{0\text{-}24h}$ (ng*h/ml)
TBAJ-876 (S)	6.25	4020
BDQ	*25*	*13571*

Logistic regression modeling by Rob van Wijk, UCSF/Univ. of Leiden

S = TBAJ-876, PaL = pretomanid (25 mg/kg BID) + linezolid (25 mg/kg BID)
T_{95} = timepoint at which 95% of mice are relapse-free

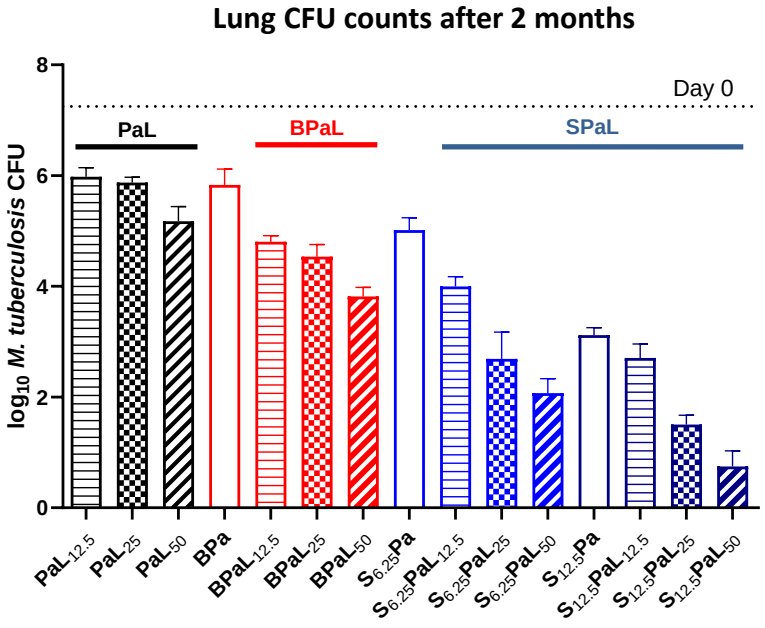
TBAJ-876 reduces selection of DARQ-resistant mutants in a dose-dependent manner in the BALB/c RMM

- BPaL can selectively amplify BDQ resistance in BALB/c mice
- TBAJ-876 (S) is more effective than BDQ at suppressing selection of DARQ-resistant mutants when used in combo with PaL



TBAJ-876 is more effective than BDQ at restricting selection of Pa-resistance in *rv0678* mutant treated with BPaL

- DARQs maintain some activity in combo with PaL against infection with an *rv0678* mutant
- TBAJ-876 (S) is more effective than BDQ
- Optimizing the dose of TBAJ-876 and L improves overall activity and reduces selection of B+Pa resistance

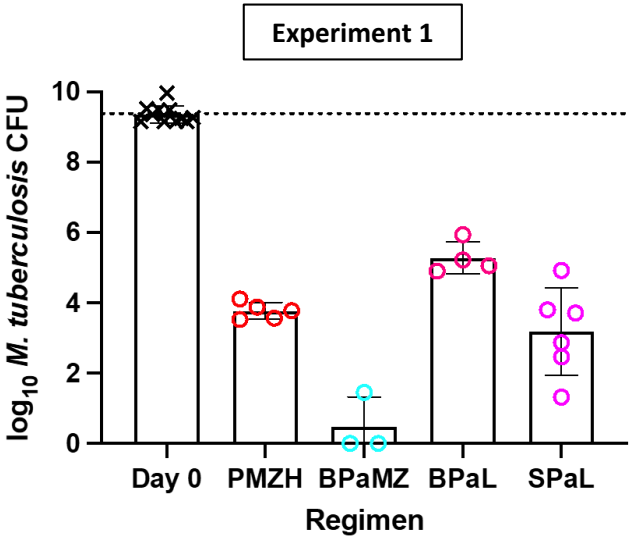


Group	Proportion mice enriched for Pa-R	% of total CFU w/ Pa-R
$PaL_{12.5}$	4/4	0.04 – 0.36%
PaL_{25}	3/4	0.01 – 0.14%
PaL_{50}	1/4	0.005%
BPa	3/4	0.002 – 0.13%
$BPaL_{12.5}$	1/4	0.01%
$BPaL_{25}$	3/4	0.03 – 0.1%
$BPaL_{50}$	1/4	0.06%
Any SPaL	0/4	N/A

Optimizing BPaL(M) with TBAJ-876 in C3HeB/FeJ ("Kramnik") mice

- TBAJ-876 (S) 6.25 mpk is superior to BDQ at 25 mpk in combo with PaL
- SPaL is at least as bactericidal as PMZH but not BPaMZ
- Addition of moxifloxacin (M) to SPaL increases bactericidal activity; and SPaLM is at least as effective as BPaMZ

Lung CFU counts after 2 months of treatment



Conclusions

- BDQ treatment exerts strong selection pressure and readily selects for *rv0678* and *pepQ* mutants with low-level resistance even while retaining some activity against them in mice.
- Selective amplification can occur even during combination therapy with BPaL, leading to relapse due to BDQ-resistant isolates if treatment is not long enough.
- Addition of M to BPaL restricts selection of BDQ-resistant mutants in mice.
- TBAJ-876 is a next-generation diarylquinoline with more potent bactericidal and sterilizing activity than BDQ in mice. Replacing BDQ with TBAJ-876 at 100 mg in the BPaL(M) regimen is predicted to shorten the treatment duration needed to cure TB.
- The more potent activity of TBAJ-876 against *Rv0678* mutants suggests it will also be more effective in treating and preventing infections caused by these emerging variants with reduced BDQ susceptibility and reduce development of additional resistance to Pa, M or L.
- It is important to dose-optimize either diarylquinoline drug.

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Collaborators

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Matt Zimmerman
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Liang Chen

Rutgers
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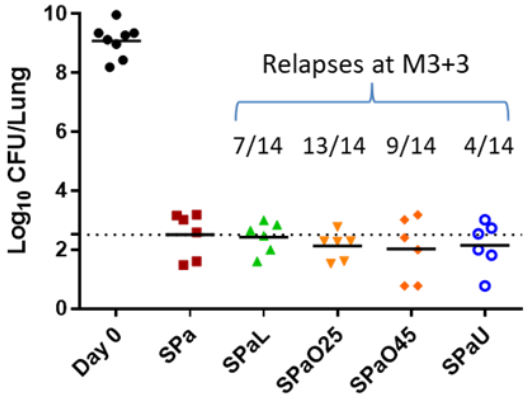
BMGF OPP1037174
FDA U18-FD-004004

Back-up slides

Selective amplification, then clearance, of *atpE* mutants in C3HeB/FeJ mice receiving TBAJ-876 + Pa + oxazolidinones

Efficacy of SPaOxa combos



Amplification of BDQ-R in relapsing mice

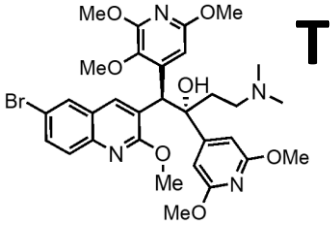
Regimen	Proportion (%) of relapses w/BDQ-R	% of CFU w/ BDQ-R (range)
SPaL	3 of 7 (43%)	13-50%
$SPaO_{25}$	6 of 13 (46%)	2-11%
$SPaO_{45}$	2 of 9 (22%)	5-6%
SPaU	0 of 4 (0%)	N/A

S = TBAJ-876
U = sutezolid
O = TBI-223 (novel oxazolidinone)

Mutations identified in *atpE*

Strain	Nucleotide change	Amino acid change
SPaL-B1	198 C --->G	I66--->M
SPaL-C1	198 C --->G	I66--->M
SPaO25-G1	187 G-->C	A 63---> P
SPaO25-H1	187 G-->C	A 63---> P
SPaO45-J1	198C --->G	I66--->M
SPaO45-L1	198C --->G	I 66---> M
HN878 Contro	Wild type	Wild type

1. Among oxazolidinones added to SPa, a trend was observed favoring sutezolid (U) over linezolid (L) and TBI-223 (O) in the prevention of relapse and relapse with a DARQ-resistant isolate
2. Remarkably, SPaL and SPaO selected for *atpE* mutations (A63V, I66V) and not *rv0678* mutations
3. Treatment for 4 months with SPaO, like 3 months of SPaU, prevented recovery of DARQ-resistant mutants (data not shown)
4. The results suggest that the higher potency of TBAJ-876 restricted selection of low-level resistant variants (*rv0678*, *pepQ*)



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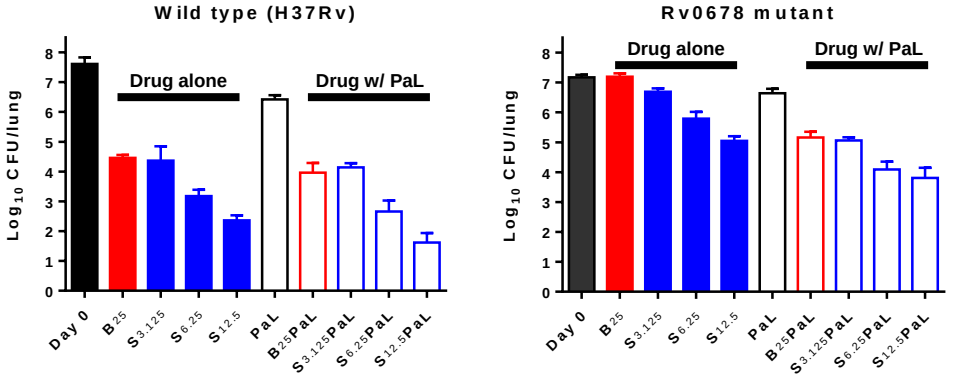


C. Cooper et al, World Microbe Forum 2021
Almeida et al, AAC 2021

Mutations identified from PA-824-containing plates after PA-824 therapy in mice

	Rv0407 fgd1 (4) 336 aa	Rv3547 ddn (12) 151 aa	Rv3261 fbiA (n= 14) 331 aa	Rv3262 fbiB (n= 4) 448 aa	Rv1173 fbiC (n= 55) 856 aa		Rv2983 cofC (n= 8) 214 aa
Point mutations	9N *63K* 191D	49P 112W 149Y	49G 120P *202P* 212V 219G 273D 286A 308P	15P 173P 397R	25G 133P 148D 169P 187R 190N 194D *215P* 273K 278P 301A 322L (2) 336K 354R *363G*	377P 562W 588P 591D 632V 682E 684T 685R 702R 707M 744S 772W 776T 827G	25S 68E 132V 147C 152R 198P
Indels	214 (+A)	38 (-T) 39 (-G) 39 (-GC) 93 (-C) 108 (+IS6110) 131 (+IS6110) Rv3540- Rv3550	47 (-G) 125 (+C) 140 (-GC) 248 (-G)	684 (-T)	20 (-C) 52 (-G) 75-6 (-4) 107 (+G) 188(+T) 225 (-A) 247 (-C) 252 (-C) 306-8 (-9) 328 (+C)	331 (-A) 363 (-C) 426 (+A) 503 (-A) 627 (-T) 680-93 (-42) 846 (-GC) fbiC+PE12 (-1kb)	27 (+C) 129 (-ATC)
Stops		20* 27*	27* 79*		20* 155* 170* 198*	400* 500* 690*	

Mutants in italics were isolated in a separate experiment

Acquired rifamycin resistance in athymic nude mice receiving weekly RPT-based continuation phase regimens (ala TBTC Study 22)

TABLE 4 MIC and mutational analysis of isolates harboring >1% resistance[a]

Treatment group and regimen	Duration of treatment (wks)	Resistant CFU[b] (%)		MIC (μg/ml)		*katG* mutation		*rpoB* mutation	
		H	R	H	R	Nucleotide	Amino acid	Nucleotide	Amino acid
BALB/c mice									
G2, P 5/7	16	0	97		>16			1592 C→T	S531L
	24	0	77		>16			1576 C→T	H526Y
Nude									
G2, P 5/7	4	<0.01	2		>16			1577 A→G	H526R
	13	<0.01	100		>16			1576 C→T	H526Y
	13	<0.01	2		2–4			1598 T→C	L533P
	13	0	100		>16			1576 C→T	H526Y
	13	<0.01	20		>16			1577 A→G	H526R
	16	0	6		>16			1565 C→T	S522L
G7, $_{(2+6)w}$RHZE + 4P 1/7	16	<0.01	3		>16			1592 C→G	S531W
	16	0.06	0.25	>16[c]	>16[c]	1513 T→C	W505R	1592 C→T	S531L
	24	<0.01	6		>16			1576 C→T	H526Y
G8, $_{(2+6)w}$RHZE + 4PH_{50} 1/7	16	33	0	>16		765 G→C	M255I		
	16	100	0	>16		691 A ins	Frame shift		
	24	0	100		>16			1592 C→T	S531L
G9, $_{(2+6)w}$RHZE + 4P$_{15}H_{50}$ 1/7	16	100	0	>16		902 AG del	Frame shift		
	16	75	0	>16		WT			
G11, $_{(2+6)w}$RH_5ZE + 4R$H_{12.5}$ 2/7	19	100	0.0014	>16		853 G ins	Frame shift		
G13, $_{(2+6)w}$RH_5ZE + 4PH_{25} 1/7	16	0	100		>16			1592 C→T	S531L
G14, $_{(2+6)w}$RH_5ZE + 4P$_{15}H_{25}$ 1/7	16	16	0	>16		1856 T→G	L619R		
	24	100	0	>16		1643 G→A	G548D		
G15, $_{(2+6)w}$RH_5ZE + 4P$_{20}H_{25}$ 1/7	16	30	0	>16		WT			
	16	0	100		>16			1592 C→T	S531L

[a]Drug doses (in mg/kg) if not otherwise specified: rifampin (R), 10; rifapentine (P), 10; isoniazid (H), 10; pyrazinamide (Z), 150; ethambutol (E), 100. (2 + 6)w, combination of 2-week plus 6-week drug administration; G, group; ins, insertion; del, deletion; WT, wild type.
[b]Resistance defined by growth on H (0.2 μg/ml) or R (1 μg/ml).
[c]MIC measured only with resistant isolates on H (0.2 μg/ml) or R (1 μg/ml).

S-W Park et al, AAC 2017

Rpt

TABLE 3 Proportions of nude mice with selective amplification of resistance and emergence of resistance between month 2 and month 6

Treatment group	Drug regimen		No. of mice with indicated result/total no. of mice					
			Selective amplification only[a]			Resistance[b]		
	0–2 mos	2–6 mos	H	R	H or R	H	R	H or R
2	P 5/7	P 5/7	0/9	1/10	1/10	0/9	9/10	9/10
3		RH 5/7	0/10	0/10	0/10	0/10	0/10	0/10
4	RHZE 5/7	P 1/7	0/10	0/10	0/10	0/10	1/10	1/10
5		PH_{50} 1/7	0/10	0/10	0/10	0/10	0/10	0/10
6		RH_{25} 2/7	0/10	0/10	0/10	0/10	0/10	0/10
7		P 1/7	0/10	1/10	1/10	1/10	6/10	6/10[c]
8	2wRHZE 5/7 + 6w$RH_{25}Z_{300}E_{200}$ 2/7	PH_{50} 1/7	0/10	0/10	0/10	3/10	1/10	4/10
9		$P_{15}H_{50}$ 1/7	0/10	0/10	0/10	2/10	0/10	2/10
10		$P_{20}H_{50}$ 1/7	0/10	0/10	0/10	0/10	1/10	1/10
11		$RH_{12.5}$ 2/7	0/10	1/10[d]	1/10	4/10[d]	0/10	4/10
12		P 1/7	0/10	1/10	1/10	2/10[d]	5/10	5/10[d]
13	2wRH_5ZE 5/7 + 6w$RH_{12.5}Z_{300}E_{200}$ 2/7	PH_{25} 1/7	0/10	0/10	0/10	1/10	1/10	2/10
14		$P_{15}H_{25}$ 1/7	0/10	0/10	0/10	1/10	0/10	1/10
15		$P_{20}H_{25}$ 1/7	0/10	0/10	0/10	1/10	1/10	2/10

Drug doses (in mg/kg) if not otherwise specified: rifampin (R,10); rifapentine (P, 10); isoniazid (H, 10); pyrazinamide (Z, 150); ethambutol (E, 100).

[a]Selective amplification defined by $0.01 < H < 1\%$ or $0.001 < R < 1\%$ of resistance on H (0.2 μg/ml) or R (1.0 μg/ml).

[b]Resistance defined by resistant CFU comprising $\geq 1\%$ of total CFU.

[c]One isolate was multidrug resistant (MDR) which was resistant to both H (0.2 μg/ml) and R (1.0 μg/ml).

[d]One isolate had heterogenous strains which were resistant to either H (0.2 μg/ml) or R (1.0 μg/ml) but not both.

Acquired moxifloxacin resistance in BALB/c mice receiving monotherapy

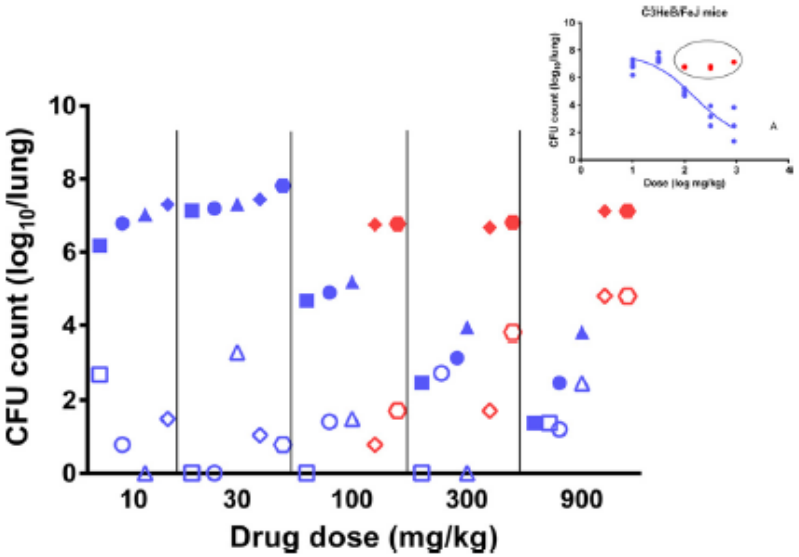
TABLE 4. Determination of mutation in QRDRs of *gyrA* and *gyrB* of MXF-resistant colonies grown from day 56 lung homogenates

Treatment group (% MXF in diet)[a]	Mouse	Grown on plate containing indicated MXF concn (μg/ml)	QRDR mutation, codon sequence change	
			gyrA	*gyrB*
3 (0.125)	1	2.0	A90V, GCG→GTG	None
4 (0.25)	1	NA[b]	NA	NA
	2	0.5	None	None
		1.0	D94G, GAC→GGC	None
		2.0	D94G, GAC→GGC	None
	3	2.0	D94G, GAC→GGC	None
		2.0	D94G, GAC→GGC	None
		2.0	D94G, GAC→GGC	None
		2.0	D94G, GAC→GGC	None
		2.0	D94G, GAC→GGC	None
	4	1.0	None	None
5 (0.5)	1	2.0	None	None
		2.0	D94G, GAC→GGC	None
	2	2.0	D94Y, GAC→TAC	None
		2.0	D94Y, GAC→TAC	None
		2.0	D94Y, GAC→TAC	None
	3	2.0	None	None
		2.0	S91P, TCG→CCG	None
6 (1)	1	2.0	A90V, GCG→GTG	None
		2.0	D94N, GAC→AAC	None
	2	2.0	None	None

[a] Treatment group 5 and 6 MXF-resistant colonies were grown from day 56 frozen lung homogenates.
[b] NA, not applicable.

A Ginsburg et al, AAC 2005

Acquired pyrazinamide resistance in BALB/c or C3HeB/FeJ mice receiving PZA monotherapy



J-P Lanoix et al, AAC 2016

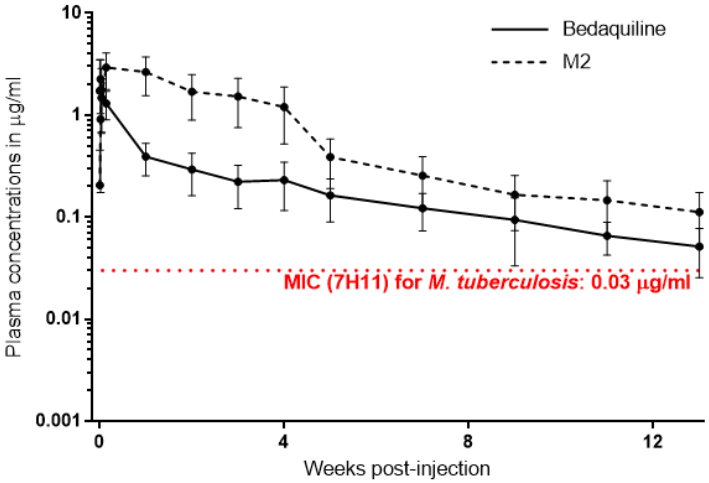
TABLE 3 Results of mutations in the *pncA* gene (Rv2043c) observed in PZA-resistant isolates

Type of mutation	Mutation(s) in mouse strain:	
	BALB/c	C3HeB/FeJ
Point mutations	K96 M G132A C138Y T142P L159V H171R	M1I, T135P L19R, H137D A46E, V139 M S67P, A146V H71Y, S164P C72F, L172P Y99stop, E173stop G108R I133N
Small indels[a]	+A in E127	−G in P54 −CG in A26 −T in I133 −CGTCAGCGGTACTC in V73–P77
Large-scale deletions	Rv2023c–Rv2048c (27 kb) Rv2027c–Rv2047c (19.8 kb)	Rv2030c–Rv2048c (21 kb) Rv2034–Rv2045c (9 kb) Rv2039c–Rv2048c (13 kb) Rv2040c–Rv2045c (3.5 kb) Rv2041c–Rv2043c (1.1 kb) Rv2042c–Rv2043c (1 kb) Rv2043c–Rv2044c (0.2 kb)
5′ UTR[b]	A→G at −11 bp (upstream)	
No *pncA* mutation		One (A3311T mutation in Rv3350c)

[a] Frameshifts.
[b] UTR, untranslated region.

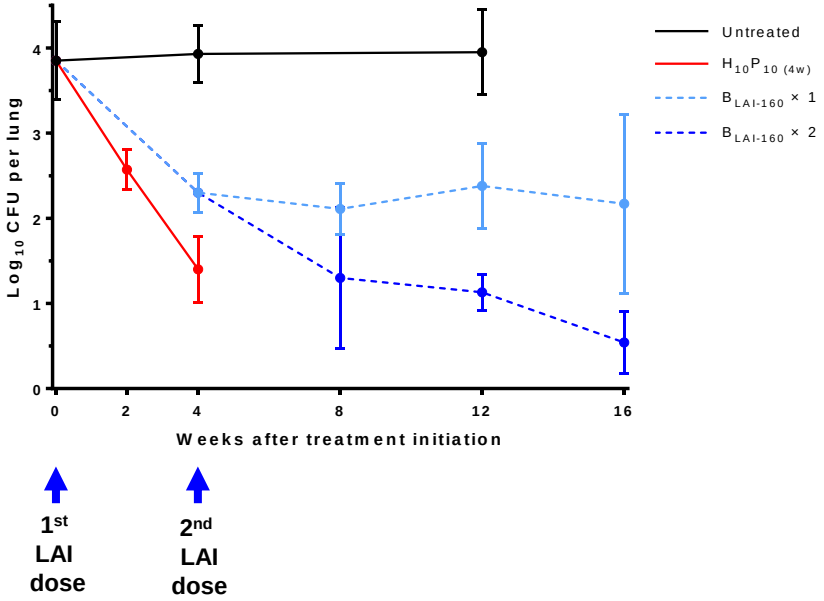
Pre-clinical evaluation of an LAI bedaquiline formulation in a mouse model of TPT

Plasma concentrations of BDQ and M2 metabolite after single IM injection to mice



Kaushik et al. *Antimicrob Agents Chemother* 2019; pii: AAC.00007-19

Efficacy of 1 or 2 monthly $B_{LAI-160}$ doses vs. 1HP

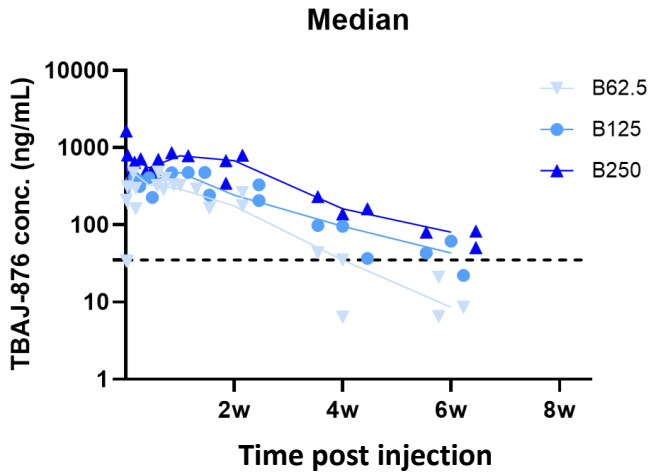


Kaushik et al, *Am J Respir Crit Care Med* 2022; doi: 10.1164/rccm.202012-4541OC

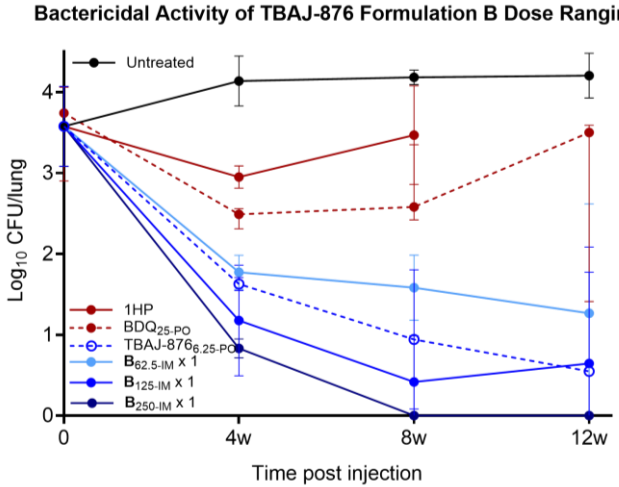
Poster 00881: **One-Dose Efficacy of Long-Acting Injectable Diarylquinoline in Mouse Model of TB Preventive Therapy**

(Johns Hopkins University, University of Liverpool CELT, TB Alliance)

A) TBAJ-876 Intramuscular LAI Mouse Plasma PK



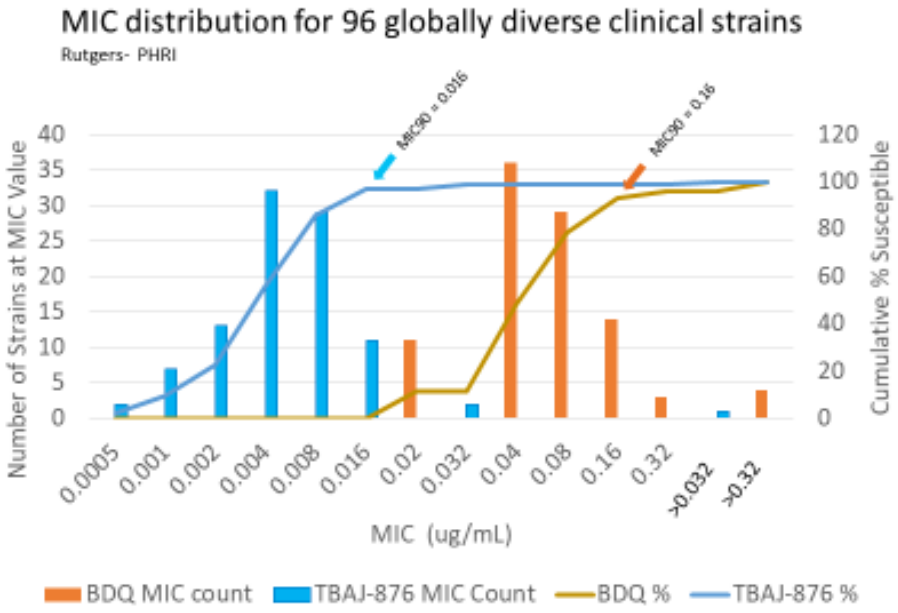
B) Mouse TPT Model M.tb CFU timecourse following treatment with TBAJ-876 LAI



Summary:

- One 125 mg/kg IM dose of any of 3 TBAJ-876 LAI formulations produced sustained plasma exposures above EC_{50} for 6 weeks, with efficacy at least as great as the same total dose administered as daily oral doses over 4 weeks in the mouse model of TPT.
- All LAI doses 62.5-250 mg/kg had superior bactericidal activity compared to 1HP and oral bedaquiline x 4 weeks.
- 23 of 25 mice receiving doses ≥125 mg/kg had no recoverable CFU at Week 12 post-dose.
- These data provide POC for a highly efficacious pan-TPT regimen comprised of a single IM dose of a TBAJ-876 LAI formulation.

In Vitro activity of TBAJ-876 and major M3 metabolite (N-monodesmethyl) *cf.* BDQ and its' M2 (N-monodesmethyl) metabolite



MICs for Parent and major metabolites for 5 globally diverse strains

UIC

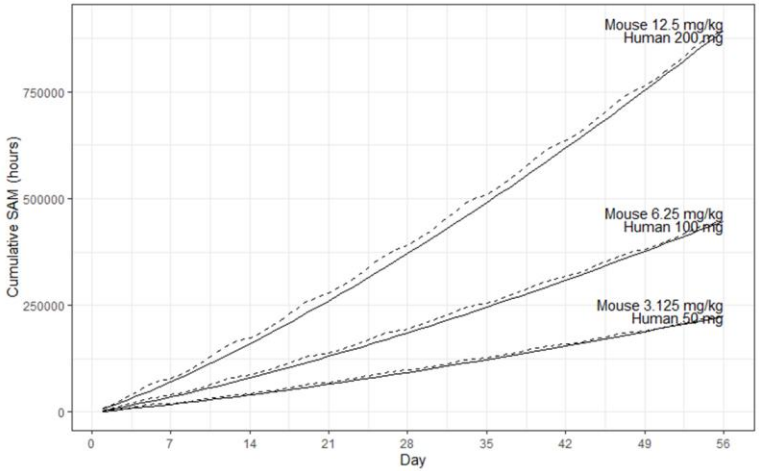
Strain Lineage		Laboratory Reference	East African Indian	East Asian	East Asian	Euro-American	Euro-American
Strain		H37Rv	X001354	X004244	X004439	X005282	X005319
		MIC (ug/mL)					
Test Compounds	BDQ	0.04	0.2	0.08	0.04	0.05	0.05
	BDQ-M2	0.25	0.81	0.25	0.11	0.35	0.47
	ΔM2/BDQ	6.3	4.1	3.1	2.8	7.0	9.4
	TBAJ-876	0.003	0.02	0.004	0.002	0.003	0.006
	876-M3	0.01	0.04	0.01	0.005	0.008	0.02
	ΔM3/876	3.3	2.0	2.5	2.5	2.7	3.3
Drug Controls	RMP	0.01	0.05	0.03	< 0.008	< 0.008	0.09
	LZD	2	4.1	2.9	0.8	0.8	3.4
	MOX	0.24	0.24	0.43	0.1	0.1	0.3
	PA824	0.1	0.5	0.99	< 0.031	< 0.031	0.98

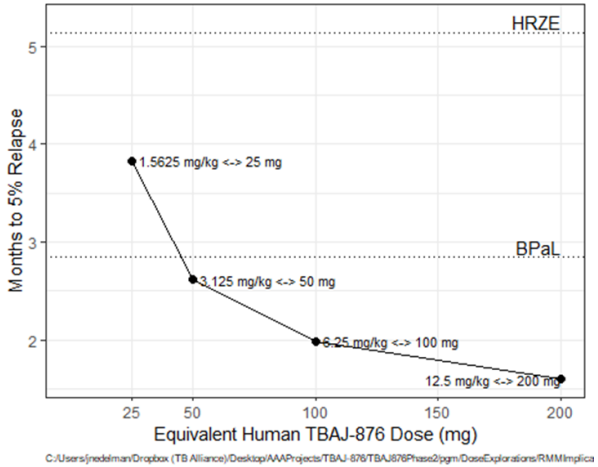
- TBAJ-876 is much more potent than BDQ against WT and rv0678 mutants

MOUSE-TO-HUMAN DOSE TRANSLATION

Sum of Active Moieties (SAM) =

$(AUC/MIC)_{parent}$ + $(AUC/MIC)_{M3\ metab.}$



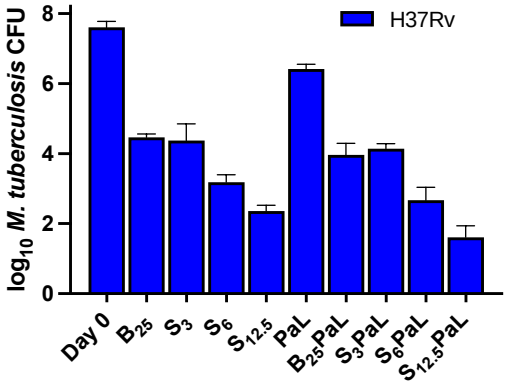


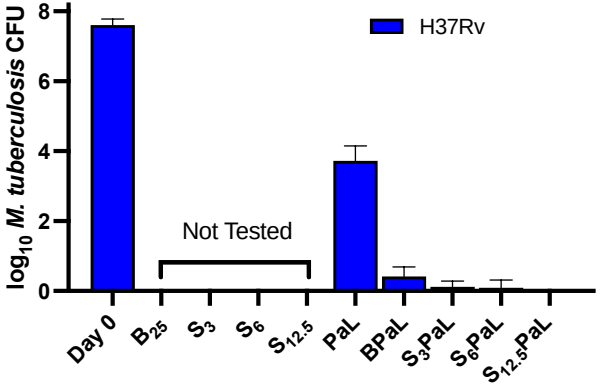
- Mouse doses of 3.125, 6.25 and 12.5 mpk represent 3 highest doses tested in Ph. 1 MAD study
- Dose translation suggests the 50 mg human dose of TBAJ-876 will be as effective as BDQ in combination with PaL, while 100 mg is superior & sterilizing activity will largely plateau between 100 and 200 mg doses

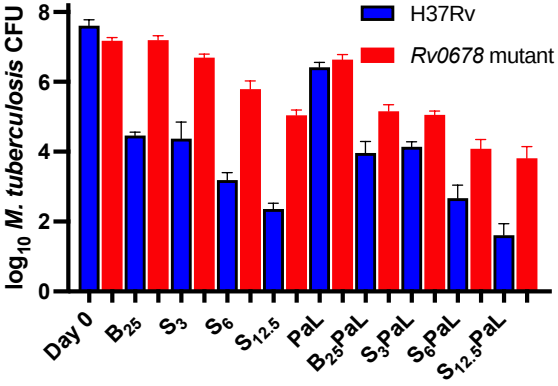
2020 Expt 2i:

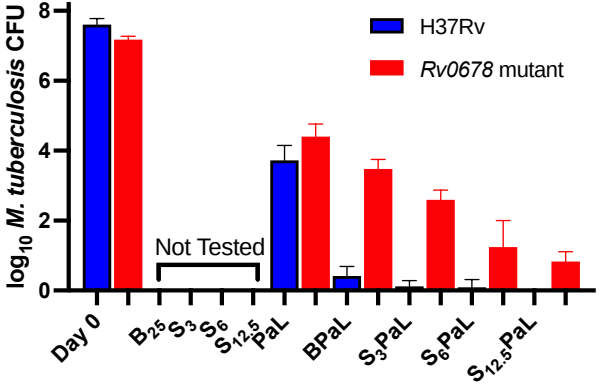
876 dose equivalent to BDQ 25 mpk is <= 3mpk

PaL dosed at 30/50 mpk bid

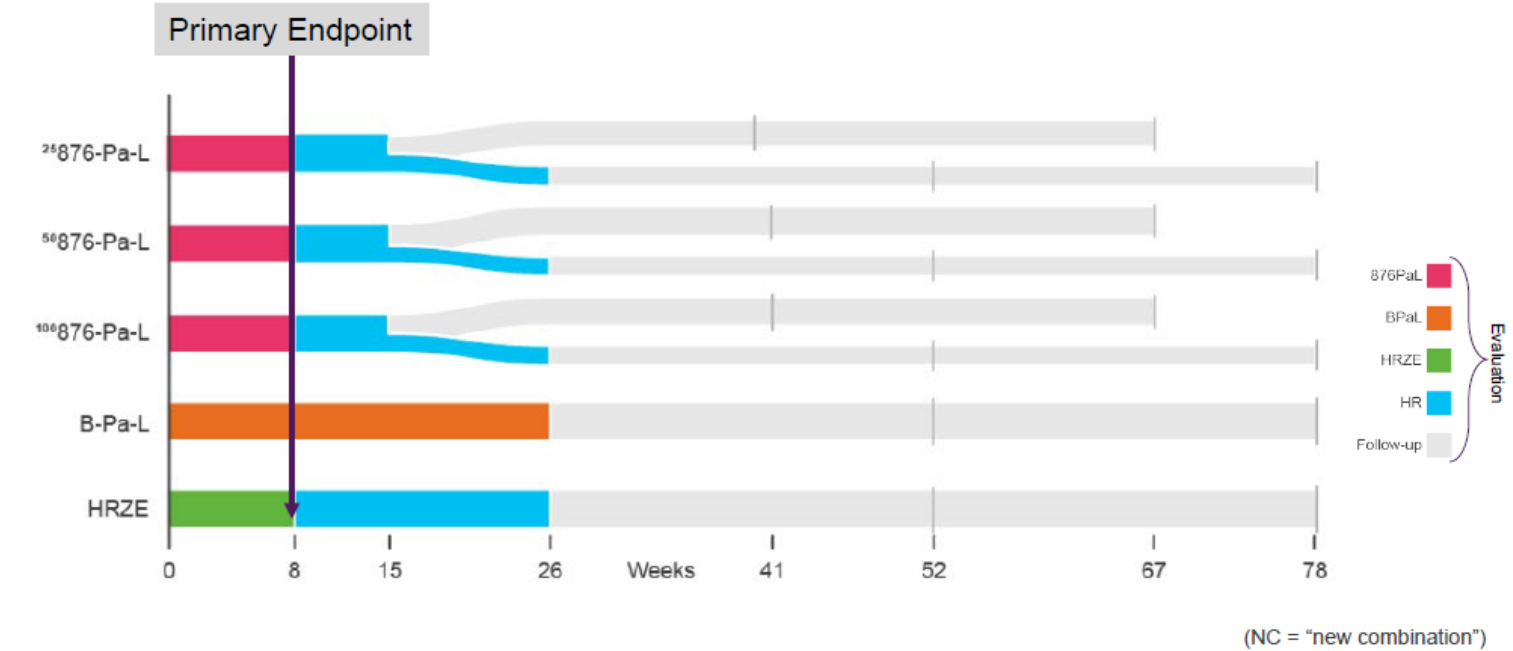








NC-009 TRIAL NOW ENROLLING



(NC = "new combination")