IMPAACT Meeting

Tuberculosis Scientific Committee Mentored Investigators Meeting

Wednesday, 29 June 2022

BPaL Update

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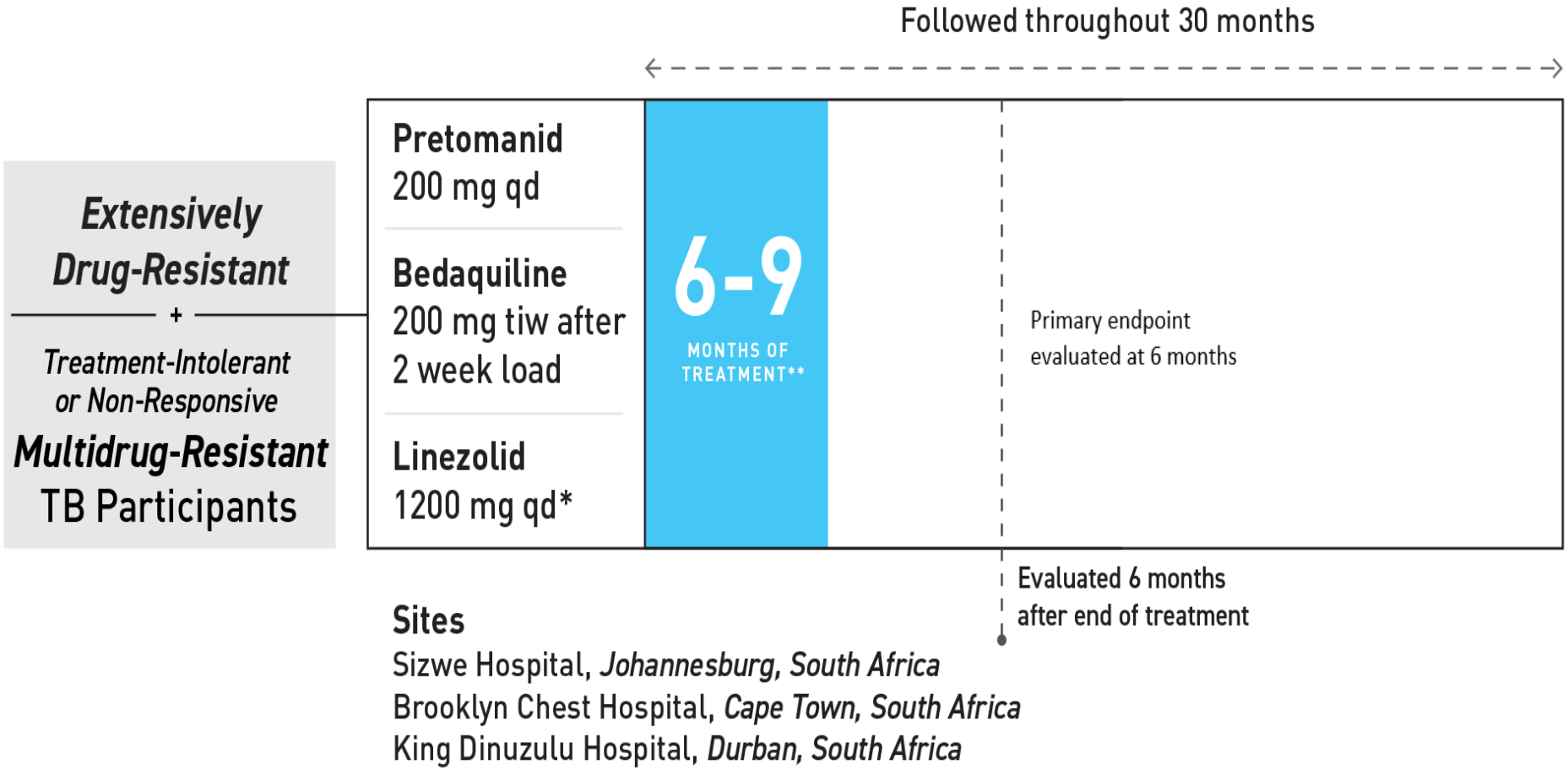
Overview

- Clinical Trials
- BPaL Clinical Access Program
- WHO Rapid Communication
- Concerns
- Next Steps

Phase 3 Trial in XDR-TB (old definition)



Sites

Sizwe Hospital, *Johannesburg, South Africa*
Brooklyn Chest Hospital, *Cape Town, South Africa*
King Dinuzulu Hospital, *Durban, South Africa*

**Amended from 600 mg bid strategy*

***If sputum culture is positive at 4 months, patients received an additional 3 months of treatment*

Primary endpoint is measured at six months of post-treatment follow up

Slide from TB Alliance

Nix Results

- Nix-TB results: 90%; (95% confidence interval, 83 to 95) had a favorable outcome in highly resistant TB with the BPaL(1200mg) regimen
- Adverse events driven by linezolid often led to dose reductions or interruptions of linezolid
  - Peripheral neuropathy (occurring in 81% of patients)
  - Myelosuppression (48%)
- Led to the initial approval of BPaL by the U.S. FDA

Source: Conradie F, Diacon AH, Ngubane N, Howell P, et al. Treatment of highly drug-resistant pulmonary tuberculosis. New England Journal of Medicine. 2020 Mar 5;382(10):893-902.

ZeNix

TB Alliance

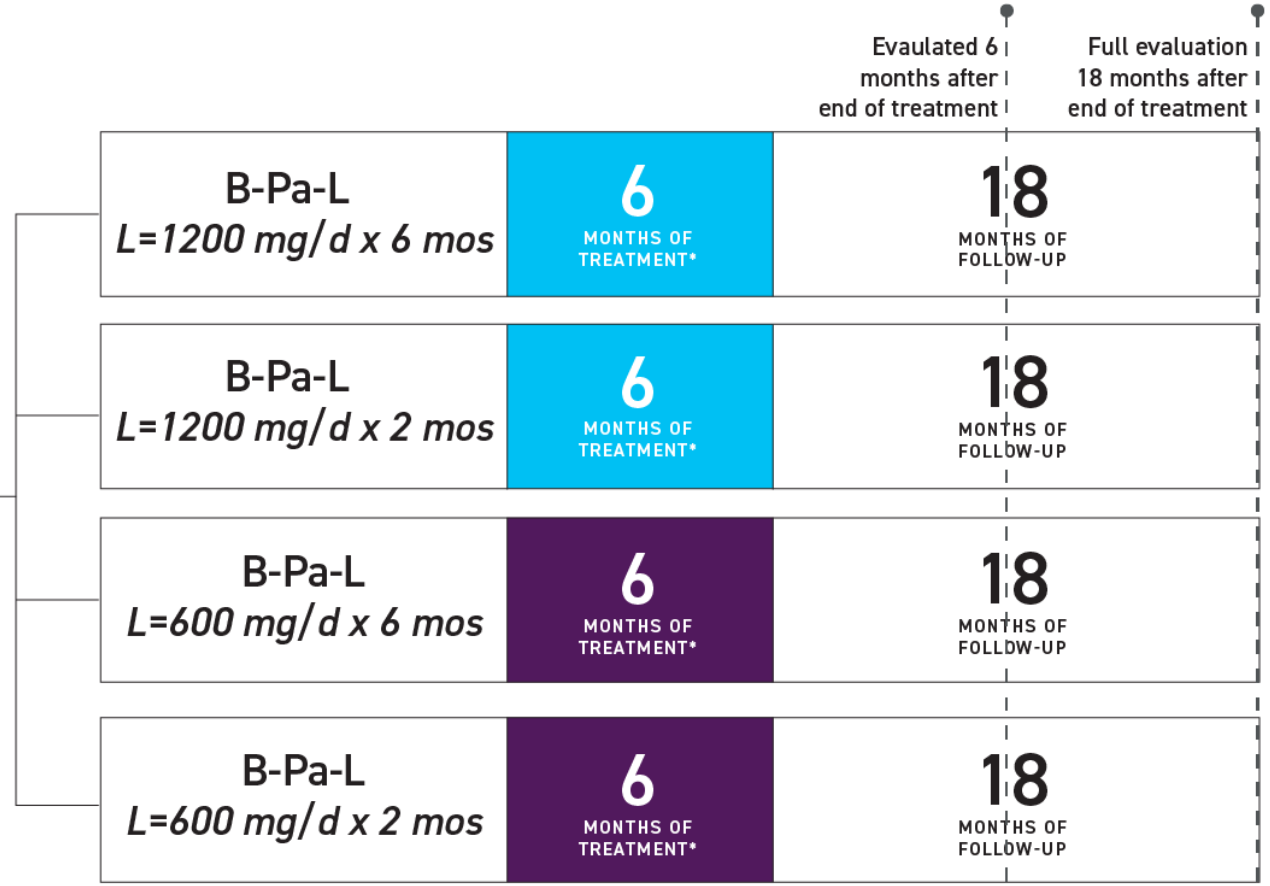
***Extensively Drug-Resistant, Pre-Extensively Drug-Resistant*†**

+

Treatment-Intolerant or Non-responsive Multidrug-Resistant

TB Participants

randomized



*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

Pa pretomanid dose = 200 mg daily

B bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

† Pre-2021 WHO Definitions of XDR-TB and Pre-XDR-TB

ZeNix - Primary Efficacy Analysis (MITT)

89.3%	Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Unassessable	1	1	1	1	4
Total assessable	44	45	44	44	177
Favourable	41 (93.2%)	40 (88.9%)	40 (90.9%)	37 (84.1%)	158 (89.3%)
Unfavourable	3 (6.8%)	5 (11.1%)	4 (9.1%)	7 (15.9%)	19 (10.7%)
95% CI for Favourable	81.3% to 98.6%	75.9% to 96.3%	78.3% to 97.5%	69.9% to 93.4%	83.7% to 93.4%

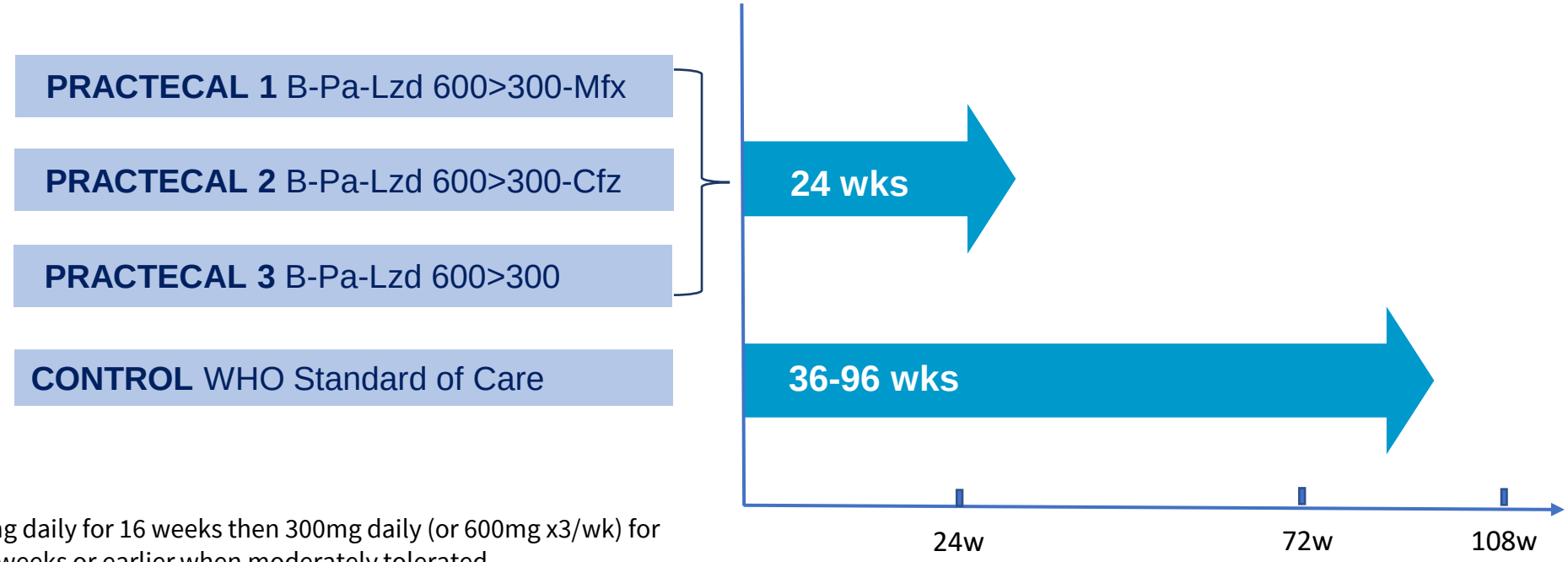
ZeNix Safety – Adverse Events

	Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Any grade ≥ 3 TEAE	14 (31.1%)	11 (23.9%)	9 (20.0%)	11 (24.4%)	45 (24.9%)
Any serious TEAE	3 (6.7%)	4 (8.7%)	1 (2.2%)	3 (6.7%)	11 (6.1%)

TB Practecal
Innovating MDR-TB Treatment

TB-PRACTECAL trial design

A randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of drug regimens containing bedaquiline and pretomanid for the treatment of patients with pulmonary rifampicin-resistant tuberculosis



MEDECINS SANS FRONTIERES

*Linezolid: 600mg daily for 16 weeks then 300mg daily (or 600mg x3/wk) for the remaining 8 weeks or earlier when moderately tolerated

Baseline characteristics

	Control	PRACTECAL Arm 1 (BPaLM)	PRACTECAL Arm 2 (BPaLC)	PRACTECAL Arm 3 (BPaL)
mITT population 72 weeks	66	62	64	60
Age (years), median (range)	36 (19 to 71)	34 (18 to 61)	29 (19 to 63)	34 (18 to 62)
Female, n (%)	33 (50.0)	26 (41.9)	24 (37.5)	28 (46.7)
BMI (kg/m²), median (IQR)	19.2 (17.3 to 22.0)	19.8 (18.1 to 22.1)	18.8 (17.4 to 22.0)	20.5 (18.2 to 22.8)
HIV positive, n (%)	15 (22.7)	14 (22.6)	14 (21.9)	14 (23.3)
CD4 count (cells/μL), median (IQR)	317 (154 to 383)	268 (182 to 364)	394 (112 to 511)	283 (153 to 424)
Smear positivity, n (%)	50 (75.8)	40 (64.5)	43 (67.2)	45 (75.0)
Cavity present, n (%)	47 (71.2)	33 (53.2)	39 (60.9)	41 (68.3)
Fluoroquinolone resistant*, n (%)	18 (27.7)	17 (28.3)	16 (25.8)	19 (33.9)
QTcF (ms), mean (SD)	398 (18)	396 (18)	393 (20)	398 (18)
ALT (IU/l), median (IQR)	20 (15 to 27)	18 (14 to 27)	18 (15 to 27)	19 (14 to 27)

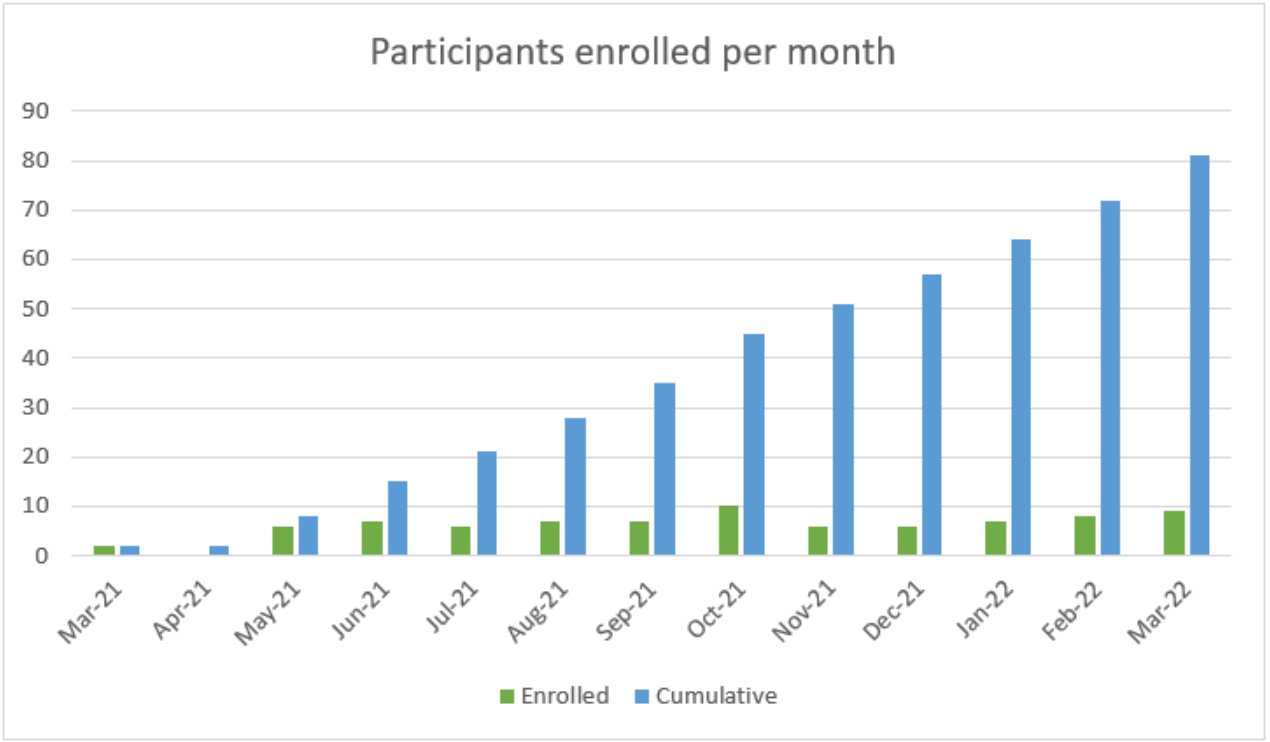
* percentage of culture positive isolates

Primary treatment outcome: Per Protocol

	Control	PRACTECAL arm 1 BPaLM	PRACTECAL arm 2 BPaLC	PRACTECAL arm 3 BPaL
PP population 72 weeks	33	57	58	52
Number with no unfavourable outcome	29 (87.9%)	55 (96.5%)	52 (89.7%)	46 (88.5%)
Number with an unfavourable outcome	4 (12.1%)	2 (3.5%)	6 (10.3%)	6 (11.5%)
Risk difference (one-sided 98.3% confidence interval)		-8.6% (-∞ to 4.5%)	-	-
Risk difference (one-sided 97.5% confidence interval)		-	-1.8% (-∞ to 11.8%)	-0.6% (-∞ to 13.5%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.001	-	-
Superiority p-value		p = 0.13	-	-
Risk ratio (one-sided 98.3% confidence interval)		0.29 (-∞ to 1.71)	-	-
Risk ratio (one-sided 97.5% confidence interval)			0.85 (-∞ to 2.81)	0.95 (-∞ to 3.12)
Deaths	2 (6.1%)	0 (0%)	1 (1.7%)	0 (0%)
Early discontinuations	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment failure	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)
Lost to follow-up at 72 weeks	2 (6.1%)	2 (3.5%)	3 (5.2%)	3 (5.8%)
Recurrence	0 (0%)	0 (0%)	1 (1.7%)	3 (5.8%)

BPaL Clinical Access Program

Figure 1.1. Enrolment by month



Per DMC report (data extracted 21 Apr 22) – 81 enrolled

Table 1.2. Reasons for not being enrolled

Total screened	**100**
Total enrolled	**81**
Total non-enrolled	**7**

Data courtesy of Dr Francesca Conradie

BPaL Clinical Access Program

Table 2.1. Baseline participant characteristics

		Total enrolled (%) unless otherwise stated
Age (years)	Median (IQR)	39.3 (33.5; 49.2)
	Min, Max	17.5, 81.4
BMI (m/kg^2)	Median (IQR)	19.7 (17.3, 22.1)
	Min, Max	14.4, 31.7
Gender	Female	22 (27.2)
	Male	59 (72.8)
Race	Black	77(95.1)
	Other	4 (4.9)
HIV Status	HIV Negative	56 (69.14)
	HIV Positive	24(29.63)
	Unknown	1 (1.23)

Table 2.2. Baseline resistance

	Total enrolled (%)
Known FQ-R RR TB	18 (22.2)
Known FQ-S RR TB	28 (34.6)
RR TB- unknown FQ status at enrolment	35(43.2)

BPaL Clinical Access Program

Table 2.3. Culture conversions

	Participants with at least 2 months follow up culture prior to treatment N=71	Culture at 2 months (for those who have had a 2 month visit) N=67*	Culture at 6 months (for those who have had a 6 month visit) N=38*
Positive	47 (66.2%)	18	2
Negative	10 (14.2%)	27	24
Pending	13 (18.3)	20	11
Contaminated	1	3	0

- Four patients were withdrawn prior to 2 months.
- Seven patients were withdrawn prior to 6 months.

Two patients have had their treatment extended beyond 26 weeks

BPaL Clinical Access Program

3. Retention and withdrawals

Table 3.1. Early withdrawals from follow-up

Participant ID	Date of enrolment	Date of withdrawal (weeks from enrolment)	Reason for early withdrawal
10001	15 Mar 2021	2	Bedaquiline resistant
40001	5 Mar 2021	8	Bedaquiline resistant
10017	15 Sep 2021	8	Optic neuritis
10011	3 Aug 2021	12	Loss to follow up
40010	1 Dec 2021	4	Bedaquiline resistant
20019	21 Mar 2022	1	Death
40015	18 Mar 2022	4	Optic neuritis
10027	20 Jan 2022	8	Peripheral neuropathy

BPaL Clinical Access Program

Table 4.2. Summary of grade 3-5 AEs

Any Grade 3-5 AEs	19	Action taken with medication
Not attributed to any drug	8	BPaL unchanged
Peripheral neuropathy	3	L interrupted
Anaemia	3	L interrupted
Raised ALT	3	BPaL interrupted
Neutropenia	2	BPaL unchanged

BPaL Clinical Access Program

4. Safety

Table 4.1 Safety Summary

	Number of participants
Total enrolled	**81**
Grade 3-5 AEs	19
Serious AEs (SAEs)	9
Deaths	1

Table 4.2. Summary of grade 3-5 AEs

Any Grade 3-5 AEs	19	Action taken with medication
Not attributed to any drug	8	BPaL unchanged
Peripheral neuropathy	3	L interrupted
Anaemia	3	L interrupted
Raised ALT	3	BPaL interrupted
Neutropenia	2	BPaL unchanged

WHO issues rapid communication on updated guidance for the treatment of drug-resistant tuberculosis

2 May 2022 | Departmental news | Geneva | Reading time: 1 min (361 words)

World Health Organization

Health Topics

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The data from the ZeNix study made it possible to identify the linezolid dose that offers the best balance in terms of efficacy and safety in patients aged above 14 years. The assessment of evidence from this study suggested that the optimal dosing of linezolid is 600 mg daily and that programmes should strive to maintain this dose throughout the treatment regimen to ensure optimal efficacy, with the possibility of dose reduction in the event of toxicity or poor tolerability.

The evidence assessment suggested that the 6-month BPaLM regimen – comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin – may be used programmatically in MDR/RR-TB patients without previous exposure to these medicines in place of the 9-month regimen (described below) or the longer (≥18 months) regimen. The BPaLM regimen showed favourable efficacy and safety when compared with the regimens given in the control arm of the TB-PRACTECAL trial. The evidence assessment also suggested that the BPaL combination (with 600 mg linezolid) retains sufficient efficacy and allows the regimen to be used without moxifloxacin in the case of documented resistance to fluoroquinolones (i.e. in patients with pre-XDR-TB). In this group of patients receiving the BPaL combination, where there is a slow response to therapy, an extension of 3 months (bringing the total regimen to 9 months) is possible.

The BPaLM and BPaL regimens showed high treatment success. The evidence from the available studies suggests that these regimens may be used in eligible patients with MDR/RR-TB and pre-XDR-TB[4] regardless of their HIV status. The available evidence was limited to patients aged above 14 years and there were no data on the use of these regimens during pregnancy or in severe forms of extrapulmonary TB (e.g. TB meningitis). Thus, the evidence provided by the TB-PRACTECAL and ZeNix studies will support new recommendations for the programmatic use of the two regimens.

Summary

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, stand to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions.

- The 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin, may be used programmatically in place of 9-month or longer (≥18 months) regimens, in patients (aged ≥15 years) with MDR/RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure). This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB). Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.

Concerns

- Resistance to BDQ
  - SA – 6% of TB is rifampicin resistant.
  - Rif resistant + FQ sensitive: BDQ resistance in ~4% (3% of total)
  - Rif resistant + FQ resistant: BDQ resistance in ~19% (4% of total)
  - BDQ resistance detection is very complicated
  - Many countries do not have BDQ resistance detection available
  - Lineage 1 effect/Group C (most studies done in areas with predominantly Group B Mtb)

Next Steps

- South Africa plans to be the first to implement BPaL/M programmatically by Aug/Sep 2022
- Guidelines to be written (modular updates)
- ROSA conference in June 2022 – knowledge and experience sharing on BPaL/M
  - Countries in attendance: Nigeria, Kenya, eSwatini, Zimbabwe, India, Vietnam, DRC, Congo-Brazzaville, Kyrgyzstan (virtual), Ukraine (virtual), South Africa
- Need new diarylquinolines (resistance) and oxazolidinones (toxicity)
- Options for paediatrics and pregnancy (?DLM vs Pa)

Thank you

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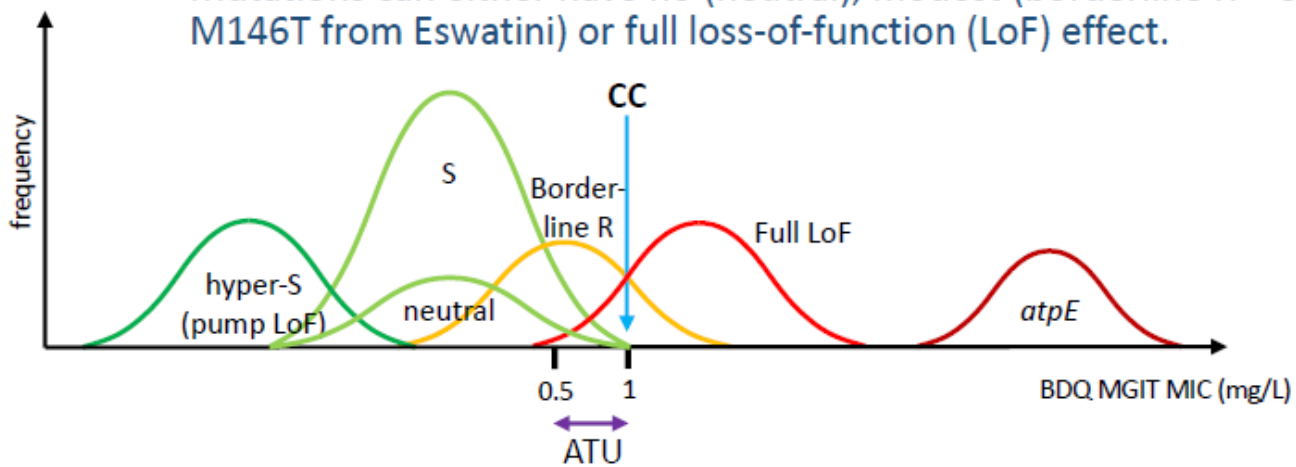
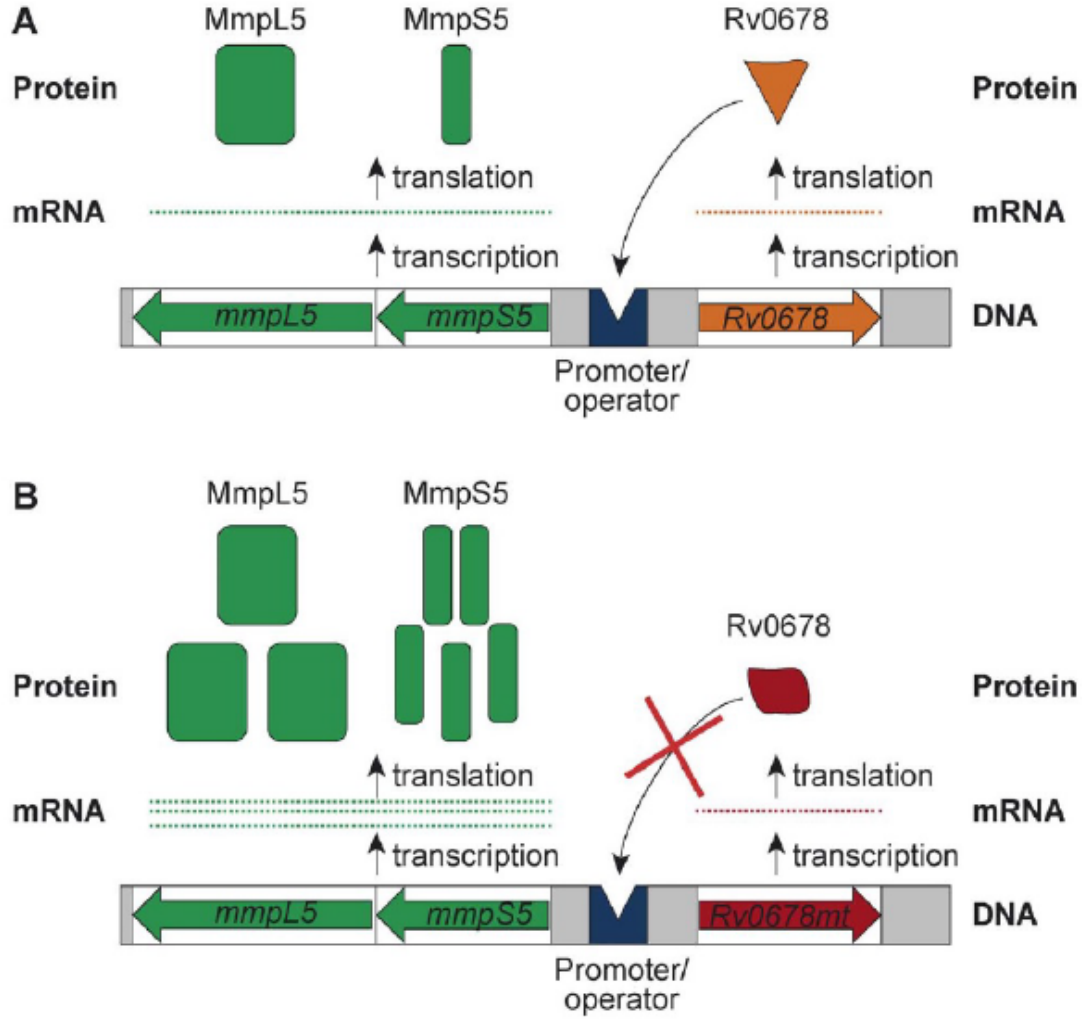
Extra Slides

BDQ DST

- BDQ-R MDRs: 19% (95% CI 14-24) of FQ-R and 4% (95% CI 3-5) of FQ-S.
- Mutation in target (*atpE*) easy to detect by pDST but these are rare.
- *Rv0678* dominant resistance mechanism but:
  - Large spectrum of mutations.
  - Mutations can either have no (neutral), modest (borderline R – e.g. M146T from Eswatini) or full loss-of-function (LoF) effect.



- LoF mutations in *mmpS5-mmpS5* efflux pump, which are rare globally but can be frequent locally (e.g. Peru, Lima), confer hyper-S to BDQ/CFZ and fully counteract the effect of *Rv0678* mutations.
- BDQ most difficult core drug to conduct DST for!



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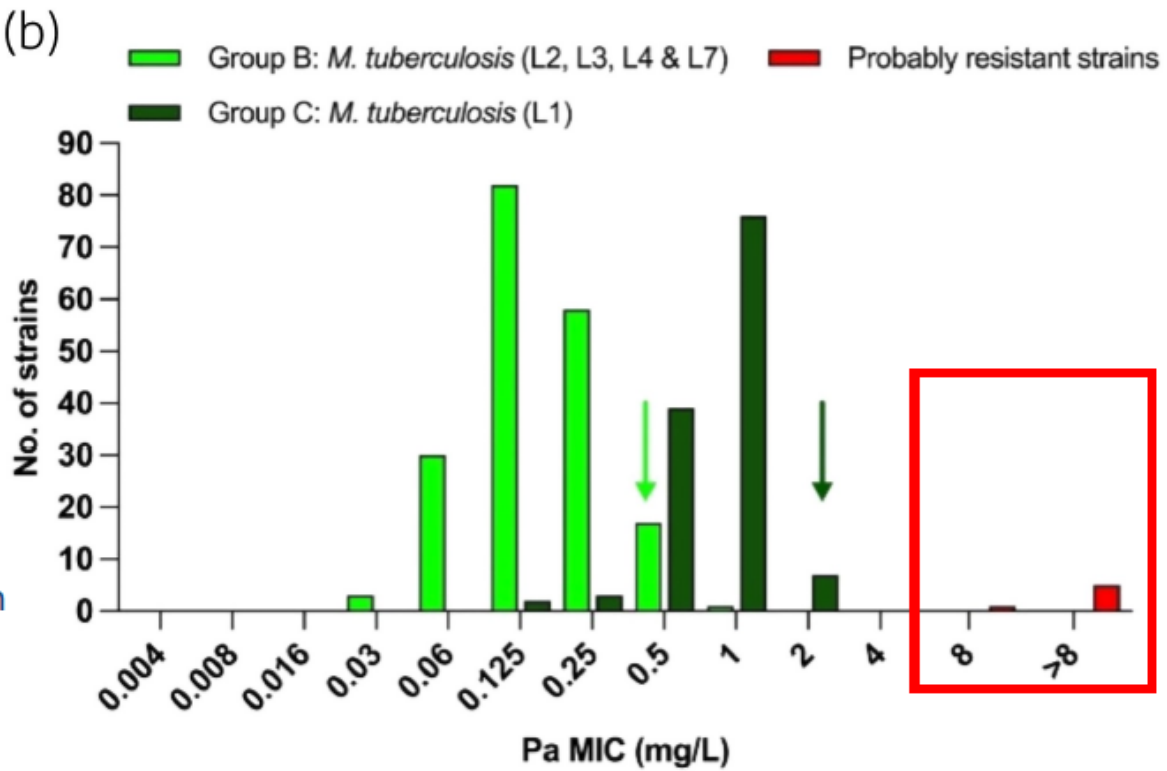
Slide from Dr Claudio Koser

PMD DST

- 1-2% (?) strains 'probably resistant' due to mutations in one of the six genes required for the activation of PMD:
  - No danger of false-S by pDST as these typically cause large MIC increases.
  - Interpretation of WGS results challenging because of large spectrum of R mutations.
- Efficacy of BPaL(M) against lineage 1 not clear:
  - Accounts for 28% of TB cases globally and <2% in South Africa.
  - WHO due to review evidence to set MGIT CC later this year.
  - Some lineage 1 strains are hyper-S to BDQ due to a LoF mutation in *mmpL5*, which may counteract any potential effect of the elevated PMD MIC.
- Some delamanid/PMD resistance mutations confer hyper-S to malachite green, a decontamination agent used in Löwenstein-Jensen, 7H10 and 7H11 solid media.
- SRL Johannesburg already has experience with PMD MIC testing in MGIT as part of TB Alliance surveillance study.



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