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Innovating MDR-TB Treatment

TB-PRACTECAL final efficacy and safety results

Bern-Thomas Nyang'wa
Médecins sans Frontières

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MULTIDRUG-RESISTANT TB TREATMENT REGIMENS

HOW IT STARTED...

> Prescrire Int. 2014 Oct;23(153):232-4.

Bedaquiline. More data needed on this dangerous antitubercular drug

No authors listed

PMID: 25964964

Abstract

...HOW IT'S GOING

BPaLM

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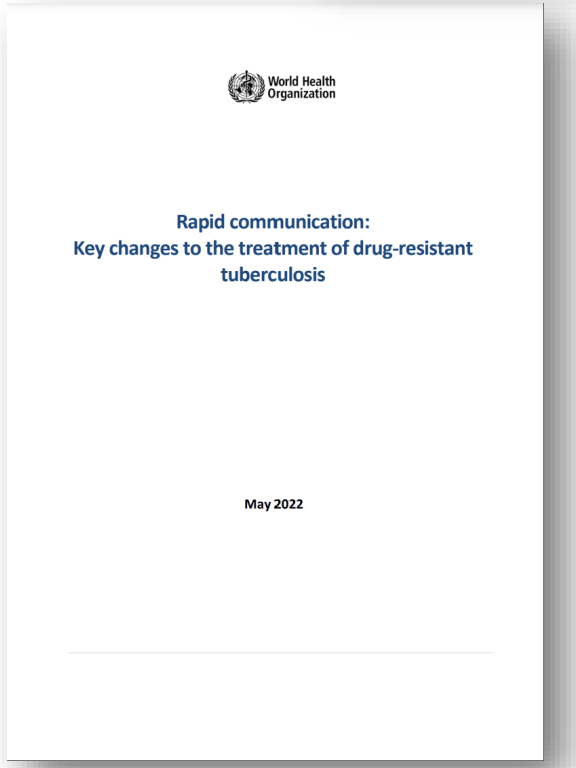
Principles for designing future regimens for multidrug-resistant tuberculosis

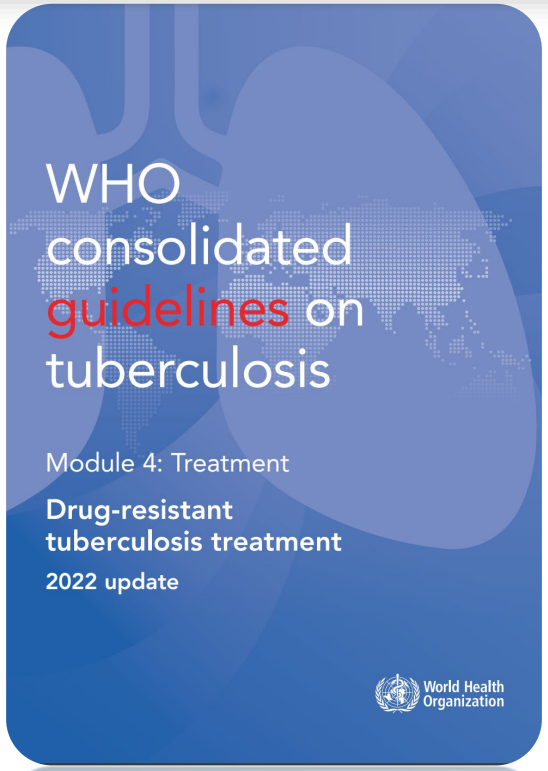
Grania Brigden,[a] Bern-Thomas Nyang'wa,[b] Philipp du Cros,[b] Francis Varaine,[c] Jennifer Hughes,[d] Michael Rich,[e] C Robert Horsburgh Jr,[f] Carole D Mitnick,[g] Eric Nuermberger,[h] Helen McIlleron,[i] Patrick PJ Phillips[j] & Manica Balasegaram[a]

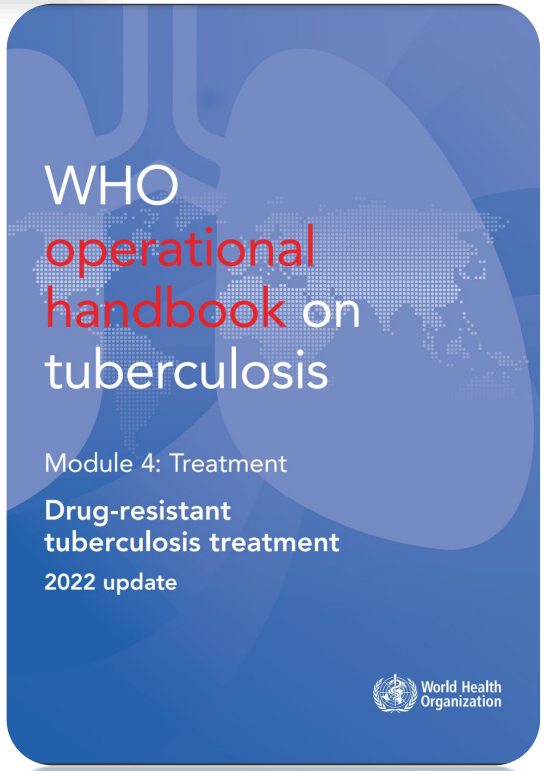
ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch., et al., for the TB-PRACTECAL Study Collaborators*







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A randomised, controlled, open-label, two stage, 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

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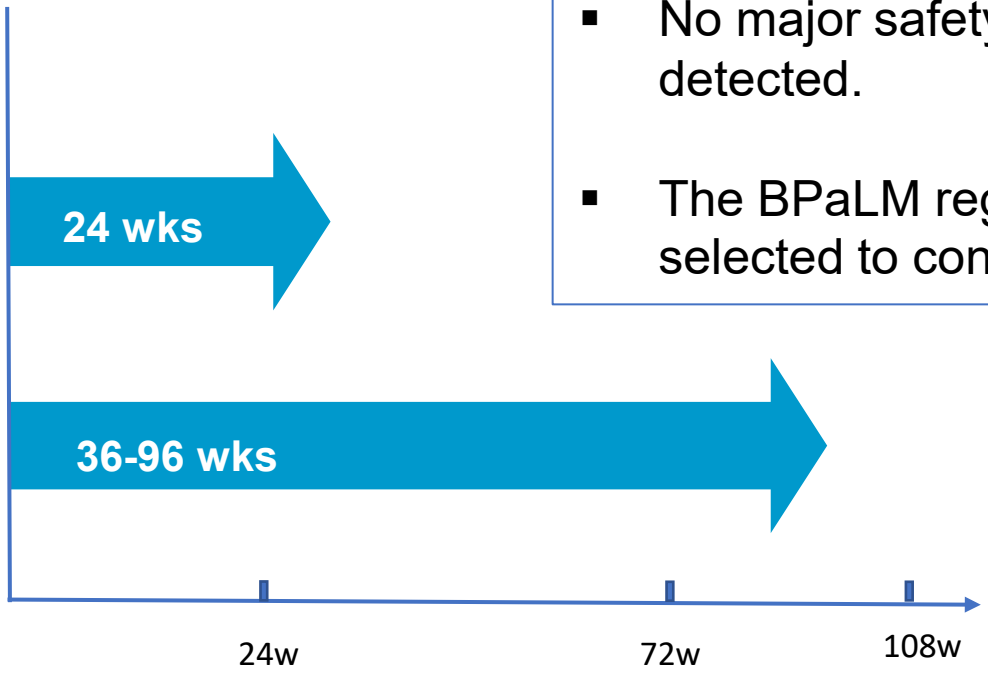
TRIAL DESIGN

BPaLM	**B-Pa-Lzd 600>300-Mfx**
BPaLC	B-Pa-Lzd 600>300-Cfz
BPaL	B-Pa-Lzd 600>300
SoC	**WHO Standard of Care**



- All 3 investigational arms met criteria for stage 2 eligibility.
- No major safety signals were detected.
- The BPaLM regimen was selected to continue to stage 2.

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CONSORT

	SoC	BPaLM	BPaLC	BPaL	Total
Total screened	680				
Total randomised	152	151	126	123	552
ITT population	151	151	126	122	550
mITT population	143	138	115	111	507
PP population	83	125	104	100	412

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BASELINE CHARACTERISTICS, MITT

	SOC	BPaLM	BPaLC	BPaL
n	143	138	115	111
Belarus, n (%)	29 (20.3)	26 (18.8)	19 (16.5)	20 (18.0)
South Africa, n (%)	49 (34.3)	49 (35.5)	43 (37.4)	41 (36.9)
Uzbekistan, n (%)	65 (45.5)	63 (45.7)	53 (46.1)	50 (45.1)
Age (years), median (range)	37 (18 to 71)	35 (17 to 71)	32 (19 to 67)	34 (15 to 72)
Female, n (%)	54 (37.8)	61 (44.2)	39 (33.9)	54 (48.7)
BMI (kg/m^2), median (IQR)	19.8 (17.5 to 22.8)	19.7 (17.7 to 22.7)	19.4 (17.6 to 22.1)	20.0 (18.1 to 22.5)
PLHIV, n (%)	39 (27.3)	34 (24.6)	31 (27.0)	36 (32.4)
CD4 count (cells/µL), median (IQR)	250 (143 to 445)	330 (223 to 547)	297 (115 to 511)	383 (161 to 550)
Smear positive, n (%)	94 (65.7)	86 (62.3)	79 (68.7)	73 (65.8)
Cavity present, n (%)	90 (62.9)	76 (55.1)	74 (64.4)	68 (61.3)
Fluoroquinolone resistant, n (%)	32 (25.2)	32 (25.8)	22 (20.2)	25 (25.5)
QTcF (ms), mean (SD)	400 (19)	399 (19)	395 (18)	399 (19)
ALT (IU/l), median (IQR)	20 (15 to 28)	19 (14 to 28)	17 (14 to 26)	19 (14 to 29)

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PRIMARY OUTCOME, MITT

	SOC	BPaLM	BPaLC	BPaL
Number in mITT population	137	138	115	111
Number with no unfavourable outcome (%)	81 (59.1%)	121 (88.3%)	88 (76.5%)	96 (86.5%)
Number with an unfavourable outcome (%)	56 (40.9%)	16 (11.7%)	27 (23.5%)	15 (13.5%)
Number non-assessable	0	1	0	0
Unadjusted risk difference (two-sided 96.6% confidence interval)		-29.2% (-39.8% to -18.6%)	-	-
Unadjusted risk difference (two-sided 95% confidence interval)		-	-17.4% (-28.7% to -6.1%)	-27.4% (-37.8% to -17.0%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001	p<0.0001	p<0.0001
Superiority p-value		p<0.0001	p=0.003	p<0.0001

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REASONS FOR UNFAVOURABLE OUTCOME, MITT

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	SOC	BPaLM	BPaLC	BPaL
Number with an unfavourable outcome	56 (40.9%)	16 (11.7%)	27 (23.5%)	15 (13.5%)
Deaths	5 (3.5%)	0 (0%)	1 (0.9%)	1 (0.9%)
Early discontinuations	52 (36.4%)	11 (8.0%)	11 (9.6%)	11 (9.9%)
Adherence issues	13	1	4	3
Adverse event	23	7	6	5
Not meeting inclusion/exclusion criteria (detected after 1st dose)	2	1	1	2
Withdrew consent whilst still on treatment	11	1	0	1
Other	3	1	0	0
Treatment failure	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Lost to follow-up at 72 weeks	1 (0.7%)	4 (2.9%)	9 (7.8%)	0 (0%)
Recurrence	0 (0%)	1 (0.7%)	5 (4.4%)	3 (2.7%)

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TREATMENT FAILURE & RECURRENCE (WEEK 108)

- Treatment failure (n=1, arm 2)
- Recurrence (n=11), 9* on mycobacterial grounds
  - 9 presented within 72 weeks
  - No baseline resistance was detected to components in the allocated regimen
- Drug sensitive recurrence (non-assessable) n=1

	SoC	**BPaLM**	BPaLC	BPaL
mITT	137	138	115	111
Number (%)	1 (0.7%)	1 (0.7%)	5 (4.3%)	4 (3.6%)
Culture proven	0	1	4*	4
New resistance to ≥ 1 drug	0	0	0	3

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*includes 1 participant where culture-proven recurrence was only established via MoH sample

SUBGROUP ANALYSES, MITT POPULATION, WEEK 72

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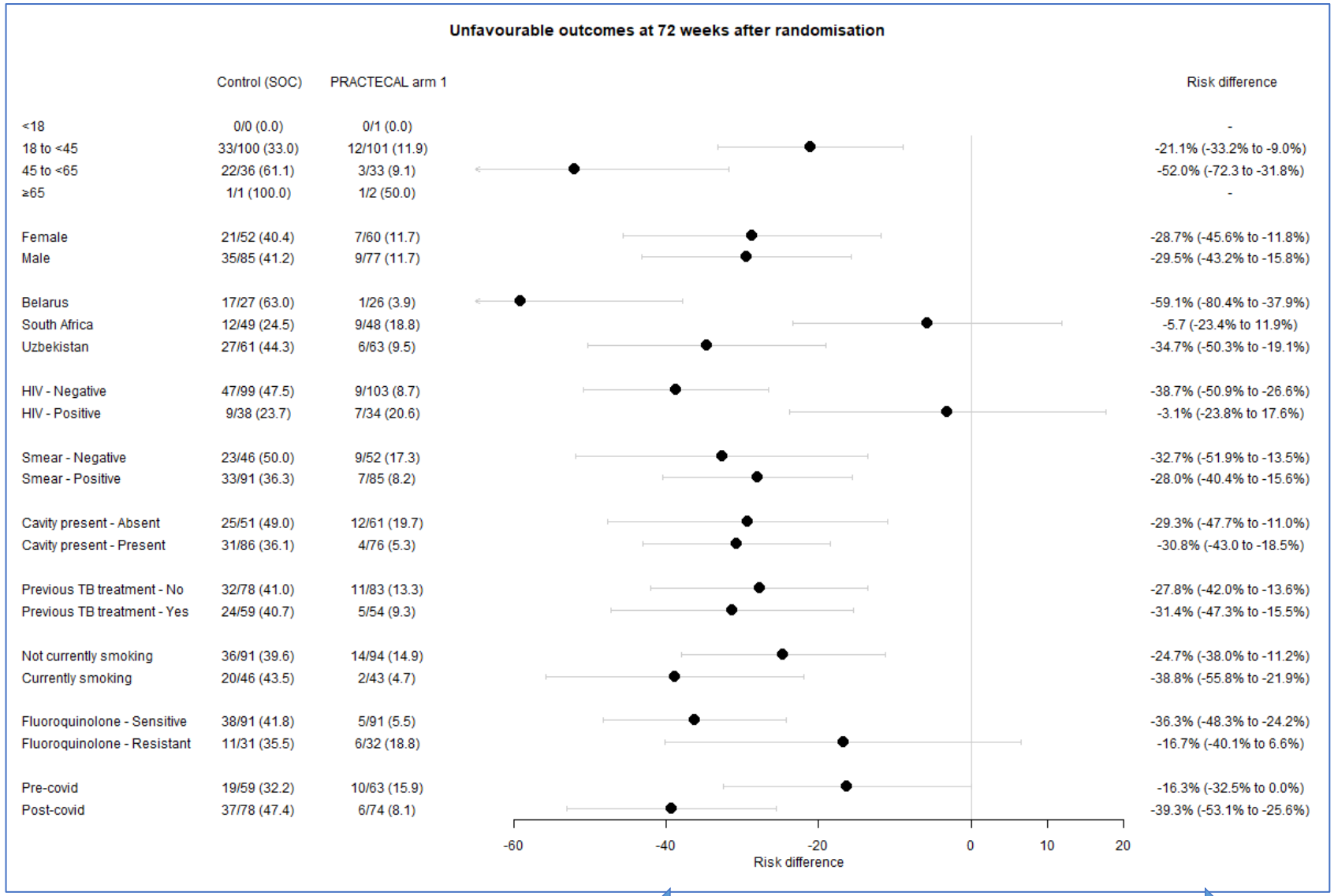

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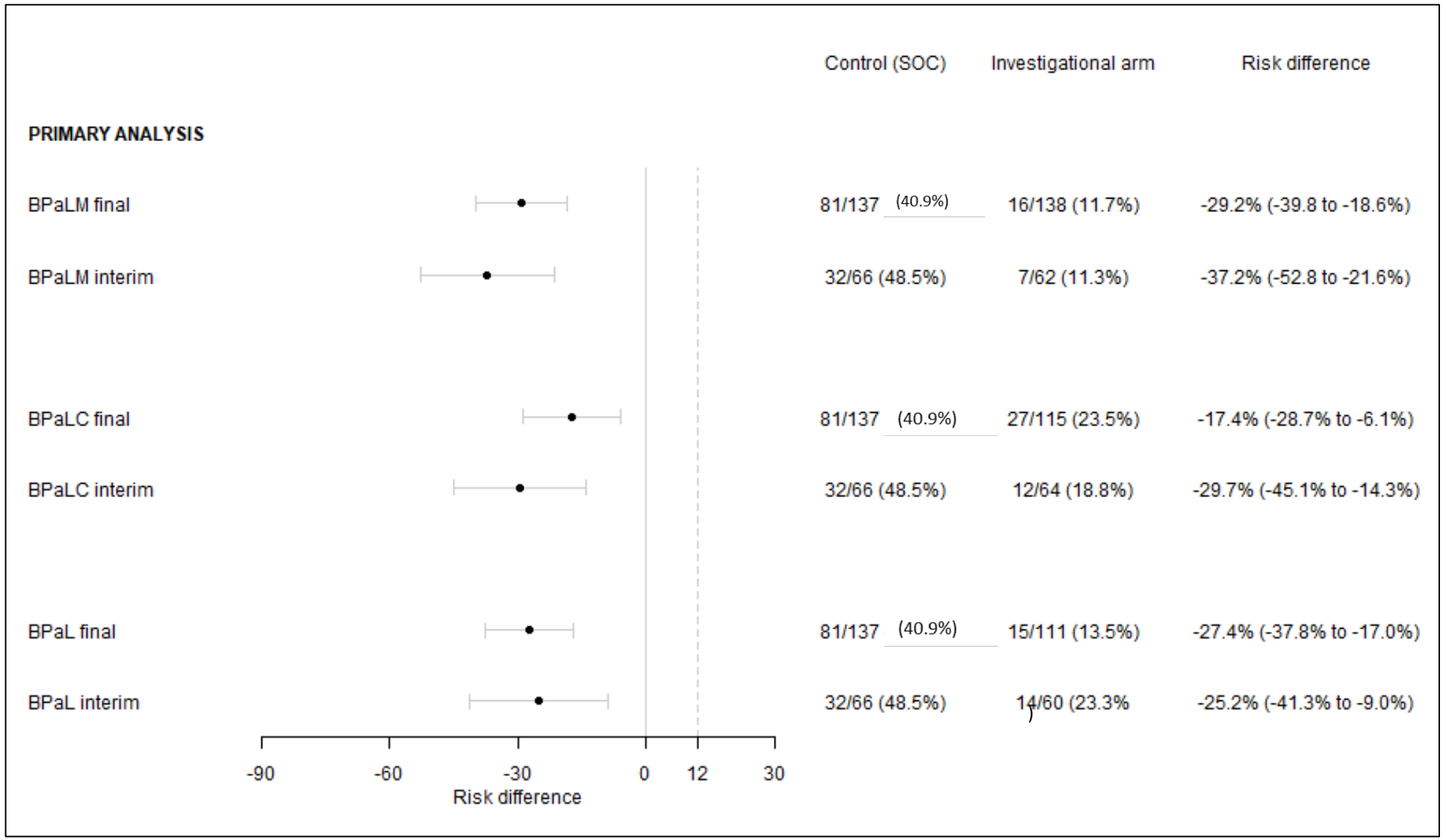
NEJM VS FINAL PRIMARY OUTCOME RESULTS



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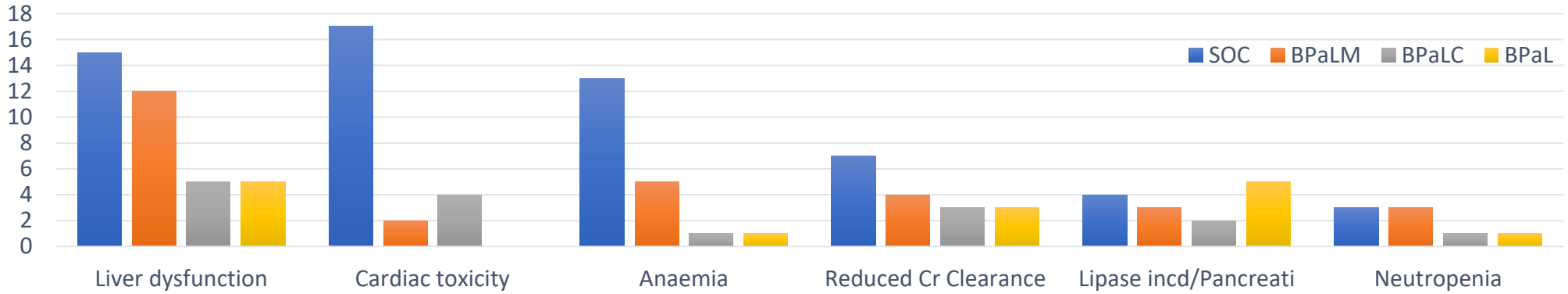
SERIOUS (SAE) AND SEVERE (grade ≥3) AE (72 WEEKS)

	SOC	BPaLM	BPaLC	BPaL
All grade ≥3 AEs or SAEs n (%)	72 (48%)	34 (23%)	38 (30%)	29 (24%)
Risk difference*	-	-25%	-18%	-25%
		(-36.1 to -14.1)	(-29.2 to -7.1)	(-35.5 to -13.8)



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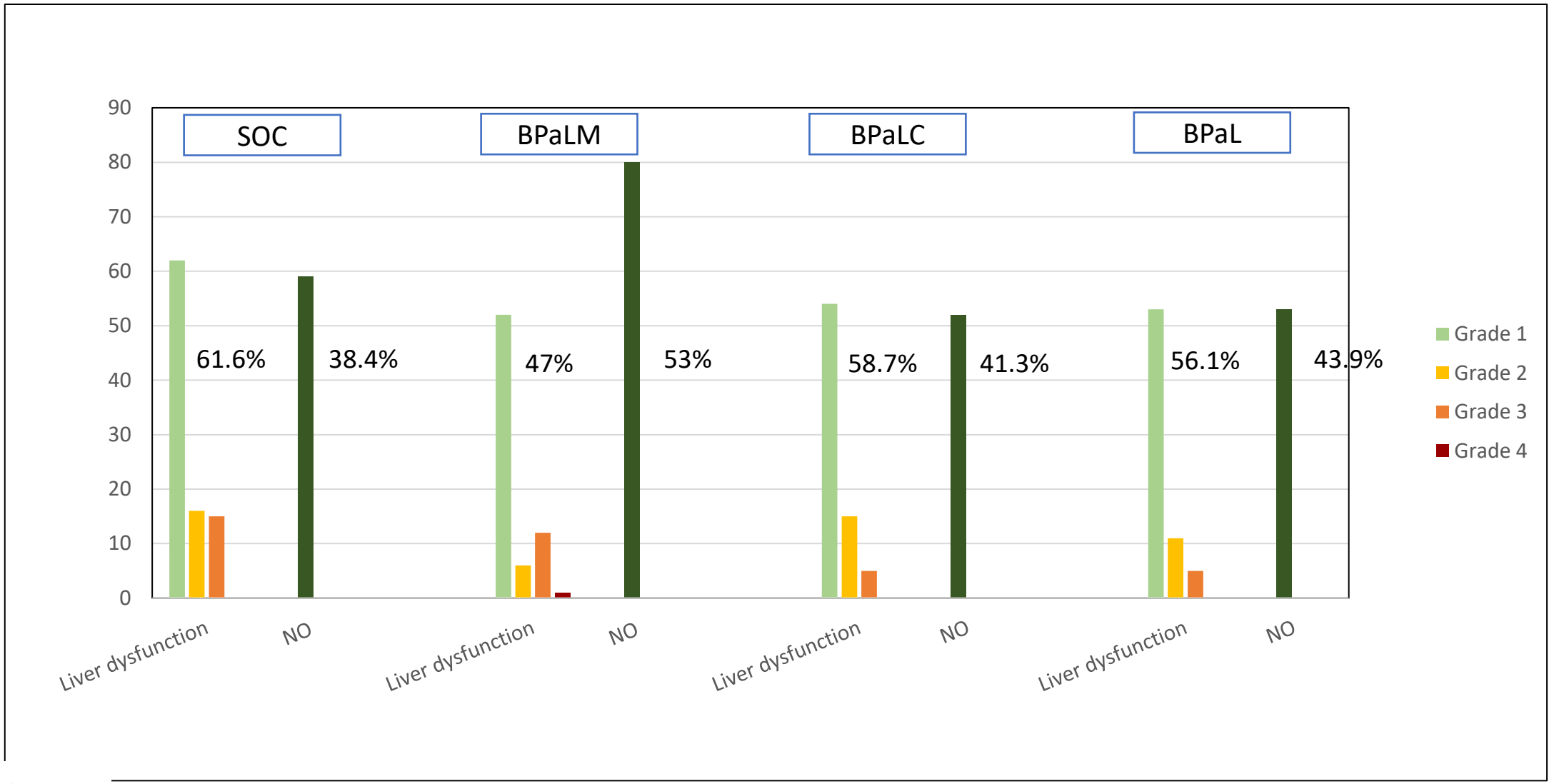
** adjusted for site*

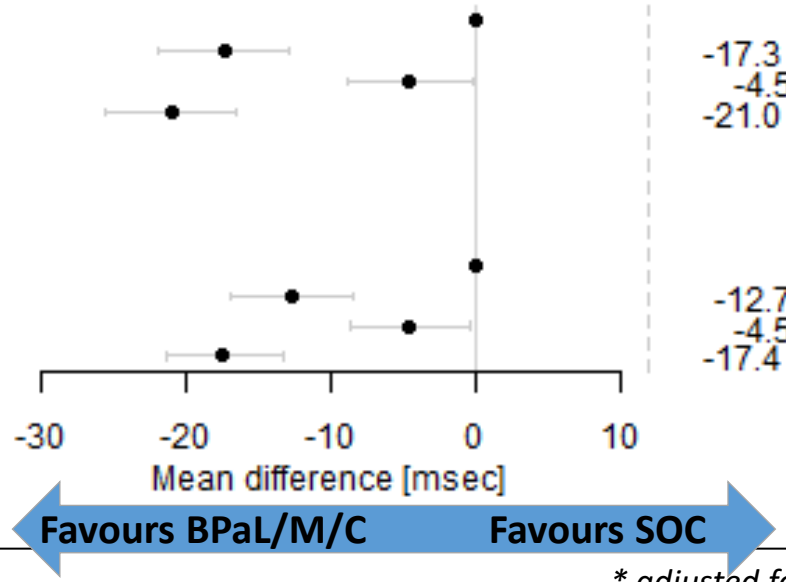
LIVER DYSFUNCTION*



* *Using agreed SMQ (pooling of PTs)*

QTCF PROLONGATION (WEEK 24)

	N	N (24 weeks)	Mean (SD) [msec]	Mean difference [msec]
QTcF at 24 weeks *				
SOC	151	97	440.9 (18.9)	
BPaLM	151	128	425.1 (20.6)	-17.3 (-21.9 to -12.8)
BPaLC	126	102	436.2 (18.2)	-4.5 (-8.8 to -0.1)
BPaL	122	101	421.9 (18.4)	-21.0 (-25.5 to -16.5)
Max QTcF over 24 weeks *				
SOC	151	151	453.8 (22.6)	
BPaLM	151	150	439.5 (20.8)	-12.7 (-16.8 to -8.5)
BPaLC	126	126	446.4 (19.0)	-4.5 (-8.7 to -0.3)
BPaL	122	121	435.5 (20.9)	-17.4 (-21.4 to -13.3)



** adjusted for site and baseline QTcF*

PERIPHERAL NEUROPATHY*

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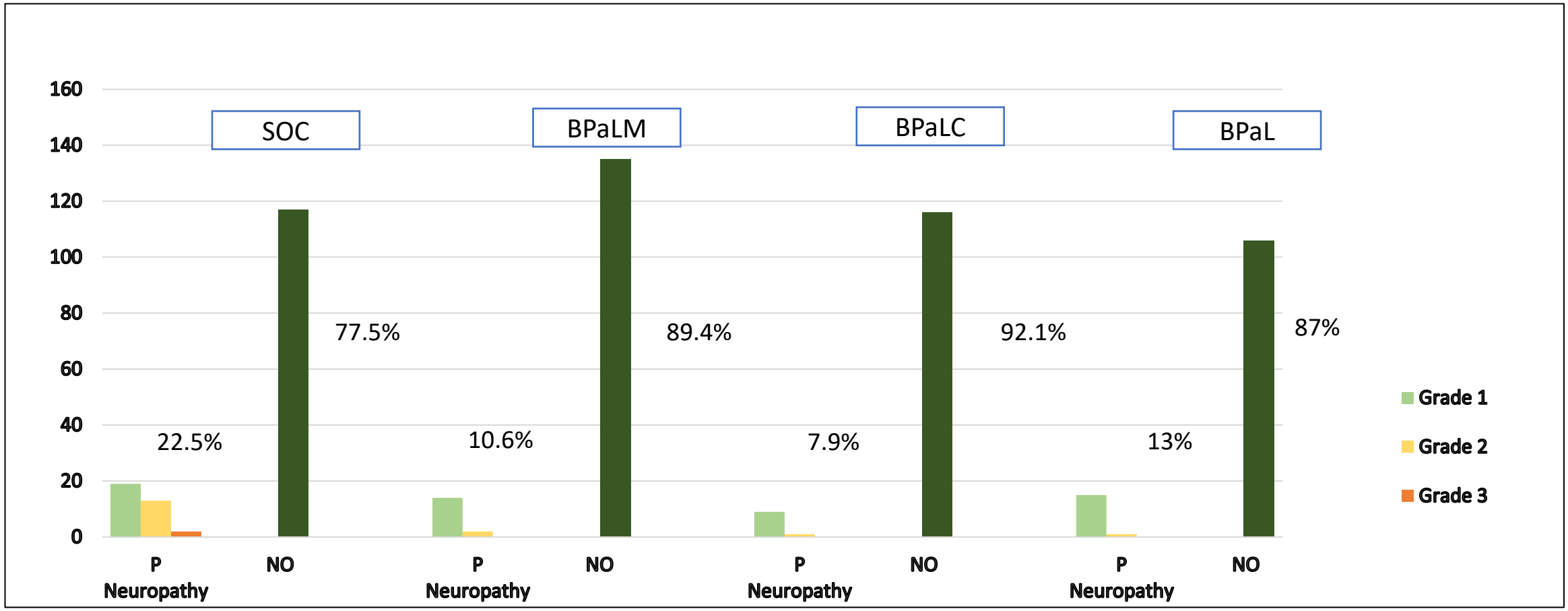

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** Using agreed SMQ (pooling of PTs)*

MYELOSUPPRESSION*

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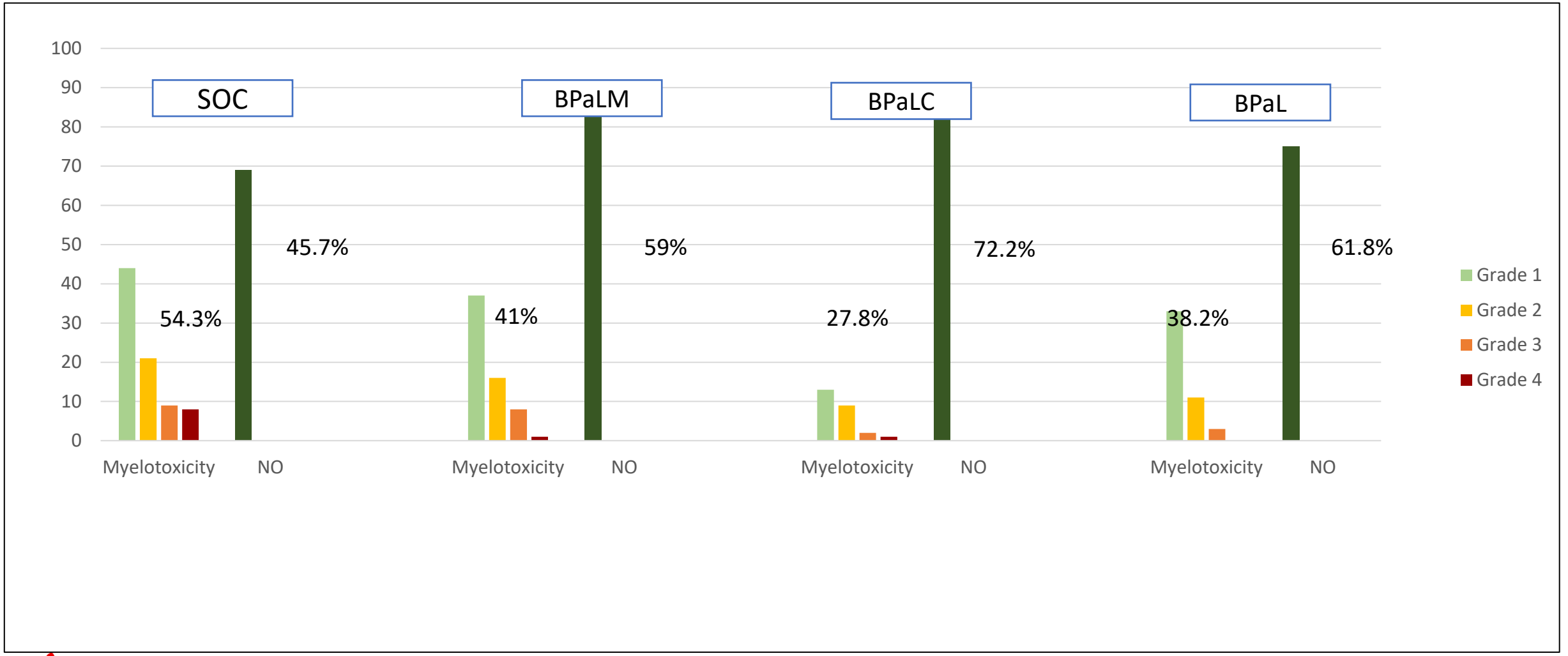

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** Using agreed SMQ (pooling of PTs)*

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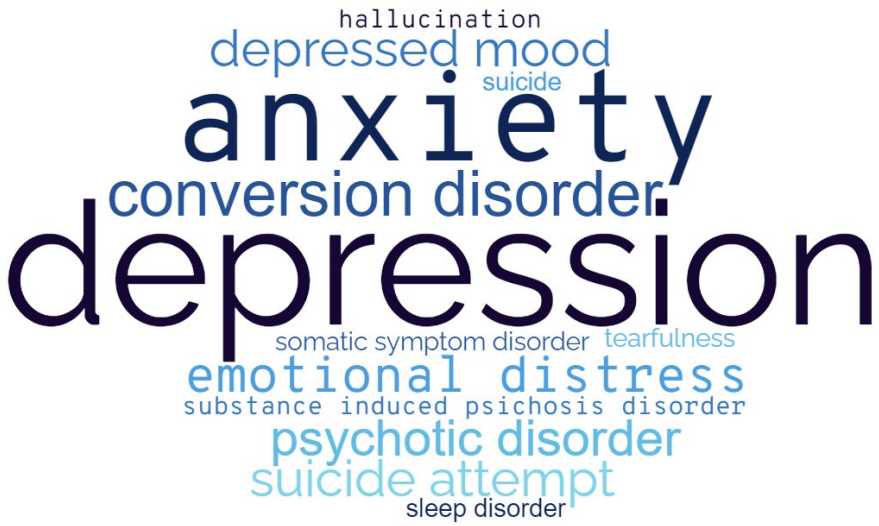
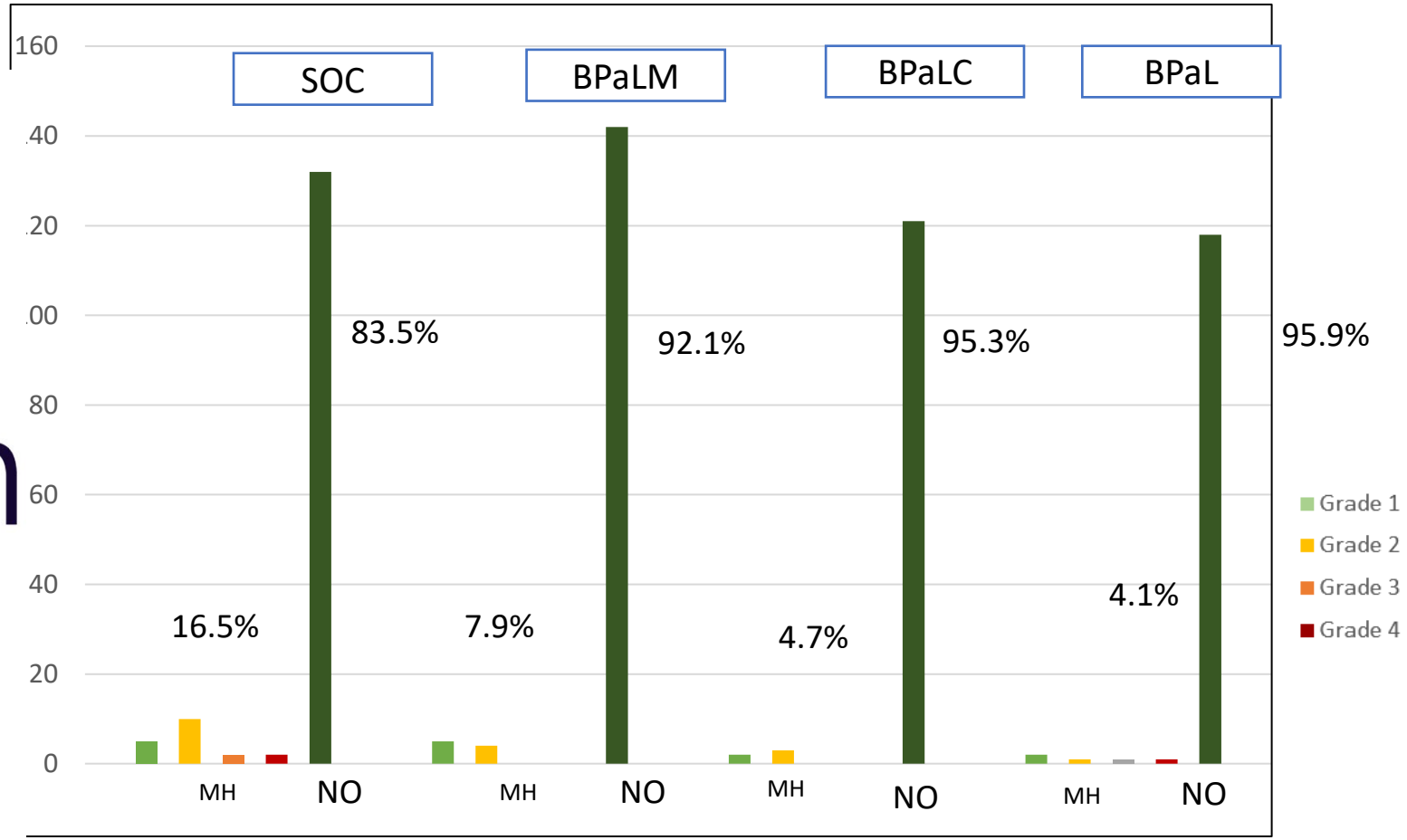
MENTAL HEALTH CONDITIONS*





* *Using agreed SMQ (pooling of PTs)*

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CONCLUSIONS

- These data confirm that BPaLM, BPaLC and BPaL regimens with a tapered linezolid dose are highly efficacious
- Adverse events were significantly lower in the investigational arms and were manageable.
- The final trial data conclusions are consistent with those communicated earlier

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COLLABORATORS

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MÉDECINS SANS FRONTIÈRES

- Médecins Sans Frontières
- Swiss Tropical & Public Health Institute
- London School of Hygiene and Tropical Medicine
- University College London
- Global Alliance for TB Drug Development
- Drugs for Neglected Diseases Initiative
- Clario, UK
- University of Sussex
- Ministry of Health, Republic of Uzbekistan
- Ministry of Health, Belarus
- Republican Specialised Scientific Practical Medical Centre of Tuberculosis and Pulmonology, Uzbekistan
- Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus
- TB & HIV Investigative Network (THINK)
- Clinical HIV Research Unit, Wits Health Consortium
- TDR, Special Programme for Research and Training in Tropical Diseases

Swiss TPH

CHRU Themba Lethu
CLINICAL HIV RESEARCH UNIT
A Division of the Wits Health Consortium (Pty) Ltd

THINK
TB & HIV INVESTIGATIVE NETWORK

DNDi
Drugs for Neglected Diseases *initiative*

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

TB Alliance

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

UCL

US UNIVERSITY OF SUSSEX

CLARIO.
THE BEST OF ERT & BIOCLINICA

EXTRA SLIDES

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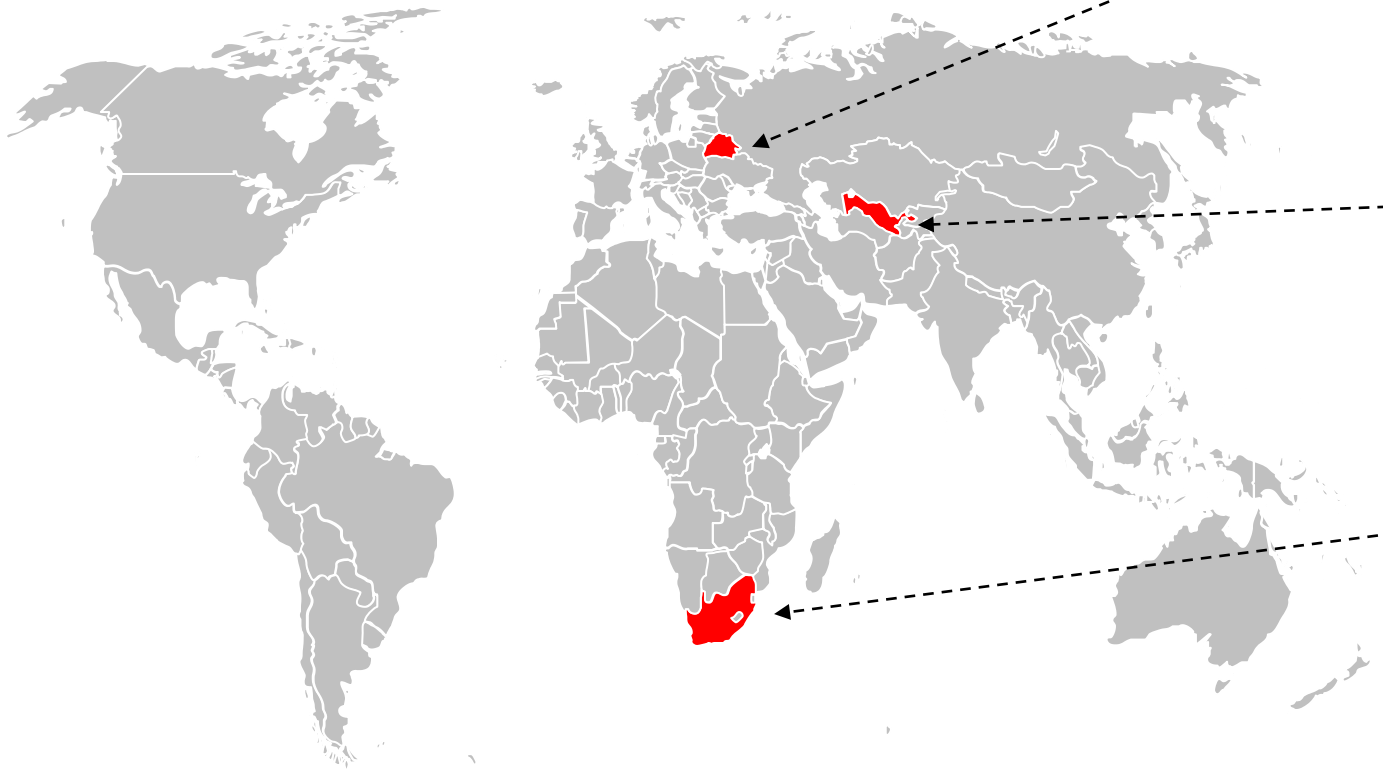

02. MINSK - Site opened: Dec 2017

01 . NUKUS - Site opened Jan 2017

04. TASHKENT - Site opened Dec 2018

03. DORIS GOODWIN - Site opened Nov 2017

03b. DON MCKENZIE - Sub-Site opened Oct 2018

05. HELEN JOSEPH - Site opened Dec 2019

06. KING DINIZULU - Site opened Nov 2019

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SENSITIVITY ANALYSIS – POST-2019 WHO GUIDELINES

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	Prior to current guideline*	Current guideline*
ITT population (n = 151)		
Long regimen	34 (72.3%)	63 (60.6%)
Containing Bdq	31	63
Containing Lzd	31	63
Short regimen	13 (27.7%)	41 (39.4%)

	SOC	BPaLM
Number in analysis	94	97
Number with no unfavourable outcome	62 (66.0%)	82 (85.4%)
Number with an unfavourable outcome	32 (34.0%)	14 (14.6%)
Number non-assessable	0	1
Unadjusted risk difference (two-sided 96.6% confidence interval)		-19.5% (-32.3% to -6.6%)

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ALL-CAUSE MORTALITY (ALL RANDOMIZATIONS)

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Study site	Cause of death	On Rx, during F/U, post discontinuation?	Treatment related?	TB-PRACTECAL Arm
UZ-01	Enterocolitis	Post disc.	No	SOC
UZ-01	Seizure	During F/U	No	BPaL
UZ-01	Completed suicide	On Rx	Yes	SOC
SA-03	Pancreatitis acute	Post disc.	Yes	SOC
BY-02	Sudden cardiac death	On Rx	Yes	SOC
UZ-04	COVID-19 pneumonia	On Rx	No	SOC
UZ-01	Pneumonia	Post disc.	No	BPaLC
SA-03	Chronic obstructive pulmonary disease	During F/U	No	BPaLC
SA-03	Stab wound	During F/U	No	SOC
BY-02	Sudden death	On Rx	Yes	SOC
SA-06	Pancreatitis acute	On Rx	No	SOC
SA-06	Lower respiratory tract infection	During F/U	No	BPaL
UZ-04	COVID-19	Post disc.	No	SOC

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BMJ Open Cost-effectiveness of new MDR-TB regimens: study protocol for the TB-PRACTECAL economic evaluation substudy

Sedona Sweeney [1], Gabriela Gomez,[2] Nichola Kitson,[1] Animesh Sinha [3], Natalia Yatskevich,[4] Suzanne Staples,[5] Ronelle Moodliar,[5] Sharon Motlhako,[6] Matshepo Maloma,[7] Mohammed Rassool,[6] Nosipho Ngubane,[7] Ella Ndlovu,[7] Bern-Thomas Nyang'wa[8]

BMJ Open Capturing patient-reported and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods substudy protocol, TB PRACTECAL-PRO

Beverley Stringer [1], Karen Lowton,[2] Nicola James [1], Bern-Thomas Nyang'wa [1,3]

BMJ Open Population pharmacokinetics and pharmacodynamics of investigational regimens' drugs in the TB-PRACTECAL clinical trial (the PRACTECAL-PKPD study): a prospective nested study protocol in a randomised controlled trial

Bern-Thomas Nyang'wa [1,2], Frank Kloprogge [3], David A.J. Moore,[2] Amaya Bustinduy,[2] Ilaria Motta,[1] Catherine Berry,[1] Geraint R Davies[4]

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