Effectiveness and Safety of varying Doses of Linezolid with Bedaquiline and Pretomanid in Adults with Pre-Extensively Drug-Resistant Pulmonary Tuberculosis: Preliminary report

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Background

- Drug-resistant tuberculosis (DR-TB) - global public health problem.

- Availability of shorter regimens for the management of highly drug-resistant tuberculosis is expected to improve treatment outcome.

- Combination of Bedaquiline (Bdq)-Pretomanid (Pa)-Linezolid (Lzd) – (BPaL) regimen showed a favourable outcome of 90% at the end of 6 months of treatment (Conradie *et al*., 2020).

- However, appropriate dose and duration of Lzd, especially with co-morbidity like malnutrition and diabetes, is not clear.

Primary Objective

To determining the effectiveness of various doses and duration of LZD in combination with BDQ and Pa in adults with either Pre-XDR or $MDR_{NR/TI}$ pulmonary TB.

Methods

A multicentric, clinical trial in India enrolled adults with pre-extensively drug-resistant (Pre-XDR) and non-responsive multidrug-resistant (MDRNR) pulmonary TB.

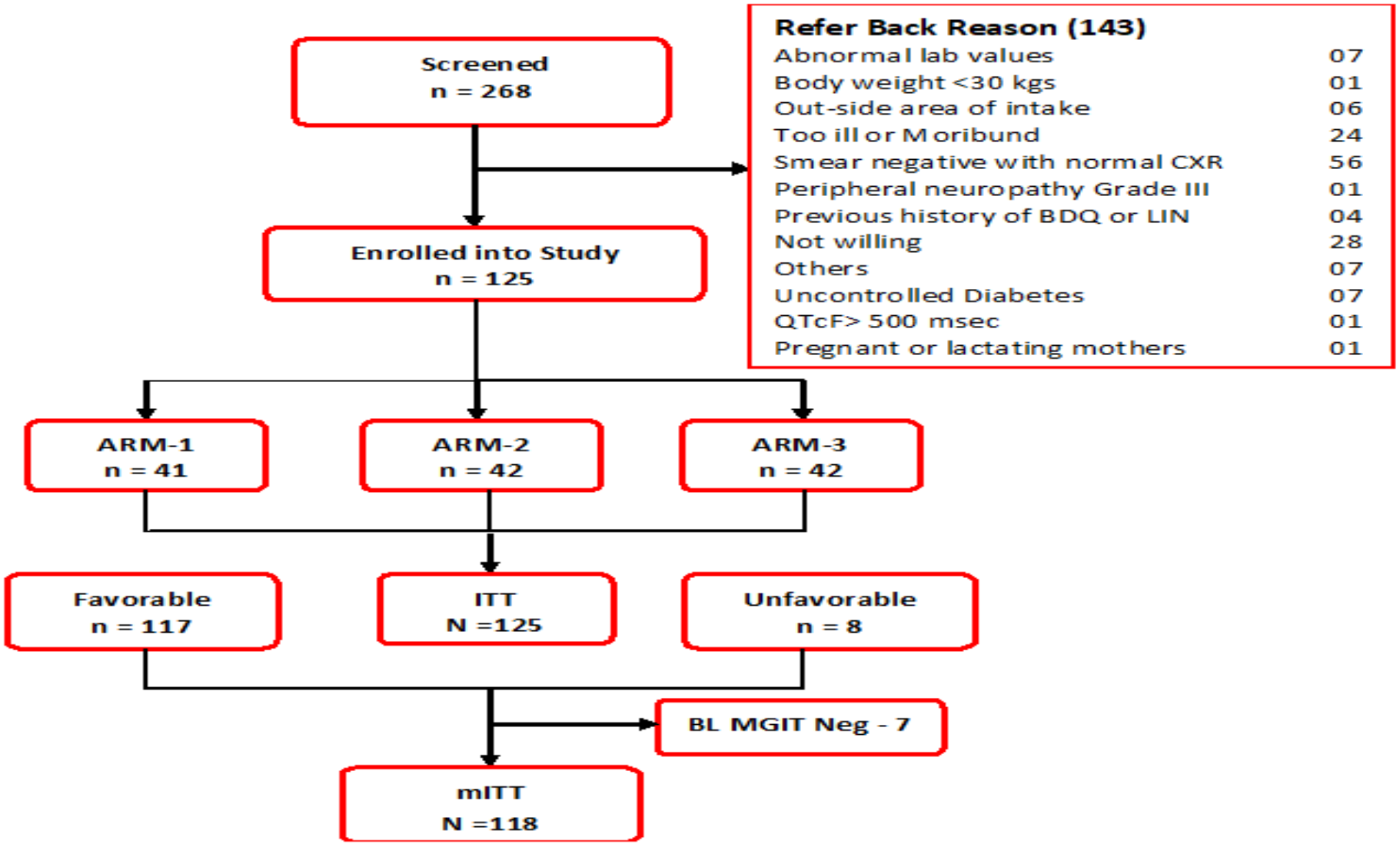
Pateints were randomly assigned to three arms:

- Arm 1- BDQ+Pa + LZD (600 mg) for **26 weeks.**
- Arm 2- BDQ+Pa + LZD (600 mg) for **9 weeks then** BDQ+Pa+ LZD (300 mg) for **17 weeks.**
- Arm 3- BDQ+Pa + LZD (600 mg) for **13 weeks then** BDQ+Pa+ LZD (300 mg) for **13 weeks.**

Primary outcome

The proportion of patients with favorable outcomes at 26-weeks defined as sustained cure and treatment completion. Safety of the regimens was also evaluated.

Checklist of participants



Baseline characteristics (N=125)

Characteristics	Arm1 (N=41)	Arm2 (N=42)	Arm3 (N=42)
Gender			
Male (55)	17	17	21
Female (70)	24	25	21
Mean Age (SD)	33 (12)	31 (12)	31 (11)
Mean Weight (SD)	46.0 (9)	46.9 (11)	47.7 (10)
Chest X- Ray			
Normal	1	0	1
Abnormal	40	42	41
Extent of lung involvement			
Unilateral (54)	17	18	19
Bilateral (69)	23	24	22
Chest x-ray zones involved			
≤ 3 Zones (87)	27	31	29
> 3 Zones (36)	13	11	12
Cavity			
Yes (45)	14	14	17
No (78)	26	28	24

Baseline characteristics (Continued..)

Type of PTB patients			
Pre-XDR	40	42	40
MDR-Intolerance (3)	1	0	2
Sputum smear at Baseline			
Negative	5	8	9
Positive Scanty	0	3	1
1+	16	13	7
2+	9	11	14
3+	11	7	11
MGIT culture at Baseline			
Positive	40	39	39
Negative	1	3	3

Adverse Events : Arm-wise with Outcome

SYSTEM	Arm1	Arm2	Arm3	Total	Resolved	Unresolved	Ongoing
LABORATORY	223*	230#	145^	**598**	550	7	39
HEPATOBILIARY	147$	145	144&	**436**	405	7	24
Respiratory	35	32	45	**112**	103	2	7
GIT	27	35	29	**91**	88		2
OTHERS	31	21	36	**88**	84	3	1
PNS	25	17@	22!	**64**	60	2	2
SKIN	13	20	13	**46**	45		1
MUSCULOSKELETAL	16	11	16	**43**	37		6
CVS	12	11	11	**34**	33		1
CNS	9	8	16	**33**	31		2
ENT	10	15	8	**33**	32		1
GENITOURINARY	5	4	4	**13**	13		
OPTHTHAL	5	5	3	**13**	13		
TOTAL	**558**	**554**	**492**	**1604**	**1494**	**21**	**86**

***Grade IV(1), Grade III(8)**
#Grade IV(1), Grade III(5)
&Grade IV(2)
@Grade III(1)
!Grade III(1)
^Grade III(7)
$Grade IV(1), Grade III(1)

Result

- In preliminary report of 125 patients, 56% were females with mean age of 31years. Seven were culture negative at baseline and not included in further analysis.

- Of the 118 patients, 112 (95%) culture converted -26 weeks
  40/40 (100%) in **arm 1**
  36/39 (92%) in **arm 2**
  36/39 (92%) in **arm 3**

➢ Two bacteriological failures - **arm 2**
➢ One clinical failure due to adverse event - **arm 3**
➢ Three deaths - arm 1-0, arm2-one (extensive lung disease, wk12) and arm 3-two (extensive lung disease, wk 3 -1, death at wk 6 due to lactic acidosis -1)

- Adverse events noticed - **514**
  20, 12 and 12 - episodes of myelosuppression
  15, 7 and 8 - episodes of peripheral neuropathy (in **arm 1**, **arm 2** & **arm 3** respectively)

Conclusion

- Favorable outcome of >90% was seen with all the three Bdq-Ptm-Lzd arms.
- Lower incidence of Lzd-associated toxicity was reported in groups that had structured reduction to 300mg after 9-13 weeks.
- Follow-up will determine the sustained cure and recurrence in the structured reduction arms.
- Overall risk–benefit ratio should be evaluated before finalizing the Lzd dose in BPaL regimen in patients with co-morbidities like malnutrition.

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Thank you