Sustained high rate of successful treatment outcomes:

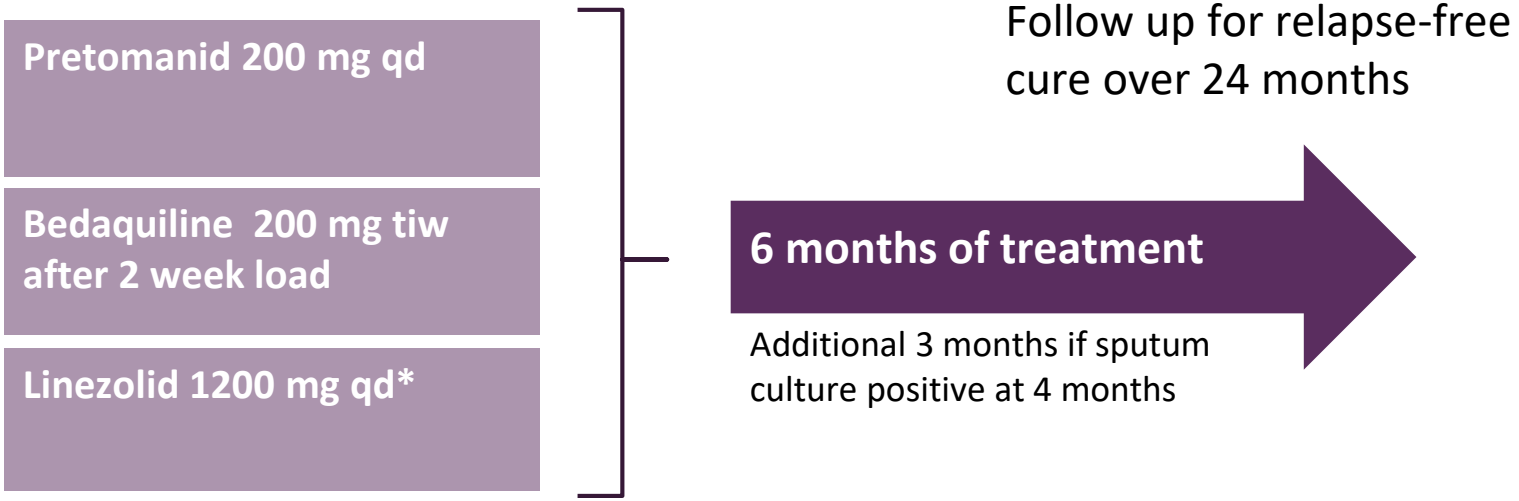
Interim results of 75 patients in the Nix-TB clinical study of pretomanid, bedaquiline and linezolid

Francesca Conradie, Andreas Diacon, Pauline Howell, Daniel Everitt, Angela Crook, Carl Mendel, Erica Egizi, Joanna Moreira, Juliano Timm, Timothy McHugh, Genevieve Wills, Christo Van Niekerk, Mengchun Li, Morounfolu Olugbosi, Melvin Spigelman

25 October 2018, The Hague, Netherlands

Nix-TB Trial Design

Open-label trial to assess the safety and efficacy of bedaquiline, pretomanid plus linezolid in participants with pulmonary infection with either extensively drug-resistant TB (XDR-TB) or treatment intolerant/non responsive multidrug-resistant TB (MDR-TB)



*Amended from 600 mg bid strategy

Primary Endpoint

- Incidence of bacteriologic failure, relapse or clinical failure through follow up until 6 months after the end of treatment
- Favourable outcome if:
  - Their clinical TB infection resolved
  - They had a negative culture status at 6 months from end of therapy
  - They had not already been classified as having an unfavourable outcome
  - Their last positive culture result (“isolated positive culture”) was followed by at least two negative culture results

Methods

- Open-label trial to assess the safety and efficacy of bedaquiline, pretomanid plus linezolid in participants with pulmonary infection with either extensively drug-resistant TB (XDR-TB) or treatment intolerant/non responsive multidrug-resistant TB (MDR-TB)
- Conducted at three sites in South Africa:
  - Sizwe Tropical Disease Hospital (Johannesburg)
  - Brooklyn Chest Hospital (Cape Town)
  - King Dinizulu (Durban): did not contribute to the first 75
- Enrolment started in April 2015
- Enrolment ended in November 2017

Key Inclusion Criteria

- Inclusion Criteria
- Male or female, aged 14 years or above
- Participants with one of the following pulmonary TB conditions:
  - a. XDR-TB documented by culture positive results (for M.tb.) within 3 months prior to screening and confirmed by molecular or phenotypic tests
  - b. MDR-TB documented by culture positive results (for M.tb.) within 3 months prior to screening with documented non-response to treatment (Fr)
  - c. MDR-TB documented by culture positive (for M.tb.) results within 3 months prior to screening who are unable to continue second line drug regimen due to a documented intolerance (TI)

Key Exclusion Criteria

- HIV infected participants having a CD4+ count < 50 cells/µL
- Significant cardiac arrhythmia requiring medication
  - participants with the following at Screening:
    - QTcF interval on ECG >500 msec
- A peripheral neuropathy of Grade 3 or 4, according to Division of Microbiology and Infectious Diseases (DMID) grading

Results

Participant demographics n=75*

Age (Mean and Range)	35.2 (18-60)
Gender	Male: 40 Female: 35
Race	Black: 57 (76.0%) Mixed race: 17 (22.7) White: 1 (1.2%)
HIV infected	38 (50.7%)
Types of TB	XDR-TB: 51 (68.0%) MDR (Fr): 13 (17.3%) MDR (TI): 11 (14.7%).
BMI (Mean and Range)	20.6 (12.4 – 41.1)

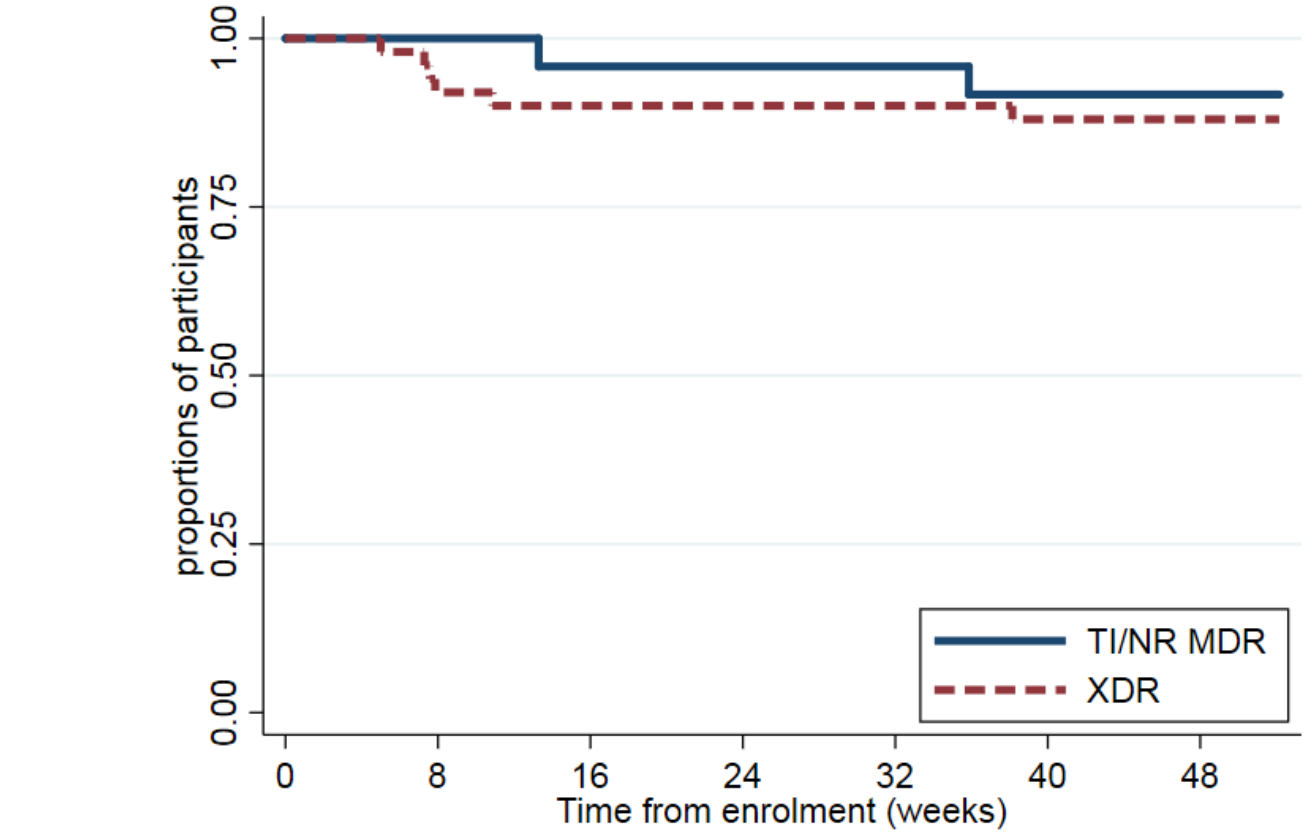
*44 patients: linezolid 600 mg bid and 31 patients : 1200 mg qd

mITT (Primary Analysis)

	Total	XDR	MDR
Total for interim analysis	75	51	24
Unassessable*	1	1	0
Total Assessable	74	50	24
Favourable	66 (89%)	44 (88%)	22 (92%)
Unfavourable**	8 (11%)	6 (12%)	2 (8%)
95% CI for Favourable	(79.8%, 95.2%)	(75.7%, 95.5%)	(73.0%, 99.0%)

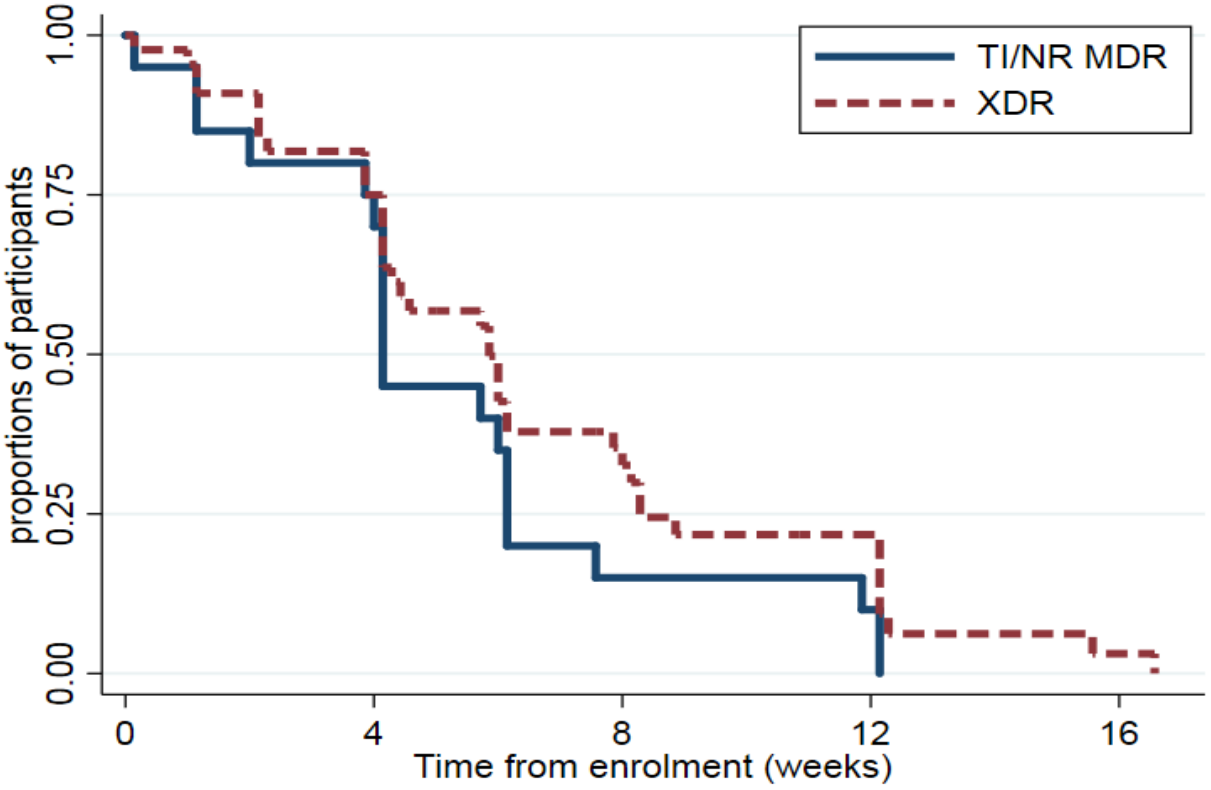
*non TB related death in follow-up
**6 deaths and two relapse

Time to Unfavourable Outcome (mITT)



Number at risk							
TI/NR MDR	24	24	23	23	23	22	22
XDR	50	46	45	45	45	44	44

Median Time to Culture Negative Status, in Weeks, for those Positive at Baseline (mITT)



Number at risk					
TI/NR MDR	20	15	3	2	0
XDR	44	33	13	7	1

Post Hoc - Primary Efficacy by HIV Status (mITT)

	Total	HIV negative	HIV positive
Total for interim analysis	75	37	38
Unassessable	1	0	1
Total Assessable	74	37	37
Favourable	66 (89%)	33 (89%)	33 (89%)
Unfavourable	8 (11%)	4 (11%)	4 (11%)
95% CI for Favourable	(79.8%, 95.2%)	(74.6%, 97.0%)	(74.6%, 97.0%)

Post Hoc - Primary Efficacy by Linezolid Dosing (MITT)

	Total	600mg bd	1200mg qd
Total for interim analysis	75	44	31
Unassessable	1	0	1
Total Assessable	74	44	30
Favourable	66 (89%)	39 (89%)	27 (90%)
Unfavourable	8 (11%)	5 (11%)	3 (10%)
95% CI for Favourable	(79.8%, 95.2%)	(75.4%, 96.2%)	(73.5%, 97.9%)

Microbiology – relapse data

- All participants met inclusion criteria with documented resistance to drugs to categorize them as having infection with either XDR or MDR-TB

	MIC
bedaquiline	≤ 1 ug/mL
pretomanid	≤ 1 ug/mL
linezolid	≤ 0.5 ug/mL

- Two relapse patients:
  - First had baseline and relapse isolates
    - An increase in the MIC to bedaquiline to 4 ug/mL
    - Whole genome sequencing (WGS) of baseline and the late isolates noted a mutation in the Rv0678 gene that has been reported to confer some degree of resistance to bedaquiline from wild type to 138_139 insG
    - WGS noted only 5 SNP differences between the 2 isolates, and the patient was considered to have a relapse of his baseline TB infection
  - Second patient did not have baseline isolate

Safety (1)

- All participants had at least one TEAE
- 16 (23%) had Serious Adverse Events
- Six patients died during treatment
  - Severe pulmonary and disseminated TB and emaciation
  - Upper gastrointestinal bleeding with ulcerated esophagitis with invasive candida
  - Respiratory failure due to severe pulmonary TB
  - Acute multi-organ failure with haemorrhagic pancreatitis and hypoglycaemia with multi-organ TB in lungs, mesentery and GI tract
  - Worsening pneumonia
  - Septic shock secondary to pneumonia
  - (An additional patient died from sepsis and gangrene after relapse of his TB)

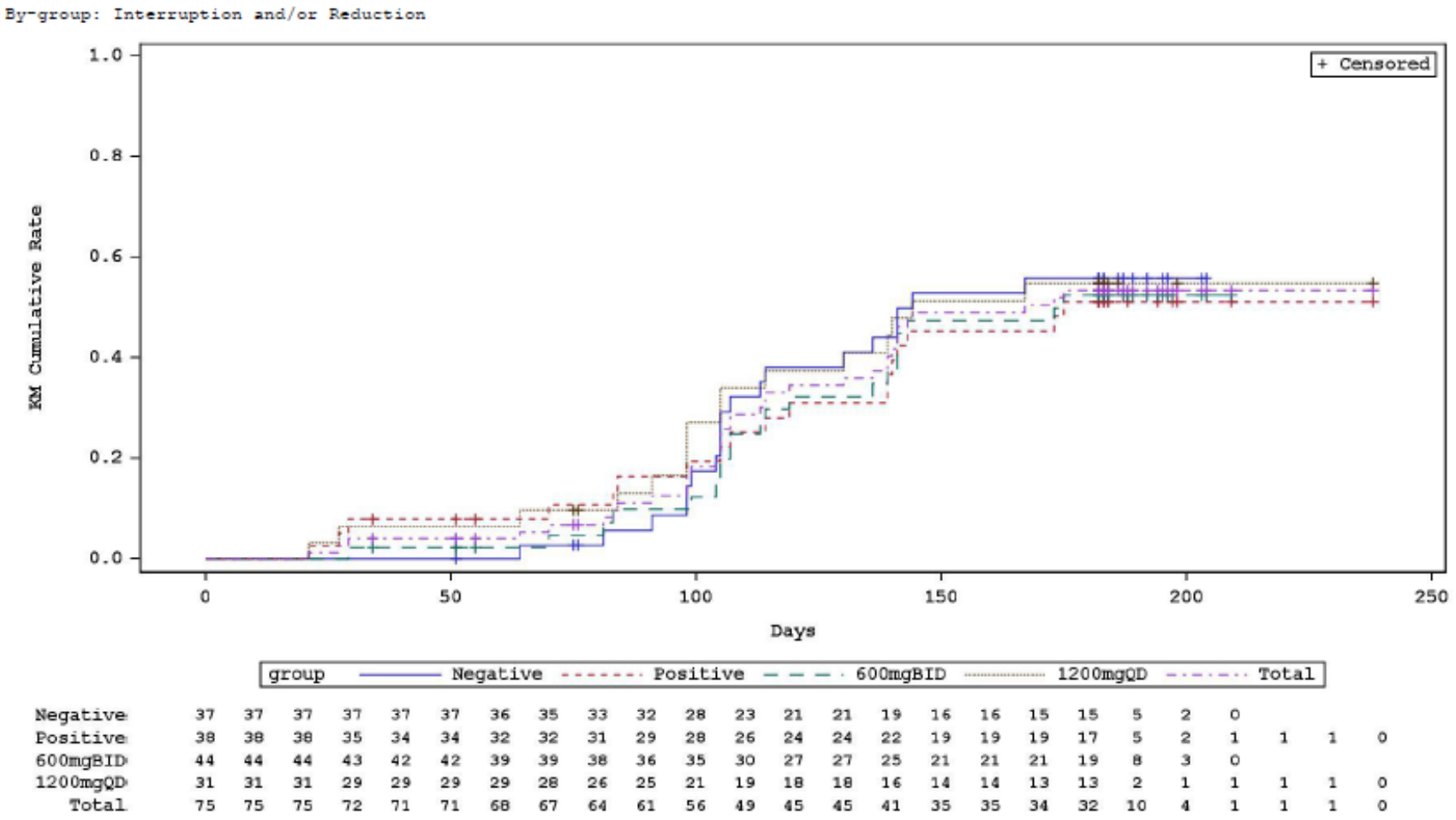
Safety (2)

- 22 (29%) permanently discontinued the use of linezolid during their treatment
- 1 liver-related TEAE - increased liver functions settled, treatment was restarted and there was no recurrence of liver related AE

TEAE of Special Interest (1) Neuropathy

- Fifty eight (68%) patients had peripheral neuropathy reported on treatment
- Majority of these occurring after the initial 3 months of treatment
- No difference between
  - HIV+/-
  - linezolid 600 mg bid vs 1200 qd
- Two patients developed optic neuritis, both resolved following permanent discontinuation of linezolid

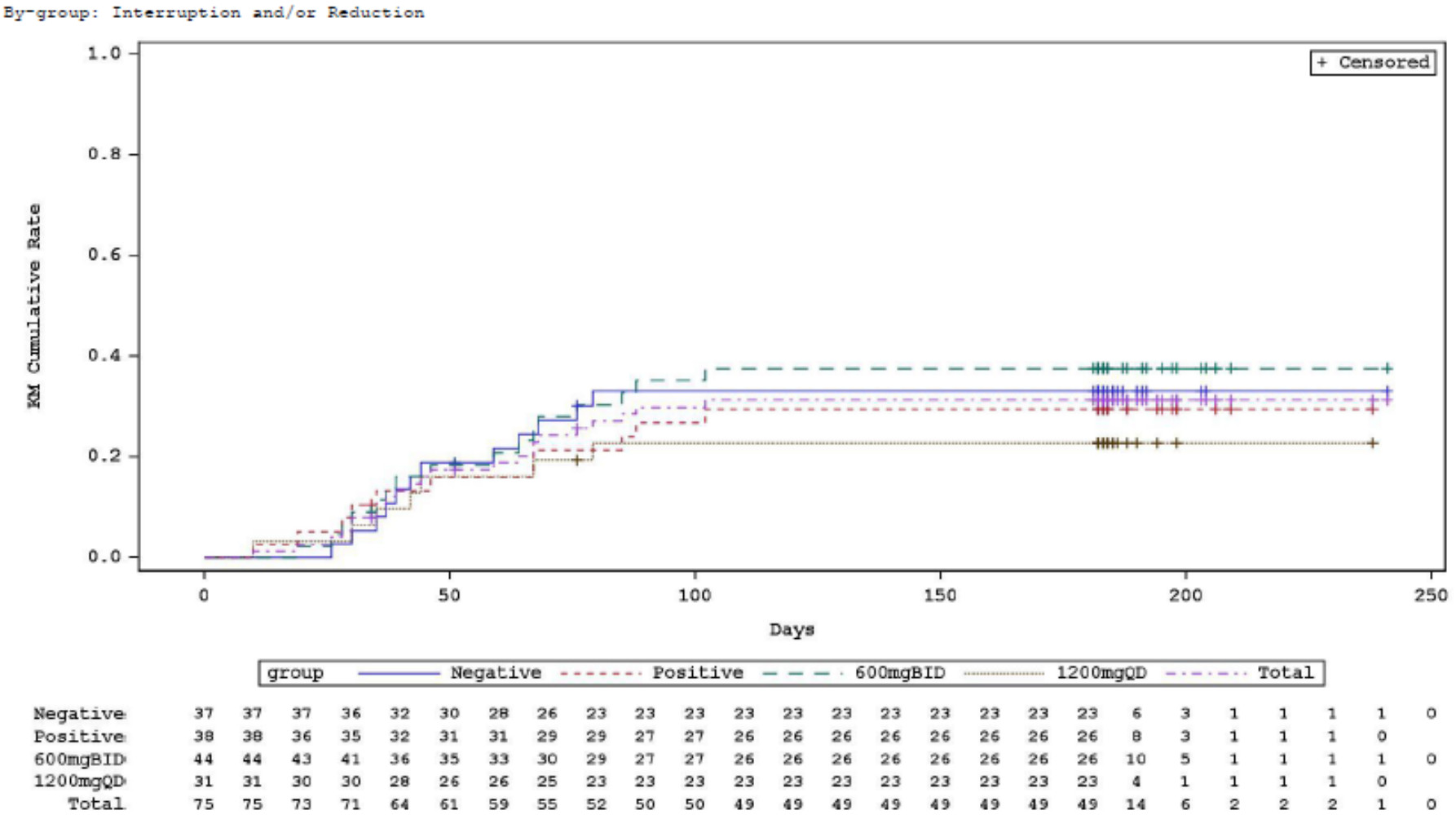
Time for First Drug Interruption or Reduction of Linezolid for Neuropathy



TEAE of Special Interest (2) Myelosuppression

- 5 participants had TEAEs of anaemia of a grade 3 or 4
- 6 had neutropenia of a grade 3 or 4
- No participants had thrombocytopenia of a grade 3 or 4
- The majority of these were in the first 2 months of treatment
- No difference between HIV+/-
- More anaemia in linezolid 600 mg bid

Time for First Drug Interruption or Reduction of Linezolid for Myelosuppression



Negative	37	37	37	36	32	30	28	26	23	23	23	23	23	23	23	23	23	23	23	6	3	1	1	1	1	0
Positive	38	38	36	35	32	31	31	29	29	27	27	26	26	26	26	26	26	26	26	8	3	1	1	1	0	
600mgBID	44	44	43	41	36	35	33	30	29	27	27	26	26	26	26	26	26	26	26	10	5	1	1	1	1	0
1200mgQD	31	31	30	30	28	26	26	25	23	23	23	23	23	23	23	23	23	23	23	4	1	1	1	1	0	
Total	75	75	73	71	64	61	59	55	52	50	50	49	49	49	49	49	49	49	49	14	6	2	2	2	1	0

Conclusion

- Interim results of this simplified, shortened all oral regimen for drug-resistant TB continue to be encouraging in terms of both efficacy and safety
  - All patients (other than the 6 who died) completed 26 weeks of treatment
  - No patients were withdrawn due to AE
  - No extensions of treatment for late conversion were needed
  - TEAEs were common but predictable and mostly handled at local facilities
  - Only one liver related SAE that completed drug therapy
- 89% of participant had a favourable outcome
- Previously reported rate of success has been surpassed by the first 75 patients who completed 6 months post treatment follow-up

Thank You

TB ALLIANCE

WITS HEALTH CONSORTIUM

TASK APPLIED SCIENCE

Additional Slides

ITT Analysis

	Total	XDR	MDR
Total for interim analysis	75	51	24
Unassessable	0	0	0
Total Assessable	75	51	24
Favourable	66 (88%)	44 (86%)	22 (92%)
Unfavourable	9 (12%)	7 (14%)	2 (8%)
95% CI for Favourable	(78.4%, 94.4%)	(73.7%, 94.3%)	(73.0%, 99.0%)

			HIV Negative (N=37)		HIV Positive (N=38)		600 mg BID (N=44)		1200 mg QD (N=31)		Total (N=75)	
Subjects with at least one TEAE	n	(%)	37	(100.0)	38	(100.0)	44	(100.0)	31	(100.0)	75	(100.)
TEAE leading to death	n	(%)	3	(8.1)	3	(7.9)	4	(9.1)	2	(6.5)	6	(8.0)
Serious TEAE (including death)	n	(%)	8	(21.6)	8	(21.1)	13	(29.5)	3	(9.7)	16	(21.3)
TEAE leading to early study withdrawal	n	(%)	3	(8.1)	3	(7.9)	4	(9.1)	2	(6.5)	6	(8.0)

			HIV Negative (N=37)		Positive (N=38)		600 mg BID (N=44)		1200 mg QD (N=31)		Total (N=75)	
TEAE leading to discontinuation of one or all drugs in the trial regimen (per investigator)	n	(%)	11	(29.7)	11	(28.9)	14	(31.8)	8	(25.8)	22	(29.3)
TEAE leading to interruption of study drug	n	(%)	15	(40.5)	18	(47.4)	23	(52.3)	10	(32.3)	33	(44.0)
Grade III AND/OR IV TEAE	n	(%)	20	(54.1)	23	(60.5)	27	(61.4)	16	(51.6)	43	(57.3)
Drug-Related TEAE	n	(%)	37	(100.0)	37	(97.4)	43	(97.7)	31	(100.0)	74	(98.7)
Serious Drug-Related TEAE	n	(%)	4	(10.8)	4	(10.5)	7	(15.9)	1	(3.2)	8	(10.7)

			HIV Negative (N=37)		Positive (N=38)		600 mg BID (N=44)		1200 mg QD (N=31)		Total (N=75)	
TEAE of special interest	n	(%)	37	(100.0)	37	(97.4)	43	(97.7)	31	(100.0)	74	(98.7)
Liver-Related TEAE	n	(%)	13	(35.1)	15	(39.5)	19	(43.2)	9	(29.0)	28	(37.3)
Drug-Related Liver-Related TEAE	n	(%)	10	(27.0)	13	(34.2)	16	(36.4)	7	(22.6)	23	(30.7)
Serious Liver-Related TEAE	n	(%)	1	(2.7)					1	(3.2)	1	(1.3)

Safety and Tolerability (1)

			Total (N=75)	
Subjects with at least one TEAE	n	(%)	75	(100%)
TEAE leading to death	n	(%)	6	(8.0%)
Serious TEAE (including death)	n	(%)	16	(21.3%)
TEAE leading to early study withdrawal	n	(%)	6	(8.0%)

* All early withdrawals were patients who died

Safety and Tolerability (2)

			Total (N=75)	
TEAE leading to discontinuation of one or all drugs in the trial regimen (per investigator)*	n	(%)	22	(29.3)
TEAE leading to interruption of study drug	n	(%)	33	(44.0)
Grade III AND/OR IV TEAE	n	(%)	43	(57.3)
Serious Drug-Related TEAE	n	(%)	8	(10.7)

* Only Linezolid was permanently discontinued and BPa was continued

Safety and Tolerability (3)

			Total (N=75)	
TEAE of special interest	n	(%)	74	(98.7)
Liver-Related TEAE	n	(%)	28	(37.3)
Serious Liver-Related TEAE*	n	(%)	1	(1.3)

* Increased liver functions settled, treatment was restarted and there was no recurrence of liver related AE