THE LANCET
Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Dooley KE, Rosenkranz SL, Conradie F, et al. QT effects of bedaquiline, delamanid or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. *Lancet Infect Dis* 2021; published online Feb 12. https://doi.org/10.1016/S1473-3099(20)30770-2.

Supplemental materials:

Sputum AFB smear and culture in liquid medium was performed for samples collected at screening and entry; weekly for weeks 1-8; weeks 10, 12, 16, 20, 24, 28, 36, 48, 84, 96, and 128; and at the time of premature study discontinuation. (Two sputum samples were collected at screening, entry, week 2 and week 4; three sputum samples were collected at the week 8 and week 24 visits.) Sputum culture results through week 28 are included in the analyses presented here.

Because characterizing sputum culture conversion was an exploratory objective, the protocol did not include an *a priori* definition of culture conversion from positive to negative.

Contaminated and indeterminate results were considered missing. Across weeks at which sputum was to be collected, the proportion of participants with a missing culture result ranged from 0% to 30%. For all visits, weeks 1-28, where no culture result was available, a value was imputed as follows.

In cases where a single missing result was "bookended" by the same value (ie, when the results immediately before and after the missing result were either both negative or both positive), the missing result was imputed to be either negative or positive to agree with results immediately before and after. (A culture sequence of NxN (where "x" denotes missing) was imputed to NNN, and PxP was imputed to PPP.) Bookending results were not imputed when there were two or more missing results in a row, or where the preceding and following results differed. (Bookend imputed values were not assigned for sequences such as PxN, NxP, PxxP, and NxxN.)

The remaining missing results (those not imputed via bookending) were handled two ways:

(1) For the ***sputum culture conversion analysis***, a value of positive was imputed for the remaining missing values. This is considered an "intent-to-treat" analysis; findings based on this dataset would be biased toward lower efficacy

    The outcome measure *confirmed culture conversion* was defined as the time of the first of two consecutive negative cultures, regardless of presence/absence of subsequent positive cultures. The measure thus reflects any bacteriological response/activity in sputum – early, late, and/or transient. Some participants had positive cultures after confirmed negative.

    The week 28 culture result was used in determination of first confirmed negative culture. That is, if culture conversion had not yet occurred at week 20, for week 24 to be considered the week of culture conversion, there had to be a non-imputed, negative culture result at week 28. If the first negative culture was at week 28, then culture conversion did not occur.

(2) Because the culture conversion estimands comprised both sustained conversions (at least through the 24 weeks of observation) and in some cases early, transient conversions, an alternative outcome was created to represent participants' late/long-term culture status. For the ***last positive week analysis***, a value of negative was imputed for the remaining missing values. In other words, only those weeks at which a positive result was available would count as the last positive week. (Findings based on this dataset would be biased toward greater efficacy; neither imputation approach was expected to favor one arm over another.)

Sputum culture conversion analysis, statistical approach

Times to culture conversion across arms were compared visually in Kaplan-Meier plots. For inference, log-rank statistic p-values were reported (with the threshold 0.05 used to deem a result statistically significant), as well as cumulative probabilities of conversion at weeks 8 and 24, with associated 95% confidence intervals (CIs).

Last positive week analysis

Last positive week was summarized descriptively, by arm, via median, 25th and 75th percentiles, minimum and maximum, and the proportion of participants with last positive week occurring on or after week 12.

Table S1. Summary statistics for last positive week, by arm

Dataset	Value imputed	Treatment arm	N	Median	25th percentile	75th percentile	Minimum	Maximum
1a	Positive	BDQ	24	6.0	2.5	14.0	0.0	24.0
		DLM	23	20.0	4.0	24.0	1.0	24.0
		BDQ+DLM	20	2.5	1.0	5.0	0.0	24.0
1b	Negative	BDQ	24	5.0	1.5	6.5	0.0	24.0
		DLM	23	5.0	2.0	20.0	0.0	24.0
		BDQ+DLM	20	2.0	0.0	4.0	0.0	10.0

Figure S1. Histogram showing the percentage of patients having their last positive culture at a given week, by arm, over 28 weeks.

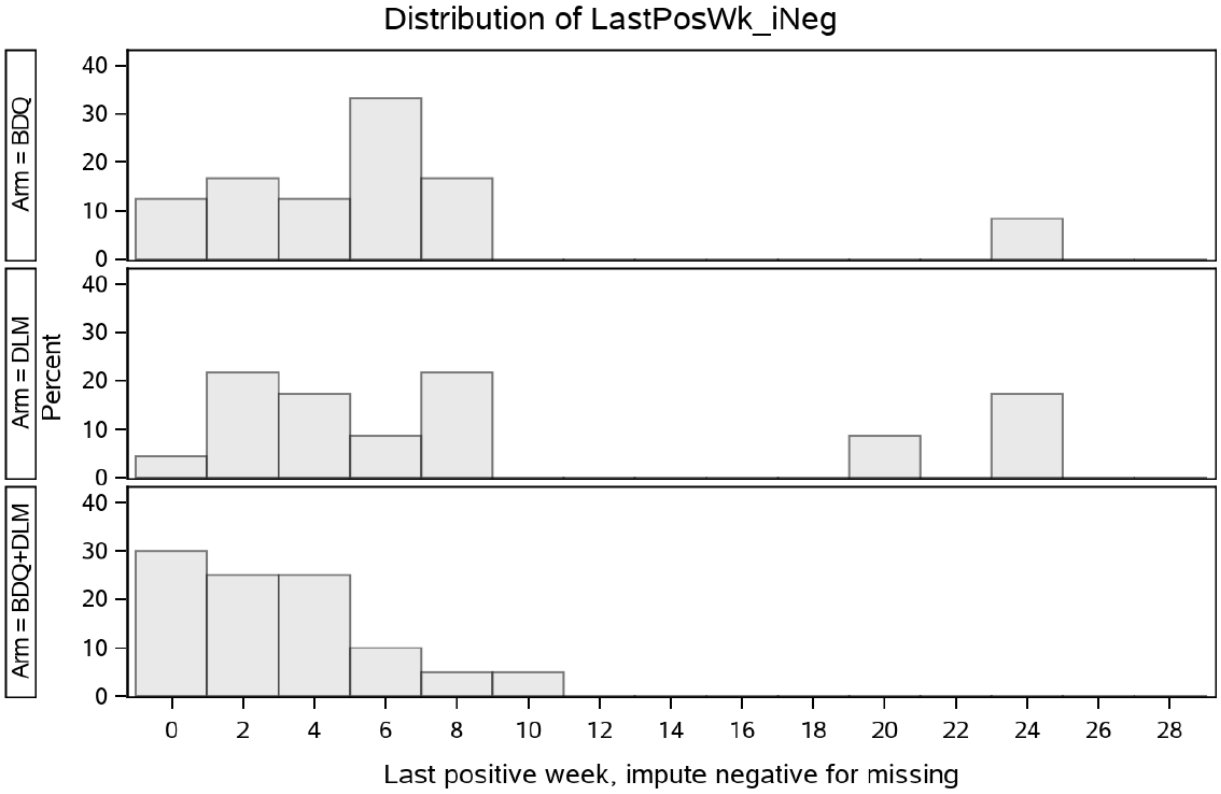

Table S2. Companion anti-TB drugs taken by study participants, by Arm.

		Treatment Arm			
		Total (N=75)	**BDQ (N=26)**	**DLM (N=25)**	**BDQ+DLM (N=24)**
MBT Regimen:	Capreomycin, Cycloserine, Ethambutol, Ethionamide, Pyrazinamide, Levofloxacin	1 (1%)	0 (0%)	1 (4%)	0 (0%)
	Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Levofloxacin	3 (4%)	1 (4%)	1 (4%)	1 (4%)
	Ethambutol, Ethionamide, Pyrazinamide, Levofloxacin	1 (1%)	0 (0%)	0 (0%)	1 (4%)
	Ethambutol, Ethionamide, Pyrazinamide, Terizidone, Levofloxacin	3 (4%)	2 (8%)	1 (4%)	0 (0%)
	Ethambutol, Isoniazid, Pyrazinamide, Levofloxacin	3 (4%)	1 (4%)	0 (0%)	2 (8%)
	Ethambutol, Isoniazid, Pyrazinamide, Terizidone, Levofloxacin	11 (15%)	1 (4%)	6 (24%)	4 (17%)
	Ethambutol, Terizidone, Levofloxacin	1 (1%)	1 (4%)	0 (0%)	0 (0%)
	Kanamycin, Cycloserine, Ethambutol, Ethionamide, Pyrazinamide, Levofloxacin	1 (1%)	0 (0%)	0 (0%)	1 (4%)
	Kanamycin, Cycloserine, Ethionamide, Pyrazinamide, Levofloxacin	1 (1%)	0 (0%)	0 (0%)	1 (4%)
	Kanamycin, Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Levofloxacin	2 (3%)	1 (4%)	1 (4%)	0 (0%)
	Kanamycin, Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Terizidone, Levofloxacin	3 (4%)	1 (4%)	1 (4%)	1 (4%)
	Kanamycin, Ethambutol, Ethionamide, Pyrazinamide, Levofloxacin	1 (1%)	1 (4%)	0 (0%)	0 (0%)
	Kanamycin, Ethambutol, Ethionamide, Pyrazinamide, Terizidone, Levofloxacin	9 (12%)	4 (15%)	4 (16%)	1 (4%)
	Kanamycin, Ethambutol, Isoniazid, Pyrazinamide, Levofloxacin	6 (8%)	3 (12%)	2 (8%)	1 (4%)
	Kanamycin, Ethambutol, Isoniazid, Pyrazinamide, Terizidone	1 (1%)	1 (4%)	0 (0%)	0 (0%)
	Kanamycin, Ethambutol, Isoniazid, Pyrazinamide, Terizidone, Levofloxacin	16 (21%)	3 (12%)	4 (16%)	9 (38%)
	Kanamycin, Ethambutol, Pyrazinamide, Terizidone, Levofloxacin	1 (1%)	1 (4%)	0 (0%)	0 (0%)
	Kanamycin, Ethionamide, Pyrazinamide, Terizidone, Levofloxacin	1 (1%)	0 (0%)	1 (4%)	0 (0%)
	Kanamycin, Linezolid, Ethambutol, Isoniazid, Pyrazinamide, Levofloxacin	1 (1%)	0 (0%)	0 (0%)	1 (4%)
	Linezolid, Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Levofloxacin	4 (5%)	2 (8%)	2 (8%)	0 (0%)
	Linezolid, Ethambutol, Isoniazid, Pyrazinamide, Levofloxacin	5 (7%)	3 (12%)	1 (4%)	1 (4%)

Table S3. Baseline characteristics for A5343 Participants included in the QT Primary Outcome Analysis

			Treatment Arm		
		Total (N=75)	**BDQ (N=26)**	**DLM (N=25)**	**BDQ+DLM (N=24)**
Age (yrs)	N	75	26	25	24
	Median (10, 90%)	36 (20, 52)	34.5 (21, 48)	36 (19,56)	38 (20, 49)
Sex	M	56 (75%)	20 (77%)	18 (72%)	18 (75%)
	F	19 (25%)	6 (23%)	7 (28%)	6 (25%)
Race	White	1 (1%)	0 (0%)	1 (4%)	0 (0%)
	Black African	36 (48%)	16 (62%)	11 (44%)	9 (38%)
	Mestizo	3 (4%)	0 (0%)	1 (4%)	2 (8%)
	Coloured	34 (45%)	10 (38%)	11 (44%)	13 (54%)
	Other	1 (1%)	0 (0%)	1 (4%)	0 (0%)
HIV-1 Positive	Yes	29 (39%)	10 (38%)	11 (44%)	8 (33%)
	No	46 (61%)	16 (62%)	14 (56%)	16 (67%)
Of HIV-1 Positive, HIV treatment status	Naïve	11 (35%)	3 (30%)	4 (36%)	4 (40%)
	Experienced	20 (65%)	7 (70%)	7 (64%)	6 (60%)
Baseline QTcF	Mean (s.d.)	398 (21.1)	397 (24.9)	405 (20.4)	392 (15.0)
	Median (10, 90%)	395 (372, 422)	393 (370, 434)	408 (379, 429)	389 (374, 415)
Days on TB Treatment Prior to Randomization	Median (10, 90%)	27 (15, 45)	26 (13, 42)	31 (16, 49)	27 (16, 42)
Taking Short-Course Regimen Prior to Randomization	Yes	20 (27%)	9 (35%)	4 (16%)	7 (29%)
	No	55 (73%)	17 (65%)	21 (84%)	17 (71%)

Table S4. Mean, Median, Minimum, and Maximum change in QTcF from Baseline, by Arm and Study Week.

Treatment Arm	Visit Week	N	Mean	Median	Minimum	Maximum
BDQ	2	27	12.73	16.70	-25.70	57.00
	4	28	11.67	15.00	-21.00	40.70
	6	26	11.19	15.30	-25.30	40.00
	8	26	8.63	12.00	-40.30	47.30
	10	25	10.14	10.30	-30.30	51.00
	12	25	11.09	9.30	-11.70	46.30
	14	25	11.79	12.70	-16.00	53.00
	16	24	16.17	15.35	-34.30	55.30
	18	24	17.01	17.65	-17.30	72.30
	20	25	10.73	9.30	-24.30	46.70
	22	24	11.83	12.00	-16.00	56.70
	24	25	13.55	11.70	-26.00	46.00
	28	25	12.49	13.30	-20.30	43.00
DLM	2	26	0.80	4.15	-25.70	24.30
	4	25	5.70	8.70	-15.70	24.70
	6	25	7.28	9.30	-19.00	37.70
	8	25	8.30	7.00	-30.30	39.00
	10	24	6.61	7.80	-25.30	37.70
	12	23	8.20	10.30	-21.00	38.70
	14	23	6.55	5.30	-18.00	49.00
	16	20	2.19	7.35	-46.00	38.70
	18	21	10.46	11.70	-28.30	39.30
	20	22	10.36	13.65	-21.30	29.30
	22	22	9.38	9.00	-15.70	34.30
	24	22	12.15	13.00	-19.30	40.30
	28	19	4.68	6.00	-25.30	38.30
BDQ+DLM	2	26	15.24	13.15	-6.70	55.70
	4	25	16.07	14.30	-8.70	50.30
	6	25	15.82	15.30	-11.00	33.70
	8	25	18.27	20.30	-14.00	47.30
	10	23	21.84	18.30	-15.00	58.30
	12	25	20.20	20.30	-20.30	50.30
	14	25	19.48	21.30	-19.00	51.00
	16	24	21.87	21.00	-22.70	62.70
	18	23	18.16	12.70	-26.70	66.30
	20	24	23.02	21.00	-18.30	70.00
	22	24	21.18	20.85	-19.30	75.00
	24	23	22.60	24.00	-19.00	46.30
	28	22	16.64	17.65	-16.00	55.70

Table S5. QTcF and QTcF changes from baseline (based on averages of 3 replicates), for delamanid (DLM) and bedaquiline plus delamanid (BDQ+DLM) arms, by baseline albumin level (<3.4 vs. ≥ 3.4 g/dL).

Treatment Arm	BL albumin	Visit Week	N QTcF	Min QTcF	Mean QTcF	Max QTcF	N QTcF, ch fr BL	Min QTcF, ch fr BL	Mean QTcF, ch fr BL	Max QTcF, ch fr BL
DLM	≥3.4 g/dL	0	11	365.7	402.5	445.0	0	.	.	.
		8	11	385.0	410.8	459.3	11	-16.3	8.3	33.3
		10	10	385.7	410.2	447.0	10	-18.3	5.4	33.7
		12	8	383.0	403.2	446.3	8	-21.0	0.2	21.0
		14	9	391.7	411.5	444.0	9	-18.0	6.6	42.3
		16	9	385.7	408.3	447.3	9	-20.0	3.4	21.3
		18	8	387.0	406.8	444.0	8	-7.3	3.8	21.3
		20	9	378.7	413.6	462.3	9	-10.7	8.7	26.0
		22	9	377.0	409.7	466.3	9	-7.7	4.8	21.3
		24	9	373.3	411.3	478.0	9	-8.0	6.4	33.0
	< 3.4 g/dL	0	14	364.3	406.7	428.7	0	.	.	.
		8	14	381.7	415.1	467.7	14	-30.3	8.3	39.0
		10	14	368.3	414.2	445.0	14	-25.3	7.5	37.7
		12	14	397.7	419.9	443.3	14	-13.0	13.2	38.7
		14	14	394.3	413.3	445.3	14	-17.7	6.5	49.0
		16	11	366.0	410.7	443.3	11	-46.0	1.2	38.7
		18	13	376.0	420.6	461.7	13	-28.3	14.6	39.3
		20	13	390.7	417.6	445.0	13	-21.3	11.5	29.3
		22	12	381.3	417.4	445.3	12	-15.7	11.9	34.3
		24	13	378.7	422.2	454.7	13	-19.3	16.2	40.3
BDQ+DLM	≥3.4 g/dL	0	11	368.3	391.5	415.0	0	.	.	.
		8	11	361.3	410.5	444.0	11	-11.0	19.0	42.7
		10	10	373.3	409.4	450.7	10	-15.0	17.0	41.3
		12	11	378.0	409.5	459.7	11	-20.3	18.0	50.3
		14	11	377.7	407.9	441.0	11	-19.0	16.4	44.0
		16	10	370.7	408.6	443.3	10	-22.7	18.3	62.7
		18	9	371.7	409.2	462.3	9	-26.7	20.3	57.0
		20	10	380.0	411.2	442.3	10	-18.3	20.9	54.0
		22	10	379.0	416.2	458.7	10	-19.3	25.8	75.0
		24	10	383.3	414.6	453.3	10	-14.3	24.3	46.3
	< 3.4 g/dL	0	13	374.3	391.9	422.3	0	.	.	.
		8	13	395.3	410.8	425.0	13	-14.0	18.9	47.3
		10	12	389.3	417.9	436.0	12	-3.0	26.1	58.3
		12	13	394.7	414.4	442.7	13	-5.7	22.5	49.3
		14	13	389.7	413.8	435.3	13	8.0	21.9	51.0
		16	13	388.3	416.7	445.7	13	9.3	24.8	45.7
		18	13	384.7	407.9	440.7	13	-5.7	16.0	66.3
		20	13	385.3	415.3	444.3	13	3.7	23.4	70.0
		22	12	365.3	410.8	434.0	12	-11.3	18.4	45.7
		24	11	357.7	415.2	443.0	11	-19.0	21.8	43.7