
Opti-Q

DMID 13-0057, NCT01918397

Prospective, Randomized, Blinded Phase II Pharmacokinetic/Pharmacodynamic Study of the Efficacy and Tolerability of Levofloxacin in Combination with Optimized Background Regimen for the Treatment of MDR-TB.

Supplementary Appendix

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2 Supplementary Methods

See the following paper for more details on the trial methodology:

<https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-2292-x>

Bouton TC, Phillips PPJ, Mitnick CD, *et al.* An optimized background regimen design to evaluate the contribution of levofloxacin to multidrug-resistant tuberculosis treatment regimens: study protocol for a randomized controlled trial. *Trials* 2017; **18**(1): 563.

3 Supplementary Results

3.1 Screening and Randomization

Figure S1.1: Total randomized by site and month

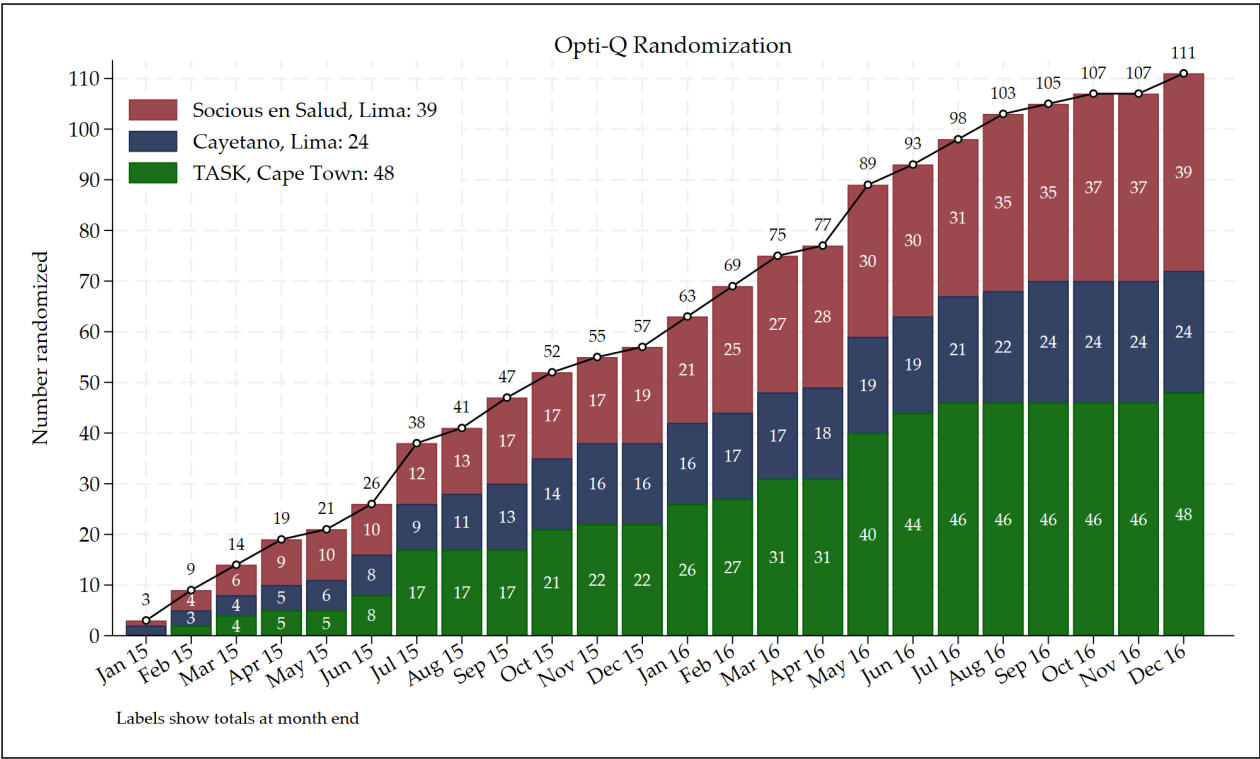


Figure S1.2: CONSORT Flowchart

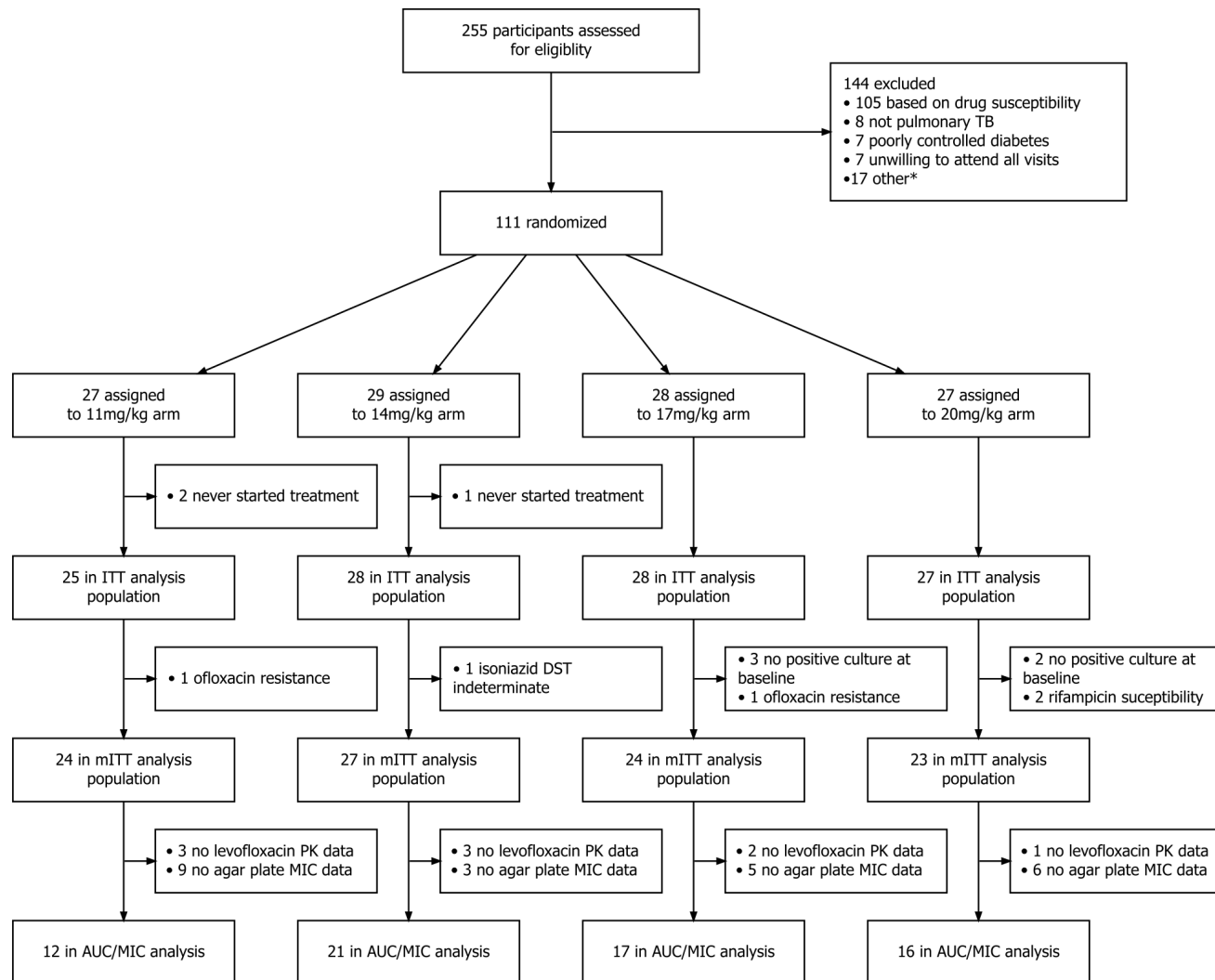


Table S1.1: Summary of screening and reasons for not being screened. Table shows first reason given on case report form (CRF).

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total screened	111	56	88	255
Total randomized	48 (43.2%)	24 (42.9%)	39 (44.3%)	111 (43.5%)
Total not randomized	63	32	49	144
Not INH and RIF resistant and FQ sensitive	53 (84.1%)	19 (59.4%)	33 (67.3%)	105 (72.9%)
Not pulmonary TB	1 (1.6%)	5 (15.6%)	2 (4.1%)	8 (5.6%)
Not willing to attend scheduled visits	0 (0.0%)	2 (6.2%)	5 (10.2%)	7 (4.9%)
Has poorly controlled diabetes (Hgb A1c > 9%)	2 (3.2%)	2 (6.2%)	3 (6.1%)	7 (4.9%)
Reason unavailable	1 (1.6%)	3 (9.4%)	0 (0.0%)	4 (2.8%)
Quinolone use for 7 days within the past 30 days	2 (3.2%)	1 (3.1%)	0 (0.0%)	3 (2.1%)
Concurrent use of known QT-prolonging drugs	1 (1.6%)	0 (0.0%)	2 (4.1%)	3 (2.1%)
Hemoglobin concentration <9.0 g/dL	0 (0.0%)	0 (0.0%)	3 (6.1%)	3 (2.1%)
Estimated Serum creatinine clearance <50, using nomogram	1 (1.6%)	0 (0.0%)	1 (2.0%)	2 (1.4%)
Not expected to survive for at least 6 months	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
No negative pregnancy test (woman of childbearing potential)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.7%)

Table S1.2: Randomization by site and treatment arm

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
TASK, Cape Town	12	12	12	12	48
Cayetano, Lima	6	7	6	5	24
Socios en Salud, Lima	9	10	10	10	39
Total	27	29	28	27	111

Table S1.3: Randomization by randomization stratification factors and treatment arm

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Cape Town: HIV negative	6	7	7	6	26
Cape Town: HIV positive	6	5	5	6	22
Cayetano, Lima	6	7	6	5	24
Socios en Salud, Lima	9	10	10	10	39
Total	27	29	28	27	111

3.2 Primary analysis populations

Table S2.1: Summary of participant analysis populations by treatment arm.

		11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total randomized		27	29	28	27	111
Excluded from ITT	Never started treatment	2	1	0	0	3
Total ITT		25	28	28	27	108
Excluded from MITT	Isoniazid DST indeterminate	0	1	0	0	1
Excluded from MITT	No positive cultures at baseline	0	0	3	2	5
Excluded from MITT	Ofloxacin resistance	1	0	1	0	2
Excluded from MITT	Rifampicin sensitivity	0	0	0	2	2
Total MITT		24	27	24	23	98
Excluded from AUC/MIC analysis	Missing AUC	2	3	1	1	7
Excluded from AUC/MIC analysis	Missing AUC and MIC (AP)	1	0	1	0	2
Excluded from AUC/MIC analysis	Missing MIC (AP)	9	3	5	6	23
Total in AUC/MIC analysis		12	21	17	16	66

Table S2.2: Summary of participant analysis populations by study site.

		TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total randomized		48	24	39	111
Excluded from ITT	Never started treatment	2	1	0	3
Total ITT		46	23	39	108
Excluded from MITT	Isoniazid DST indeterminate	1	0	0	1
Excluded from MITT	No positive cultures at baseline	5	0	0	5
Excluded from MITT	Ofloxacin resistance	1	0	1	2
Excluded from MITT	Rifampicin sensitivity	1	1	0	2
Total MITT		38	22	38	98
Excluded from AUC/MIC analysis	Missing AUC	4	1	2	7
Excluded from AUC/MIC analysis	Missing AUC and MIC (AP)	1	1	0	2
Excluded from AUC/MIC analysis	Missing MIC (AP)	15	6	2	23
Total in AUC/MIC analysis		18	14	34	66

3.3 Off-trial use of fluoroquinolones

Although not permitted by the protocol, eight study participants received additional levofloxacin or moxifloxacin during the study for various reasons and for varying durations. This is summarized below.

Table S3.1: Listing of participants that have taken off-trial fluoroquinolones.

Participant	Randomization	PK Sampling	Details of fluoroquinolone usage	Last Dose
32-33-018	07/Jul/2015	29/Jul/2015	Moxi from 28/Dec/15 to 25/Jan/16	27/Dec/2015
32-33-024	30/Jul/2015	11/Aug/2015	Moxi from 14/Oct/15 to 03/Nov/15	18/Jan/2016
32-33-028	12/Oct/2015	11/Nov/2015	Levo from 15/Oct/15 to 10/Feb/16	21/Dec/2015
32-33-031	29/Oct/2015	18/Nov/2015	Moxi from 22/Oct/15 to 19/Jan/16, 27/Jan/16 to 24/Feb/16	25/Jan/2016
32-33-092	24/Jun/2016	14/Jul/2016	One dose of Moxi on 20/Jul/16	10/Dec/2016
32-33-096	21/Jul/2016	10/Aug/2016	Moxi from 28/Sep/16 to 03/Oct/16	08/Jan/2017
32-33-110*	23/Dec/2016	08/Feb/2017	Levo from 03/Jan/17 to 10/Jan/17	09/Jun/2017
32-38-032	27/Oct/2015	16/Nov/2015	Treatment failure led to switch from Levo to Moxi	04/Dec/2015

* Participant 32-33-110 had PK samples taken on two occasions, this is the later sampling date (the earlier being 12/Jan/2017)

Given this, data from two participants (32-33-028 and 32-33-031) that had *additional fluoroquinolone at the time that PK sampling was done* are excluded from all PK analyses. Data from all other participants are included in PK analyses.

Sensitivity analyses have also been conducted whereby all eight participants are excluded to explore how sensitive the results are to this additional fluoroquinolone intake.

3.4 Baseline characteristics

Table S4.1: Baseline characteristics by treatment arm

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total randomised					
	27	29	28	27	111
Prior TB diagnoses					
None	16 (59%)	22 (76%)	17 (61%)	20 (74%)	75 (68%)
Treatment for DS-TB only	7 (26%)	7 (24%)	9 (32%)	7 (26%)	30 (27%)
Treatment for MDR-TB	4 (15%)	0	2 (7%)	0	6 (5%)
Outcome of most recent TB treatment episode					
Cure/Completion	5 (19%)	5 (17%)	8 (29%)	5 (19%)	23 (21%)
Default	3 (11%)	0	2 (7%)	1 (4%)	6 (5%)
No prior TB episode	16 (59%)	22 (76%)	17 (61%)	20 (74%)	75 (68%)
Resistance detected	2 (7%)	1 (3%)	1 (4%)	0	4 (4%)
Treatment Failure	1 (4%)	1 (3%)	0	0	2 (2%)
Wrong diagnosis	0	0	0	1 (4%)	1 (1%)
Karnofsky score					
<90	7 (26%)	9 (31%)	9 (32%)	8 (30%)	33 (30%)
Number missing	5 (19%)	6 (21%)	5 (18%)	6 (22%)	22 (20%)
≥90	15 (56%)	14 (48%)	14 (50%)	13 (48%)	56 (50%)
HIV status					
Negative	21 (78%)	24 (83%)	23 (82%)	21 (78%)	89 (80%)
Positive	6 (22%)	5 (17%)	5 (18%)	6 (22%)	22 (20%)
Cavitation on chest X-ray					
Absent	5 (19%)	8 (28%)	8 (29%)	7 (26%)	28 (25%)
Present, <4cm	10 (37%)	10 (34%)	8 (29%)	12 (44%)	40 (36%)
Present, ≥4cm	12 (44%)	11 (38%)	12 (43%)	8 (30%)	43 (39%)
Smear grading					
Negative	0	0	2 (7%)	0	2 (2%)
Scanty	1 (4%)	0	3 (11%)	2 (7%)	6 (5%)
1+	8 (30%)	8 (28%)	6 (21%)	7 (26%)	29 (26%)
2+	5 (19%)	4 (14%)	2 (7%)	8 (30%)	19 (17%)

Table S4.1: Baseline characteristics by treatment arm (*continued*)

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
3+	13 (48%)	17 (59%)	15 (54%)	10 (37%)	55 (50%)
Days to positivity in MGIT					
Median (IQR)	8.5 (7.5, 11.2)	8.2 (6.7, 11.1)	9.2 (5.5, 10.9)	8.3 (7.1, 10.3)	8.4 (6.7, 11.1)
Minimum, Maximum	4.0, 26.2	4.2, 25.5	3.9, 19.4	4.4, 23.4	3.9, 26.2
Number missing	0	0	3	2	5
Sex					
Female	10 (37%)	9 (31%)	10 (36%)	14 (52%)	43 (39%)
Male	17 (63%)	20 (69%)	18 (64%)	13 (48%)	68 (61%)
Ethnicity					
Hispanic or Latino	14 (52%)	17 (59%)	16 (57%)	15 (56%)	62 (56%)
Not Hispanic or Latino	12 (44%)	12 (41%)	12 (43%)	12 (44%)	48 (43%)
Unknown	1 (4%)	0	0	0	1 (1%)
Race					
Black	5 (19%)	7 (24%)	6 (21%)	6 (22%)	24 (22%)
Other	22 (81%)	22 (76%)	22 (79%)	21 (78%)	87 (78%)
Age (years)					
Median (IQR)	32.0 (25.0, 43.0)	25.0 (23.0, 31.0)	26.0 (22.0, 37.5)	31.0 (21.0, 44.0)	26.0 (22.0, 42.0)
Minimum, Maximum	18.0, 69.0	18.0, 61.0	18.0, 60.0	18.0, 67.0	18.0, 69.0
CD4 count (cells/mm³)					
Median (IQR)	293.0 (180.0, 331.0)	366.0 (267.0, 384.0)	383.0 (371.0, 412.0)	266.0 (177.0, 292.0)	312.0 (178.5, 383.5)
Minimum, Maximum	145.0, 504.0	54.0, 440.0	41.0, 731.0	175.0, 378.0	41.0, 731.0
Number missing	1	0	0	1	2
Weight (kg)					
Median (IQR)	55.5 (48.2, 63.2)	57.0 (49.5, 62.8)	52.4 (49.4, 57.0)	53.8 (50.0, 61.7)	54.1 (49.0, 61.6)
Minimum, Maximum	40.7, 70.8	40.8, 84.7	38.7, 74.7	42.8, 67.4	38.7, 84.7
BMI (kg/m²)					
Median (IQR)	20.9 (17.9, 23.5)	20.5 (19.3, 22.6)	19.5 (18.0, 21.5)	20.1 (18.9, 22.4)	20.4 (18.2, 22.6)
Minimum, Maximum	16.1, 27.6	14.9, 29.8	12.9, 27.8	17.6, 27.9	12.9, 29.8
Weight-adjusted levofloxacin dose (mg/kg)					
Median (IQR)	13.5 (11.9, 15.5)	15.7 (14.6, 16.3)	19.3 (18.0, 20.3)	24.2 (23.1, 25.0)	17.5 (14.6, 22.7)
Minimum, Maximum	10.6, 18.5	11.8, 18.4	16.7, 25.9	22.3, 29.2	10.6, 29.2

Table S4.1: Baseline characteristics by treatment arm (*continued*)

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Number of TB drugs in regimen at baseline (excluding fluoroquinolones, and pyridoxine)					
4	2 (7%)	1 (3%)	0	1 (4%)	4 (4%)
5	17 (63%)	21 (72%)	20 (71%)	20 (74%)	78 (70%)
6	7 (26%)	7 (24%)	8 (29%)	6 (22%)	28 (25%)
Number missing	1 (4%)	0	0	0	1 (1%)
Days of treatment in current TB episode prior to randomization					
<3 days	8 (30%)	10 (34%)	10 (36%)	11 (41%)	39 (35%)
3-6 days	7 (26%)	10 (34%)	7 (25%)	10 (37%)	34 (31%)
7-13 days	11 (41%)	9 (31%)	10 (36%)	5 (19%)	35 (32%)
≥14 days	0	0	1 (4%)	1 (4%)	2 (2%)
Number missing	1 (4%)	0	0	0	1 (1%)

Table S4.2: Baseline characteristics by site

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total randomised	48	24	39	111
Prior TB diagnoses				
None	24 (50%)	24 (100%)	27 (69%)	75 (68%)
Treatment for DS-TB only	22 (46%)	0	8 (21%)	30 (27%)
Treatment for MDR-TB	2 (4%)	0	4 (10%)	6 (5%)
Outcome of most recent TB treatment episode				
Cure/Completion	16 (33%)	0	7 (18%)	23 (21%)
Default	2 (4%)	0	4 (10%)	6 (5%)
No prior TB episode	24 (50%)	24 (100%)	27 (69%)	75 (68%)
Resistance detected	4 (8%)	0	0	4 (4%)
Treatment Failure	1 (2%)	0	1 (3%)	2 (2%)
Wrong diagnosis	1 (2%)	0	0	1 (1%)
Karnofsky score				
<90	17 (35%)	2 (8%)	14 (36%)	33 (30%)
Number missing	19 (40%)	3 (12%)	0	22 (20%)
≥90	12 (25%)	19 (79%)	25 (64%)	56 (50%)
HIV status				
Negative	26 (54%)	24 (100%)	39 (100%)	89 (80%)
Positive	22 (46%)	0	0	22 (20%)
Cavitation on chest X-ray				
Absent	11 (23%)	4 (17%)	13 (33%)	28 (25%)
Present, <4cm	7 (15%)	11 (46%)	22 (56%)	40 (36%)
Present, ≥4cm	30 (62%)	9 (38%)	4 (10%)	43 (39%)
Smear grading				
Negative	1 (2%)	1 (4%)	0	2 (2%)
Scanty	5 (10%)	1 (4%)	0	6 (5%)
1+	10 (21%)	5 (21%)	14 (36%)	29 (26%)
2+	8 (17%)	5 (21%)	6 (15%)	19 (17%)
3+	24 (50%)	12 (50%)	19 (49%)	55 (50%)
Days to positivity in MGIT				

Table S4.2: Baseline characteristics by site (*continued*)

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Median (IQR)	10.1 (7.8, 14.2)	9.1 (7.3, 11.0)	6.8 (5.5, 8.6)	8.4 (6.7, 11.1)
Minimum, Maximum	4.4, 25.5	5.9, 26.2	3.9, 18.4	3.9, 26.2
Number missing	5	0	0	5
Sex				
Female	18 (38%)	8 (33%)	17 (44%)	43 (39%)
Male	30 (62%)	16 (67%)	22 (56%)	68 (61%)
Ethnicity				
Hispanic or Latino	0	24 (100%)	38 (97%)	62 (56%)
Not Hispanic or Latino	48 (100%)	0	0	48 (43%)
Unknown	0	0	1 (3%)	1 (1%)
Race				
Black	24 (50%)	0	0	24 (22%)
Other	24 (50%)	24 (100%)	39 (100%)	87 (78%)
Age (years)				
Median (IQR)	33.5 (26.0, 46.5)	24.0 (20.5, 32.5)	24.0 (19.0, 29.0)	26.0 (22.0, 42.0)
Minimum, Maximum	18.0, 67.0	18.0, 67.0	18.0, 69.0	18.0, 69.0
CD4 count (cells/mm³)				
Median (IQR)	312.0 (178.5, 383.5)			312.0 (178.5, 383.5)
Minimum, Maximum	41.0, 731.0			41.0, 731.0
Number missing	2			2
Weight (kg)				
Median (IQR)	53.1 (48.9, 60.0)	57.3 (51.9, 63.5)	53.8 (47.7, 61.6)	54.1 (49.0, 61.6)
Minimum, Maximum	38.7, 70.5	45.4, 84.7	40.7, 70.8	38.7, 84.7
BMI (kg/m²)				
Median (IQR)	18.9 (17.6, 20.4)	21.5 (20.5, 24.2)	21.0 (18.7, 23.8)	20.4 (18.2, 22.6)
Minimum, Maximum	12.9, 26.0	17.8, 27.8	15.3, 29.8	12.9, 29.8
Number of TB drugs in regimen at baseline (excluding fluoroquinolones, and pyridoxine)				
4	3 (6%)	0	1 (3%)	4 (4%)
5	18 (38%)	23 (96%)	37 (95%)	78 (70%)
6	27 (56%)	1 (4%)	0	28 (25%)
Number missing	0	0	1 (3%)	1 (1%)

Table S4.2: Baseline characteristics by site (*continued*)

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Days of treatment in current TB episode prior to randomization				
<3 days	0	2 (8%)	37 (95%)	39 (35%)
3-6 days	14 (29%)	20 (83%)	0	34 (31%)
7-13 days	32 (67%)	2 (8%)	1 (3%)	35 (32%)
≥14 days	2 (4%)	0	0	2 (2%)
Number missing	0	0	1 (3%)	1 (1%)

Table S4.3: Baseline characteristics by whether AUC and MIC (Agar Plate) are missing or not (restricted to MITT analysis population)

	Missing AUC or MIC	AUC and MIC not missing	Total
Total randomised			
	32	66	98
Prior TB diagnoses			
None	18 (56%)	52 (79%)	70 (71%)
Treatment for DS-TB only	13 (41%)	10 (15%)	23 (23%)
Treatment for MDR-TB	1 (3%)	4 (6%)	5 (5%)
Outcome of most recent TB treatment episode			
Cure/Completion	9 (28%)	8 (12%)	17 (17%)
Default	0	6 (9%)	6 (6%)
No prior TB episode	18 (56%)	52 (79%)	70 (71%)
Resistance detected	3 (9%)	0	3 (3%)
Treatment Failure	2 (6%)	0	2 (2%)
Karnofsky score			
<90	7 (22%)	21 (32%)	28 (29%)
Number missing	10 (31%)	6 (9%)	16 (16%)
≥90	15 (47%)	39 (59%)	54 (55%)
HIV status			
Negative	23 (72%)	57 (86%)	80 (82%)
Positive	9 (28%)	9 (14%)	18 (18%)
Cavitation on chest X-ray			
Absent	7 (22%)	17 (26%)	24 (24%)
Present, <4cm	8 (25%)	26 (39%)	34 (35%)
Present, ≥4cm	17 (53%)	23 (35%)	40 (41%)
Smear grading			
Negative	0	1 (2%)	1 (1%)
Scanty	2 (6%)	0	2 (2%)
1+	7 (22%)	18 (27%)	25 (26%)
2+	3 (9%)	13 (20%)	16 (16%)
3+	20 (62%)	34 (52%)	54 (55%)
Days to positivity in MGIT			
Median (IQR)	8.8 (6.8, 11.2)	8.1 (6.6, 10.1)	8.3 (6.7, 10.7)

Table S4.3: Baseline characteristics by whether AUC and MIC (Agar Plate) are missing or not (restricted to MITT analysis population) (*continued*)

	Missing AUC or MIC	AUC and MIC not missing	Total
Minimum, Maximum	4.0, 26.2	3.9, 25.5	3.9, 26.2
Sex			
Female	7 (22%)	30 (45%)	37 (38%)
Male	25 (78%)	36 (55%)	61 (62%)
Ethnicity			
Hispanic or Latino	12 (38%)	48 (73%)	60 (61%)
Not Hispanic or Latino	20 (62%)	18 (27%)	38 (39%)
Race			
Black	12 (38%)	8 (12%)	20 (20%)
Other	20 (62%)	58 (88%)	78 (80%)
Age (years)			
Median (IQR)	32.5 (24.0, 43.5)	25.0 (21.0, 33.0)	26.0 (22.0, 38.0)
Minimum, Maximum	18.0, 61.0	18.0, 69.0	18.0, 69.0
CD4 count (cells/mm³)			
Median (IQR)	331.0 (180.0, 371.0)	293.0 (266.0, 383.0)	312.0 (223.0, 380.5)
Minimum, Maximum	54.0, 504.0	41.0, 412.0	41.0, 504.0
Number missing	2	0	2
Weight (kg)			
Median (IQR)	54.0 (49.5, 61.5)	54.0 (48.2, 61.7)	54.0 (49.5, 61.7)
Minimum, Maximum	41.8, 67.8	38.7, 84.7	38.7, 84.7
BMI (kg/m²)			
Median (IQR)	19.4 (18.0, 21.5)	20.8 (18.7, 23.5)	20.6 (18.3, 23.0)
Minimum, Maximum	14.9, 25.2	12.9, 29.8	12.9, 29.8
Weight-adjusted levofloxacin dose (mg/kg)			
Median (IQR)	16.3 (13.7, 20.3)	17.5 (15.5, 23.1)	17.5 (14.6, 22.4)
Minimum, Maximum	11.7, 29.2	10.6, 27.9	10.6, 29.2
Number of TB drugs in regimen at baseline (excluding fluoroquinolones, and pyridoxine)			
4	0	3 (5%)	3 (3%)
5	21 (66%)	49 (74%)	70 (71%)
6	10 (31%)	14 (21%)	24 (24%)
Number missing	1 (3%)	0	1 (1%)

Table S4.3: Baseline characteristics by whether AUC and MIC (Agar Plate) are missing or not (restricted to MITT analysis population) (*continued*)

	Missing AUC or MIC	AUC and MIC not missing	Total
Days of treatment in current TB episode prior to randomization			
<3 days	4 (12%)	34 (52%)	38 (39%)
3-6 days	13 (41%)	19 (29%)	32 (33%)
7-13 days	13 (41%)	12 (18%)	25 (26%)
≥14 days	1 (3%)	1 (2%)	2 (2%)
Number missing	1 (3%)	0	1 (1%)

Table S4.4: Baseline drug resistance by treatment arm

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total randomised	27	29	28	27	111
Rifampicin on Gene Xpert MTB/RIF					
Resistant	8 (30%)	12 (41%)	11 (39%)	7 (26%)	38 (34%)
NA	19 (70%)	17 (59%)	17 (61%)	20 (74%)	73 (66%)
Rifampicin on Hain MTBDRplus					
Resistant	27 (100%)	29 (100%)	28 (100%)	26 (96%)	110 (99%)
Two inconsistent results	0	0	0	1 (4%)	1 (1%)
Isoniazid on Hain MTBDRplus					
Sensitive	0	0	0	1 (4%)	1 (1%)
Resistant	27 (100%)	29 (100%)	27 (96%)	26 (96%)	109 (98%)
NA	0	0	1 (4%)	0	1 (1%)
Fluoroquinolone on Hain MTBDRsl					
Sensitive	26 (96%)	28 (97%)	27 (96%)	27 (100%)	108 (97%)
NA	1 (4%)	1 (3%)	1 (4%)	0	3 (3%)
Rifampicin on MGIT Drug Susceptibility					
Sensitive	0	0	0	2 (7%)	2 (2%)
Resistant	26 (96%)	27 (93%)	26 (93%)	24 (89%)	103 (93%)
Two inconsistent results	1 (4%)	2 (7%)	0	0	3 (3%)
NA	0	0	2 (7%)	1 (4%)	3 (3%)
Isoniazid on MGIT Drug Susceptibility					
Sensitive	0	0	0	1 (4%)	1 (1%)
Resistant	27 (100%)	28 (97%)	25 (89%)	24 (89%)	104 (94%)
Two inconsistent results	0	0	0	1 (4%)	1 (1%)
NA	0	1 (3%)	3 (11%)	1 (4%)	5 (5%)
Levofloxacin on MGIT Drug Susceptibility					
Sensitive	15 (56%)	19 (66%)	16 (57%)	18 (67%)	68 (61%)
NA	12 (44%)	10 (34%)	12 (43%)	9 (33%)	43 (39%)
Moxifloxacin on MGIT Drug Susceptibility					
Sensitive	2 (7%)	2 (7%)	0	3 (11%)	7 (6%)
NA	25 (93%)	27 (93%)	28 (100%)	24 (89%)	104 (94%)
Ofloxacin on MGIT Drug Susceptibility					
Sensitive	25 (93%)	27 (93%)	24 (86%)	24 (89%)	100 (90%)
Resistant	1 (4%)	0	1 (4%)	0	2 (2%)
NA	1 (4%)	2 (7%)	3 (11%)	3 (11%)	9 (8%)
Pyrazinamide on MGIT Drug Susceptibility					
Sensitive	10 (37%)	10 (34%)	8 (29%)	13 (48%)	41 (37%)
Resistant	14 (52%)	18 (62%)	15 (54%)	11 (41%)	58 (52%)
NA	3 (11%)	1 (3%)	5 (18%)	3 (11%)	12 (11%)
Ethambutol on MGIT Drug Susceptibility					
Sensitive	9 (33%)	17 (59%)	10 (36%)	12 (44%)	48 (43%)
Resistant	15 (56%)	10 (34%)	12 (43%)	12 (44%)	49 (44%)
NA	3 (11%)	2 (7%)	6 (21%)	3 (11%)	14 (13%)

Table S4.4: Baseline drug resistance by treatment arm (*continued*)

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Kanamycin on MGIT Drug Susceptibility					
Sensitive	13 (48%)	16 (55%)	14 (50%)	17 (63%)	60 (54%)
Resistant	2 (7%)	3 (10%)	2 (7%)	1 (4%)	8 (7%)
NA	12 (44%)	10 (34%)	12 (43%)	9 (33%)	43 (39%)
Amikacin on MGIT Drug Susceptibility					
Sensitive	24 (89%)	26 (90%)	21 (75%)	23 (85%)	94 (85%)
Resistant	1 (4%)	1 (3%)	4 (14%)	1 (4%)	7 (6%)
NA	2 (7%)	2 (7%)	3 (11%)	3 (11%)	10 (9%)
Kanamycin or Amikacin on MGIT Drug Susceptibility					
Sensitive	13 (48%)	14 (48%)	14 (50%)	14 (52%)	55 (50%)
Resistant	2 (7%)	3 (10%)	4 (14%)	1 (4%)	10 (9%)
NA	12 (44%)	12 (41%)	10 (36%)	12 (44%)	46 (41%)
Capreomycin on MGIT Drug Susceptibility					
Sensitive	6 (22%)	5 (17%)	6 (21%)	4 (15%)	21 (19%)
Resistant	0	2 (7%)	0	1 (4%)	3 (3%)
NA	21 (78%)	22 (76%)	22 (79%)	22 (81%)	87 (78%)
Streptomycin on MGIT Drug Susceptibility					
Sensitive	7 (26%)	6 (21%)	5 (18%)	5 (19%)	23 (21%)
Resistant	8 (30%)	11 (38%)	6 (21%)	9 (33%)	34 (31%)
NA	12 (44%)	12 (41%)	17 (61%)	13 (48%)	54 (49%)
Cycloserine on MGIT Drug Susceptibility					
Sensitive	6 (22%)	7 (24%)	6 (21%)	5 (19%)	24 (22%)
NA	21 (78%)	22 (76%)	22 (79%)	22 (81%)	87 (78%)

Table S4.5: Baseline drug resistance by site

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total randomised	48	24	39	111
Rifampicin on Gene Xpert MTB/RIF				
Resistant	37 (77%)	1 (4%)	0	38 (34%)
NA	11 (23%)	23 (96%)	39 (100%)	73 (66%)
Rifampicin on Hain MTBDRplus				
Resistant	47 (98%)	24 (100%)	39 (100%)	110 (99%)
Two inconsistent results	1 (2%)	0	0	1 (1%)
Isoniazid on Hain MTBDRplus				
Sensitive	1 (2%)	0	0	1 (1%)
Resistant	46 (96%)	24 (100%)	39 (100%)	109 (98%)
NA	1 (2%)	0	0	1 (1%)
Fluoroquinolone on Hain MTBDRsl				
Sensitive	46 (96%)	23 (96%)	39 (100%)	108 (97%)
NA	2 (4%)	1 (4%)	0	3 (3%)
Rifampicin on MGIT Drug Susceptibility				
Sensitive	1 (2%)	1 (4%)	0	2 (2%)
Resistant	41 (85%)	23 (96%)	39 (100%)	103 (93%)
Two inconsistent results	3 (6%)	0	0	3 (3%)
NA	3 (6%)	0	0	3 (3%)
Isoniazid on MGIT Drug Susceptibility				
Sensitive	1 (2%)	0	0	1 (1%)
Resistant	41 (85%)	24 (100%)	39 (100%)	104 (94%)
Two inconsistent results	1 (2%)	0	0	1 (1%)
NA	5 (10%)	0	0	5 (5%)
Levofloxacin on MGIT Drug Susceptibility				
Sensitive	5 (10%)	24 (100%)	39 (100%)	68 (61%)
NA	43 (90%)	0	0	43 (39%)
Moxifloxacin on MGIT Drug Susceptibility				
Sensitive	7 (15%)	0	0	7 (6%)
NA	41 (85%)	24 (100%)	39 (100%)	104 (94%)
Ofloxacin on MGIT Drug Susceptibility				
Sensitive	38 (79%)	24 (100%)	38 (97%)	100 (90%)
Resistant	1 (2%)	0	1 (3%)	2 (2%)
NA	9 (19%)	0	0	9 (8%)
Pyrazinamide on MGIT Drug Susceptibility				
Sensitive	20 (42%)	12 (50%)	9 (23%)	41 (37%)
Resistant	16 (33%)	12 (50%)	30 (77%)	58 (52%)
NA	12 (25%)	0	0	12 (11%)
Ethambutol on MGIT Drug Susceptibility				
Sensitive	21 (44%)	13 (54%)	14 (36%)	48 (43%)
Resistant	13 (27%)	11 (46%)	25 (64%)	49 (44%)
NA	14 (29%)	0	0	14 (13%)

Table S4.5: Baseline drug resistance by site (*continued*)

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Kanamycin on MGIT Drug Susceptibility				
Sensitive	5 (10%)	20 (83%)	35 (90%)	60 (54%)
Resistant	0	4 (17%)	4 (10%)	8 (7%)
NA	43 (90%)	0	0	43 (39%)
Amikacin on MGIT Drug Susceptibility				
Sensitive	36 (75%)	22 (92%)	36 (92%)	94 (85%)
Resistant	2 (4%)	2 (8%)	3 (8%)	7 (6%)
NA	10 (21%)	0	0	10 (9%)
Kanamycin or Amikacin on MGIT Drug Susceptibility				
Sensitive	0	20 (83%)	35 (90%)	55 (50%)
Resistant	2 (4%)	4 (17%)	4 (10%)	10 (9%)
NA	46 (96%)	0	0	46 (41%)
Capreomycin on MGIT Drug Susceptibility				
Sensitive	0	21 (88%)	0	21 (19%)
Resistant	0	3 (12%)	0	3 (3%)
NA	48 (100%)	0	39 (100%)	87 (78%)
Streptomycin on MGIT Drug Susceptibility				
Sensitive	14 (29%)	9 (38%)	0	23 (21%)
Resistant	19 (40%)	15 (62%)	0	34 (31%)
NA	15 (31%)	0	39 (100%)	54 (49%)
Cycloserine on MGIT Drug Susceptibility				
Sensitive	0	24 (100%)	0	24 (22%)
NA	48 (100%)	0	39 (100%)	87 (78%)

Table S4.6: Summary of baseline regimens by treatment arm.

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total	27 (100.0%)	29 (100.0%)	28 (100.0%)	27 (100.0%)	111 (100.0%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Cycloserine	5 (18.5%)	11 (37.9%)	8 (28.6%)	5 (18.5%)	29 (26.1%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Terizidone, Isoniazid	6 (22.2%)	7 (24.1%)	8 (28.6%)	6 (22.2%)	27 (24.3%)
Pyrazinamide, Ethambutol, Ethionamide, Amikacin, Cycloserine	5 (18.5%)	5 (17.2%)	7 (25.0%)	9 (33.3%)	26 (23.4%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Terizidone	3 (11.1%)	0	2 (7.1%)	3 (11.1%)	8 (7.2%)
Pyrazinamide, Ethambutol, Kanamycin, Terizidone, Isoniazid	1 (3.7%)	3 (10.3%)	1 (3.6%)	1 (3.7%)	6 (5.4%)
Pyrazinamide, Ethionamide, Kanamycin, Terizidone, Isoniazid	0	1 (3.4%)	1 (3.6%)	0	2 (1.8%)
Pyrazinamide, Ethionamide, Kanamycin, Terizidone	1 (3.7%)	0	0	1 (3.7%)	2 (1.8%)
Pyrazinamide, Ethambutol, Ethionamide, Capreomycin, Cycloserine	1 (3.7%)	0	0	1 (3.7%)	2 (1.8%)
Pyrazinamide, Ethionamide, Capreomycin, Cycloserine, P-aminosalicylic acid	0	1 (3.4%)	0	0	1 (0.9%)
Pyrazinamide, Ethionamide, Amikacin, Cycloserine	1 (3.7%)	0	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Terizidone, Isoniazid	0	1 (3.4%)	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Terizidone, Isoniazid	1 (3.7%)	0	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Isoniazid	0	0	0	1 (3.7%)	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Amikacin, Kanamycin, Cycloserine	1 (3.7%)	0	0	0	1 (0.9%)
Ethionamide, Capreomycin, Cycloserine, P-aminosalicylic acid, Amoxicillin/clavulanic acid	1 (3.7%)	0	0	0	1 (0.9%)
Ethambutol, Ethionamide, Kanamycin, Cycloserine, P-aminosalicylic acid	0	0	1 (3.6%)	0	1 (0.9%)
Not recorded	1 (3.7%)	0	0	0	1 (0.9%)

Table S4.7: Summary of baseline regimens by study site.

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total	48 (100.0%)	24 (100.0%)	39 (100.0%)	111 (100.0%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Cycloserine	0	13 (54.2%)	16 (41.0%)	29 (26.1%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Terizidone, Isoniazid	27 (56.2%)	0	0	27 (24.3%)
Pyrazinamide, Ethambutol, Ethionamide, Amikacin, Cycloserine	0	9 (37.5%)	17 (43.6%)	26 (23.4%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Terizidone	8 (16.7%)	0	0	8 (7.2%)
Pyrazinamide, Ethambutol, Kanamycin, Terizidone, Isoniazid	6 (12.5%)	0	0	6 (5.4%)
Pyrazinamide, Ethionamide, Kanamycin, Terizidone, Isoniazid	2 (4.2%)	0	0	2 (1.8%)
Pyrazinamide, Ethionamide, Kanamycin, Terizidone	2 (4.2%)	0	0	2 (1.8%)
Pyrazinamide, Ethambutol, Ethionamide, Capreomycin, Cycloserine	0	0	2 (5.1%)	2 (1.8%)
Pyrazinamide, Ethionamide, Capreomycin, Cycloserine, P-aminosalicylic acid	0	1 (4.2%)	0	1 (0.9%)
Pyrazinamide, Ethionamide, Amikacin, Cycloserine	0	0	1 (2.6%)	1 (0.9%)
Pyrazinamide, Ethambutol, Terizidone, Isoniazid	1 (2.1%)	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Terizidone, Isoniazid	1 (2.1%)	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Kanamycin, Isoniazid	1 (2.1%)	0	0	1 (0.9%)
Pyrazinamide, Ethambutol, Ethionamide, Amikacin, Kanamycin, Cycloserine	0	1 (4.2%)	0	1 (0.9%)
Ethionamide, Capreomycin, Cycloserine, P-aminosalicylic acid, Amoxicillin/clavulanic acid	0	0	1 (2.6%)	1 (0.9%)
Ethambutol, Ethionamide, Kanamycin, Cycloserine, P-aminosalicylic acid	0	0	1 (2.6%)	1 (0.9%)
Not recorded	0	0	1 (2.6%)	1 (0.9%)

3.5 Summary of dosing by treatment arm

Figure S5.1: Summary by weight and weight-adjusted dose

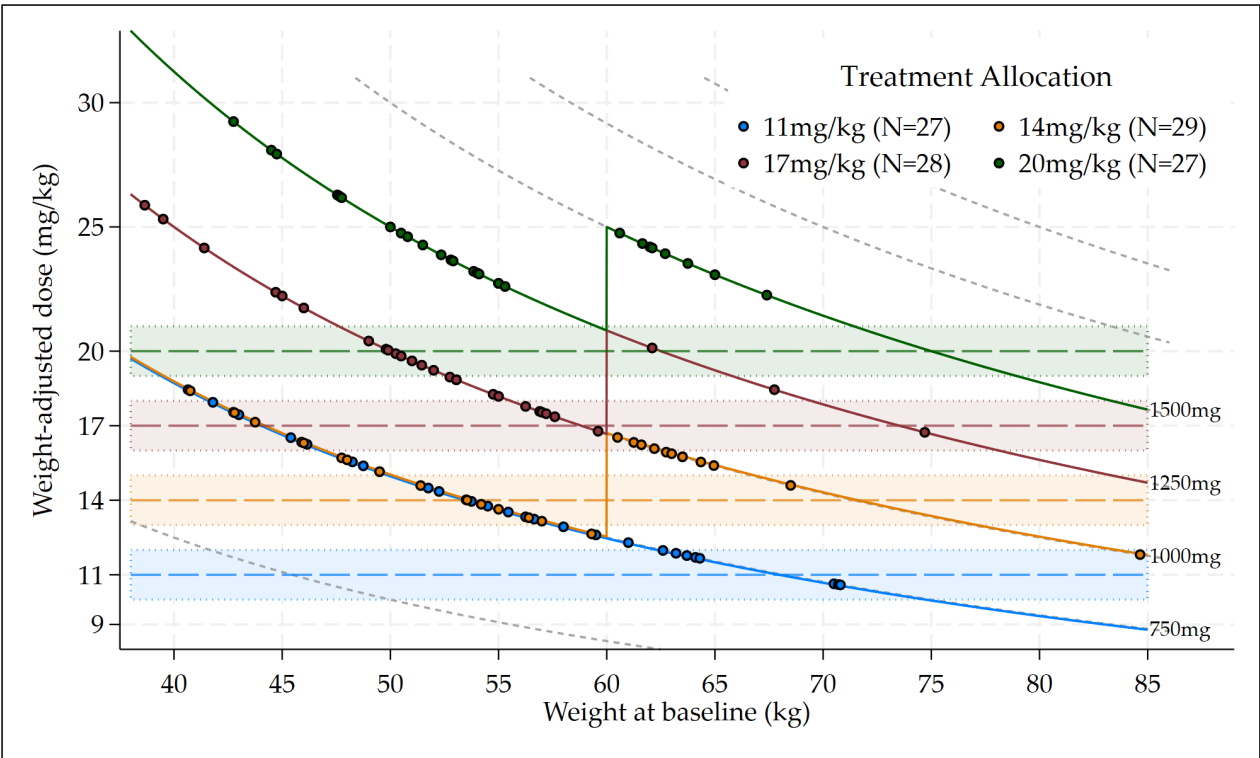


Figure S5.2: Summary by weight and actual dose received

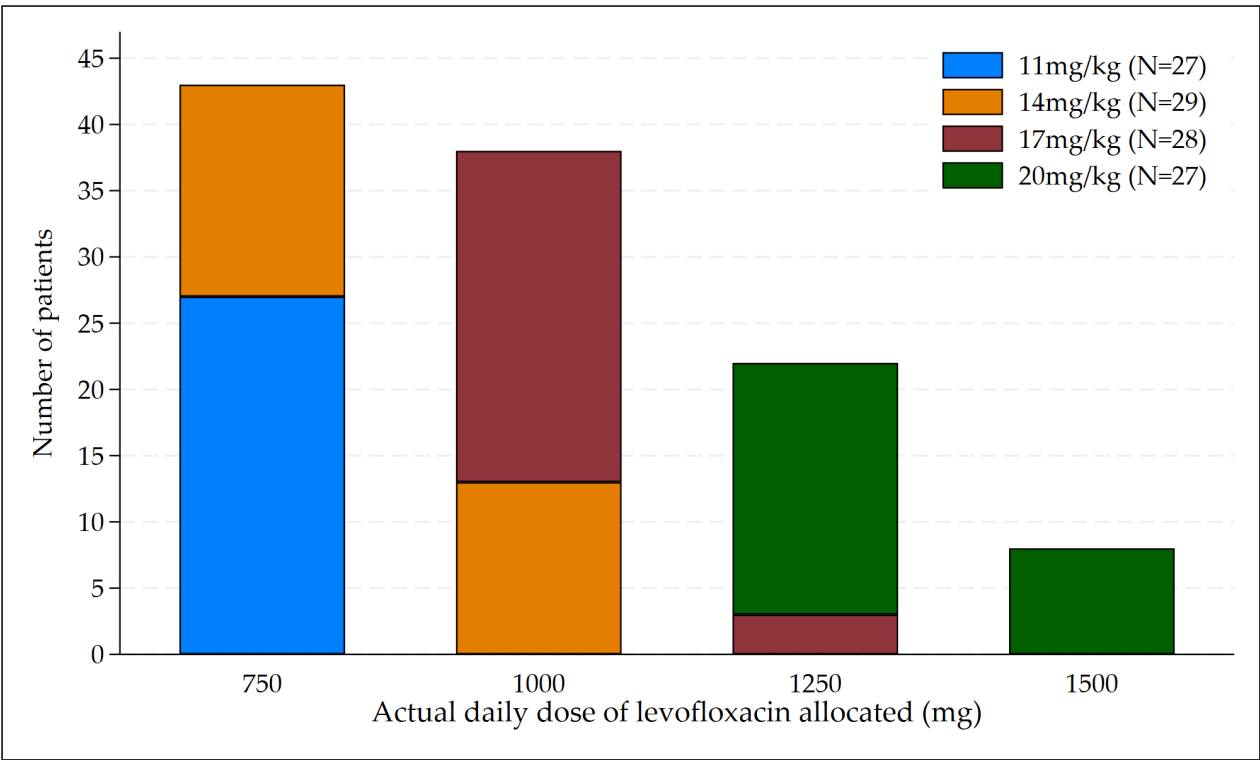
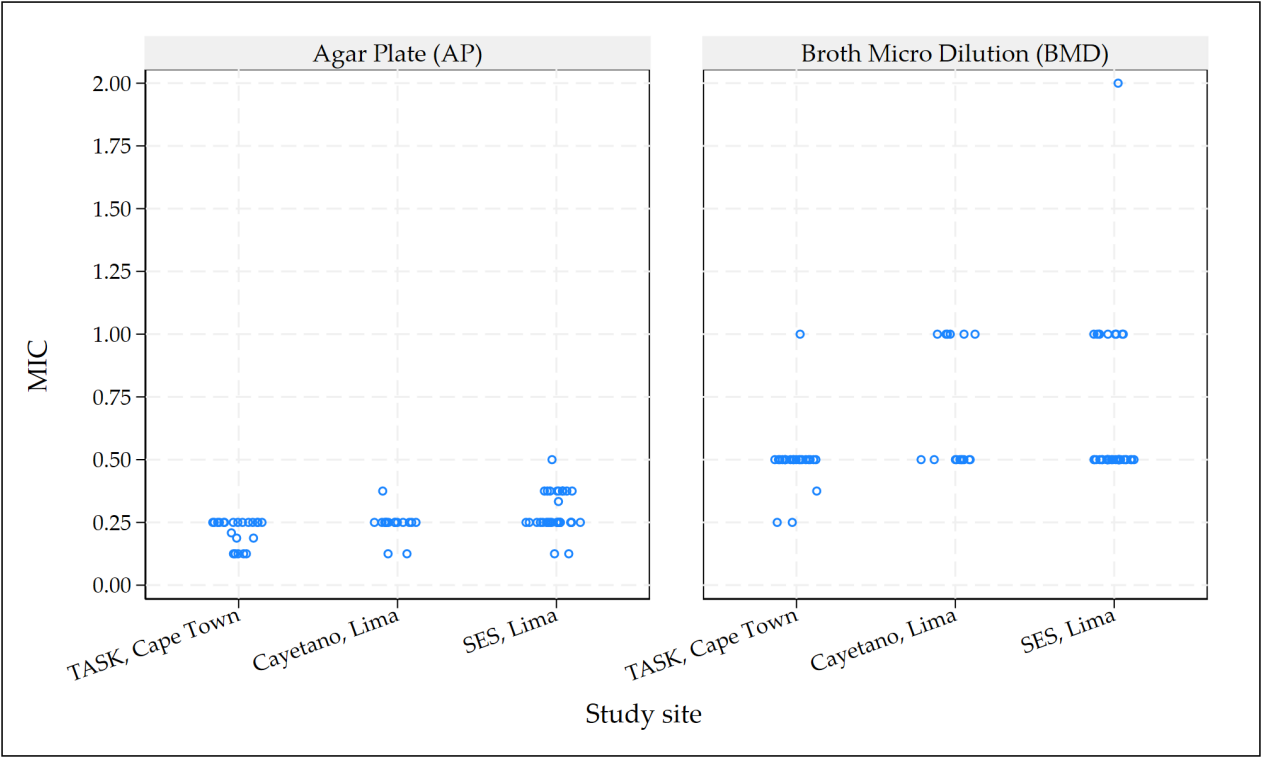




Figure S6.2: Summary of MIC by study site.



3.7 Pharmacokinetics

Figure S7.1: Summary of AUC by weight-adjusted dose, treatment arm and actual dose allocated.

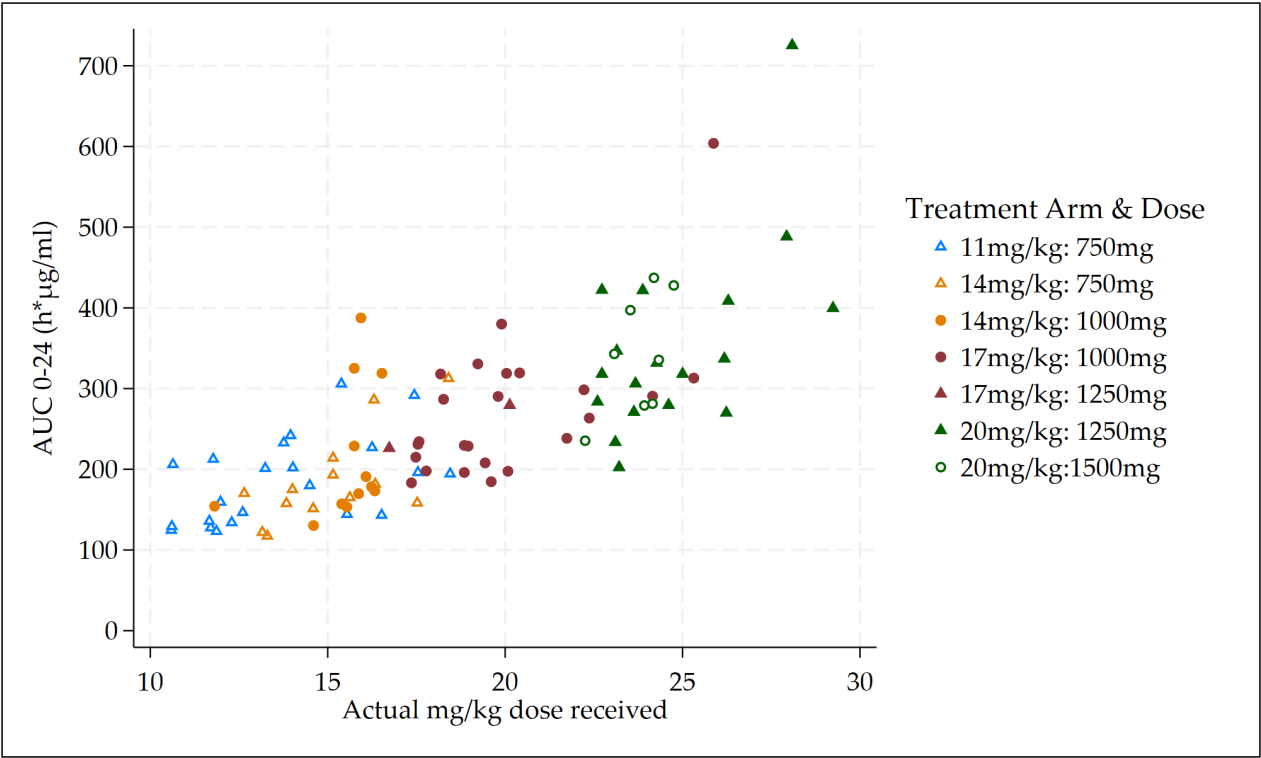


Figure S7.2: Summary of C_{max} by weight-adjusted dose, treatment arm and actual dose allocated.

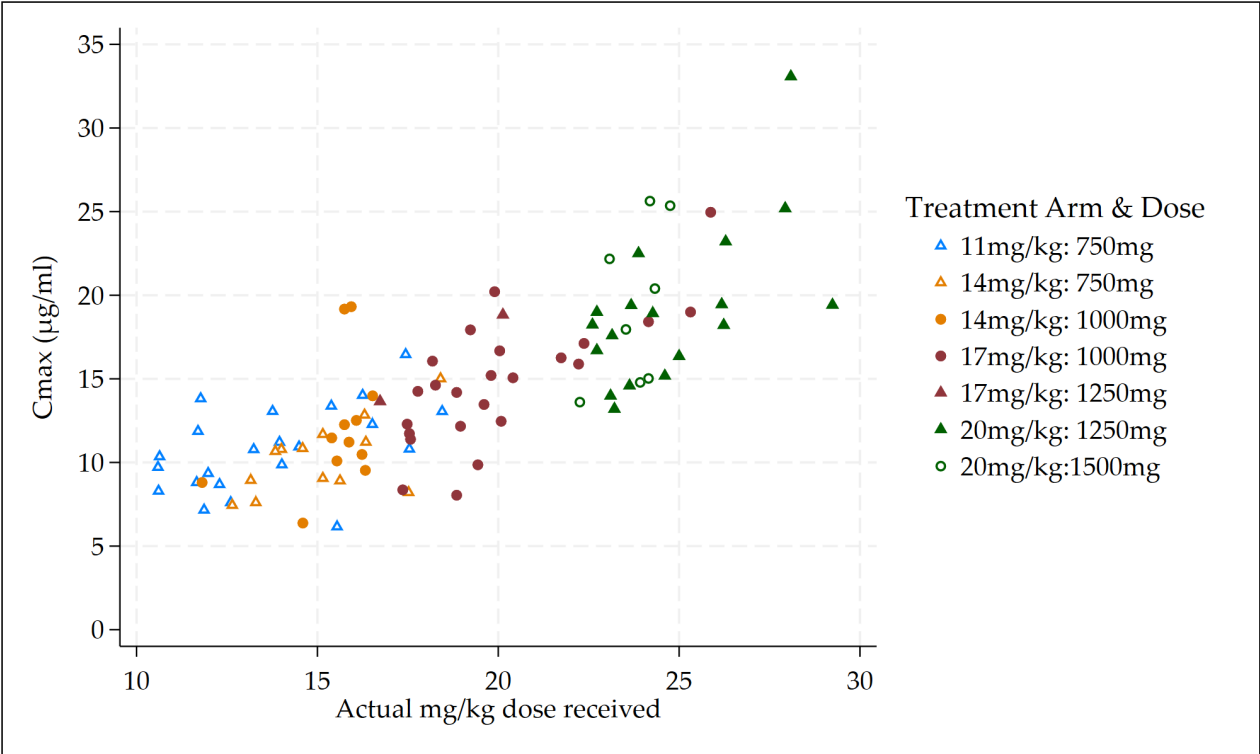


Figure S7.3: Summary of AUC by treatment arm. Black bar shows inter-quartile range, red triangle shows median.

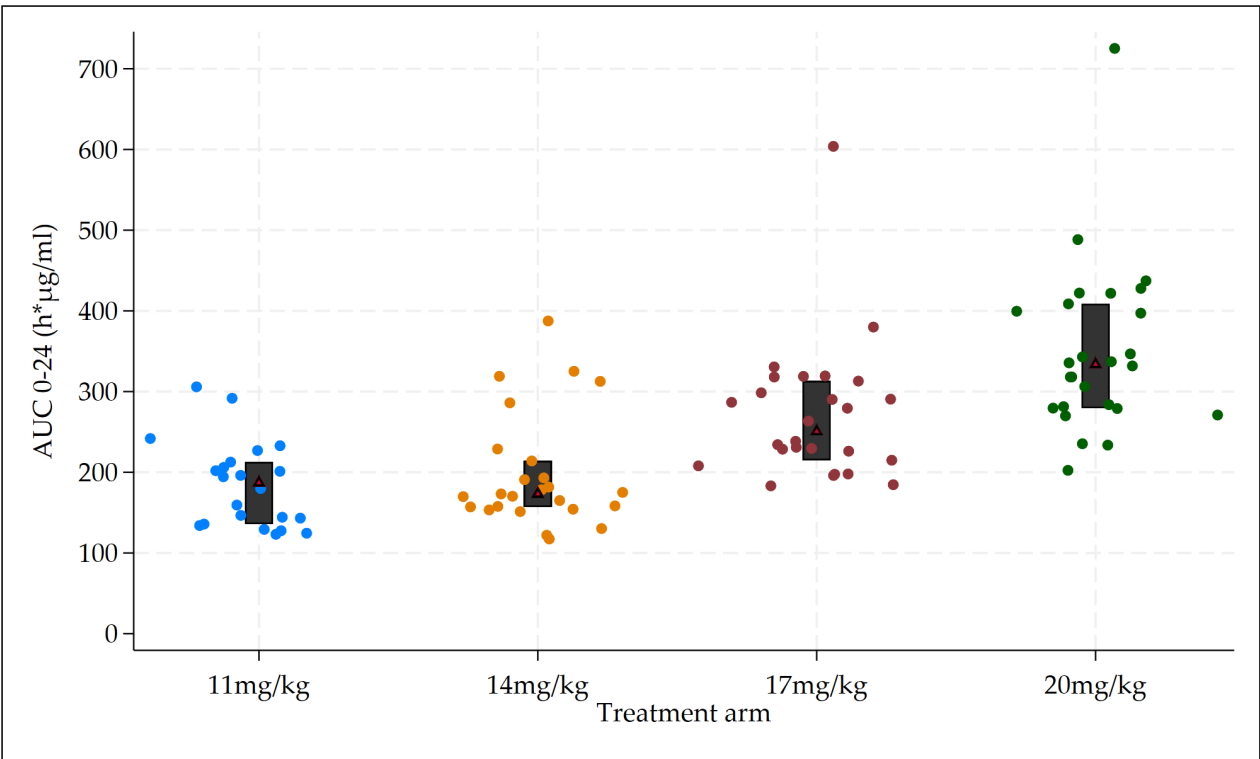


Figure S7.4: Summary of AUC/MIC (AP) by treatment arm. Black bar shows inter-quartile range, red triangle shows median.

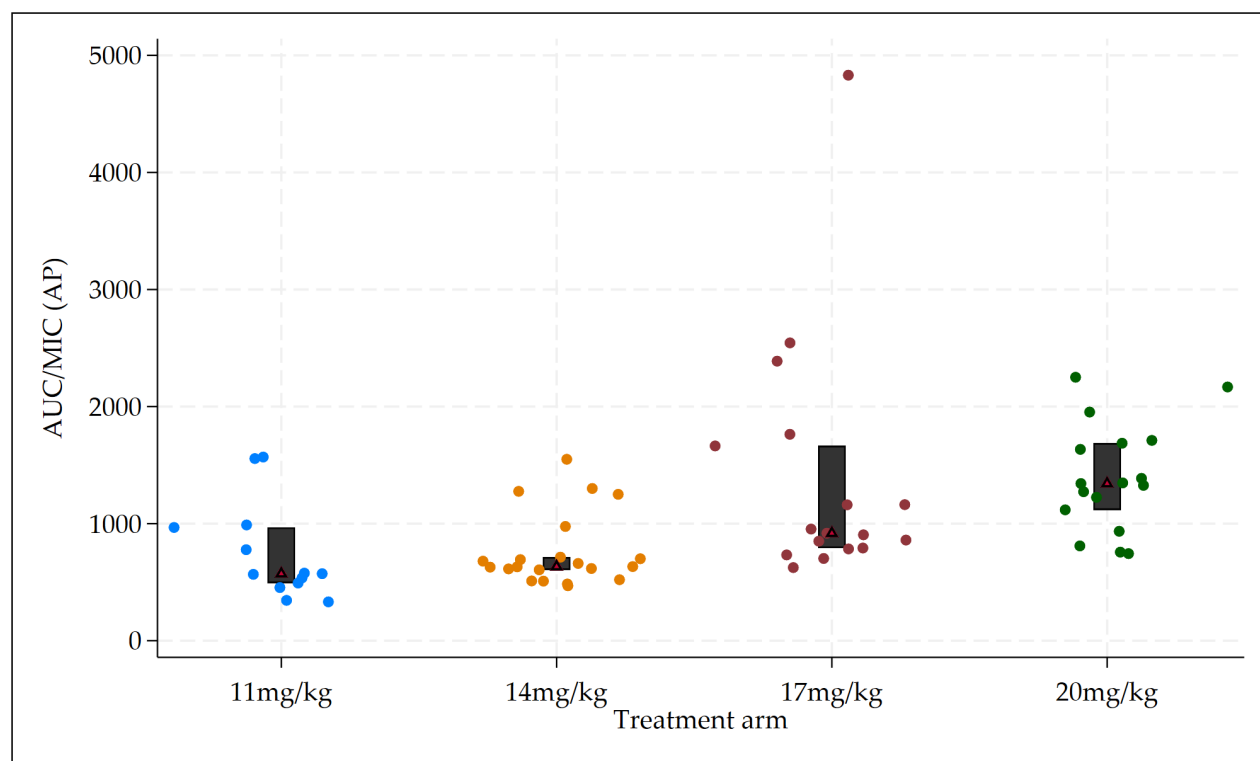


Figure S7.5: Summary of AUC/MIC (BMD) by treatment arm. Black bar shows inter-quartile range, red triangle shows median.

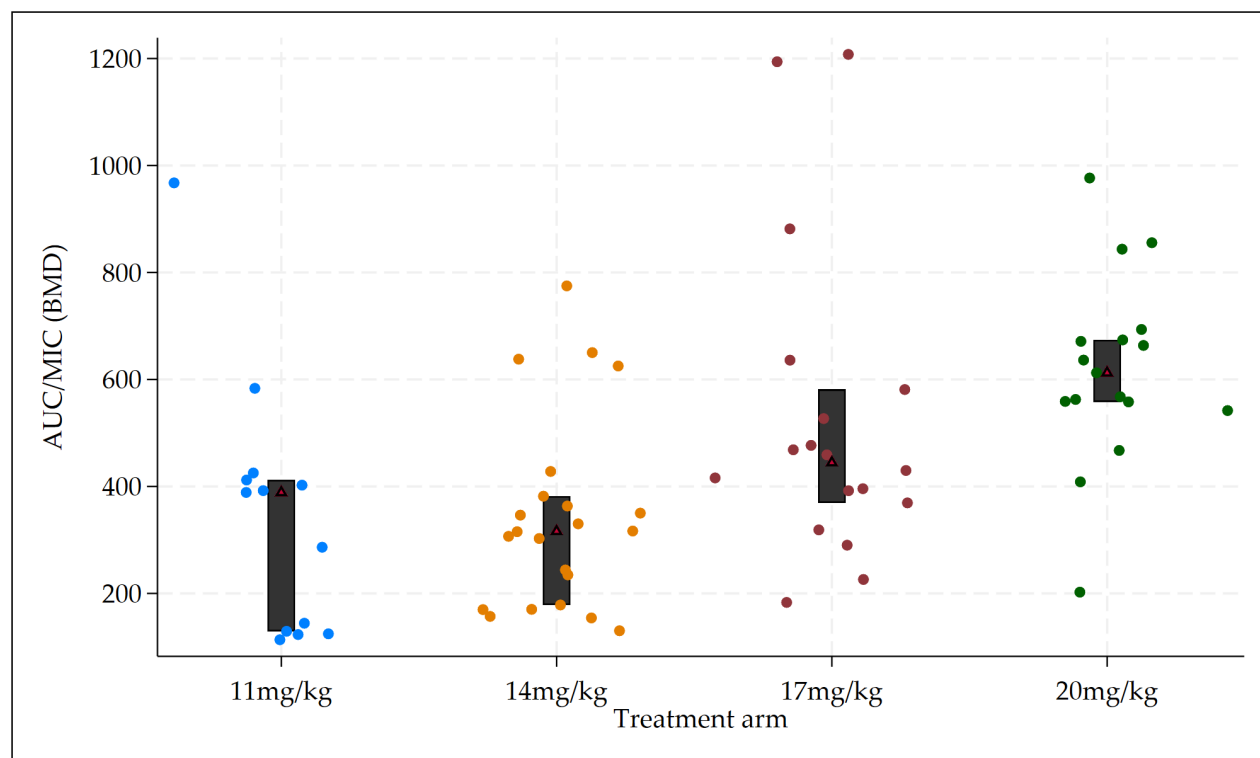


Figure S7.6: Summary of C_{max} by treatment arm. Black bar shows inter-quartile range, red triangle shows median.

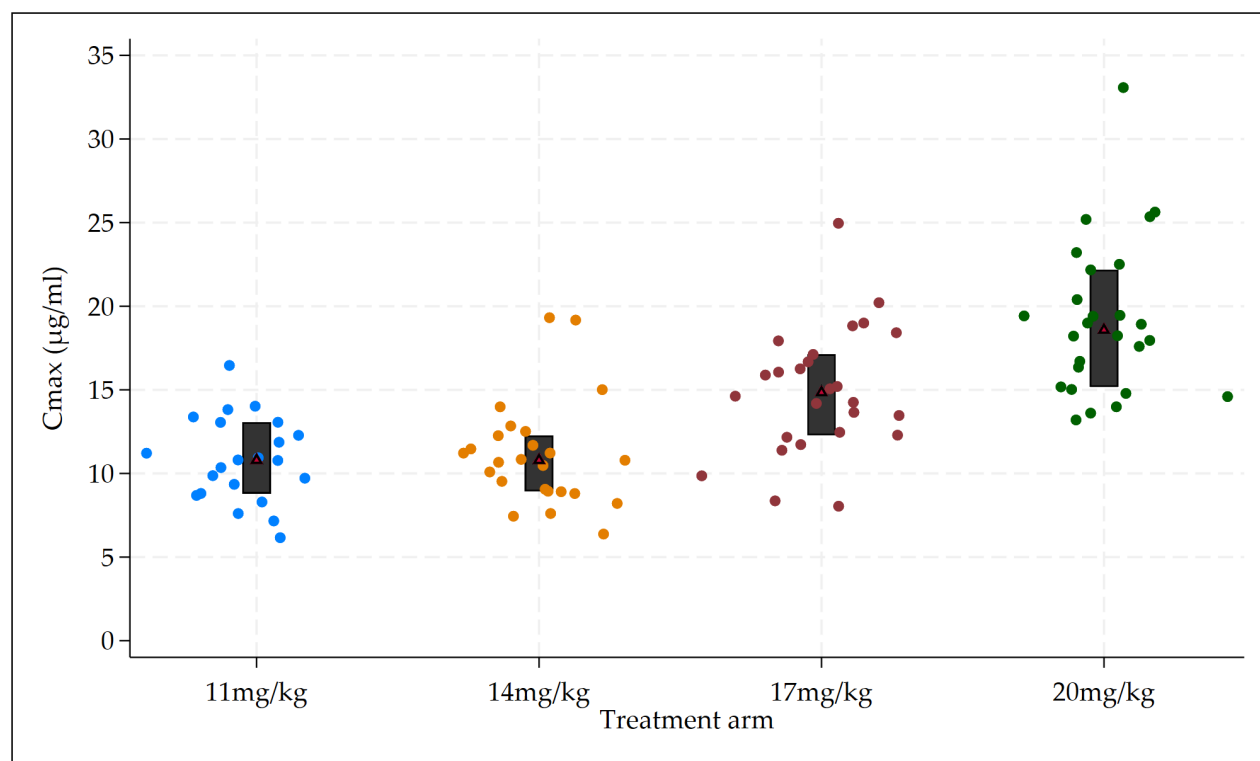


Figure S7.7: Summary of AUC by study site. Black bar shows inter-quartile range, red triangle shows median.

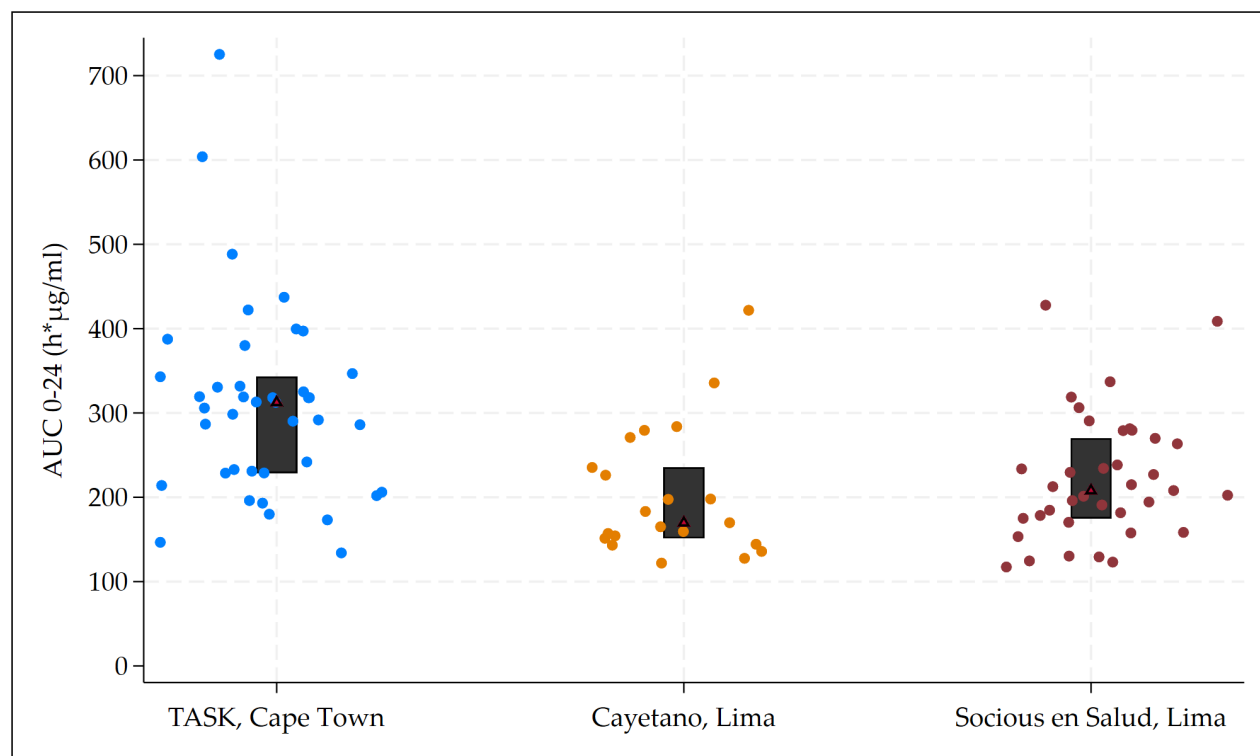


Figure S7.8: Summary of C_{max} by study site. Black bar shows inter-quartile range, red triangle shows median.

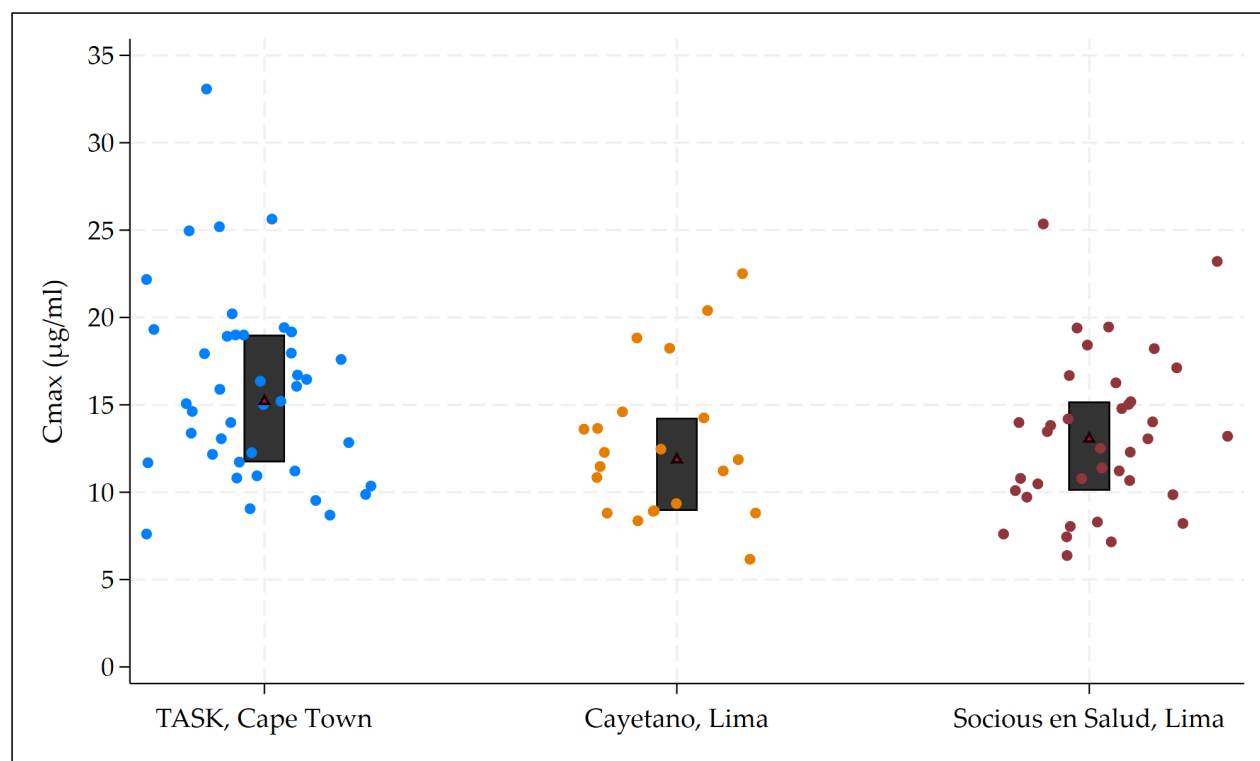


Figure S7.9: Summary of AUC/MIC (AP) by site. Black bar shows inter-quartile range, red triangle shows median.

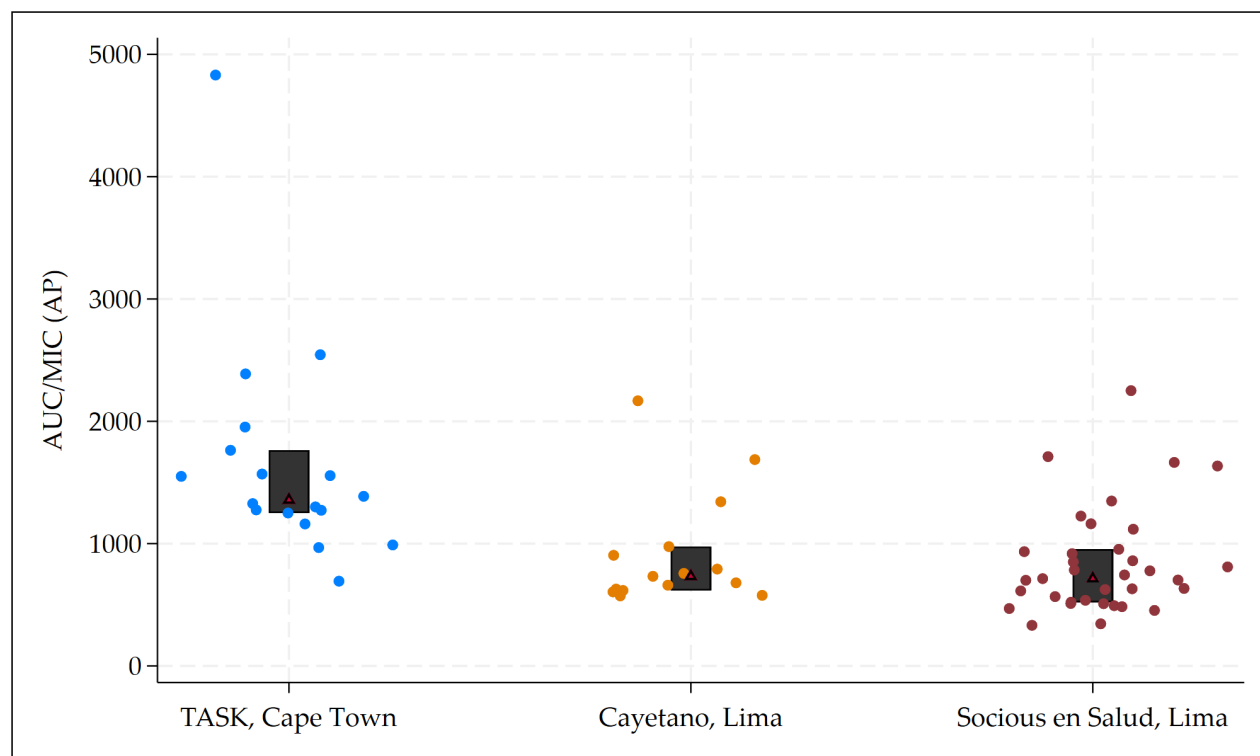


Figure S7.10: Summary of AUC/MIC (BMD) by site. Black bar shows inter-quartile range, red triangle shows median.

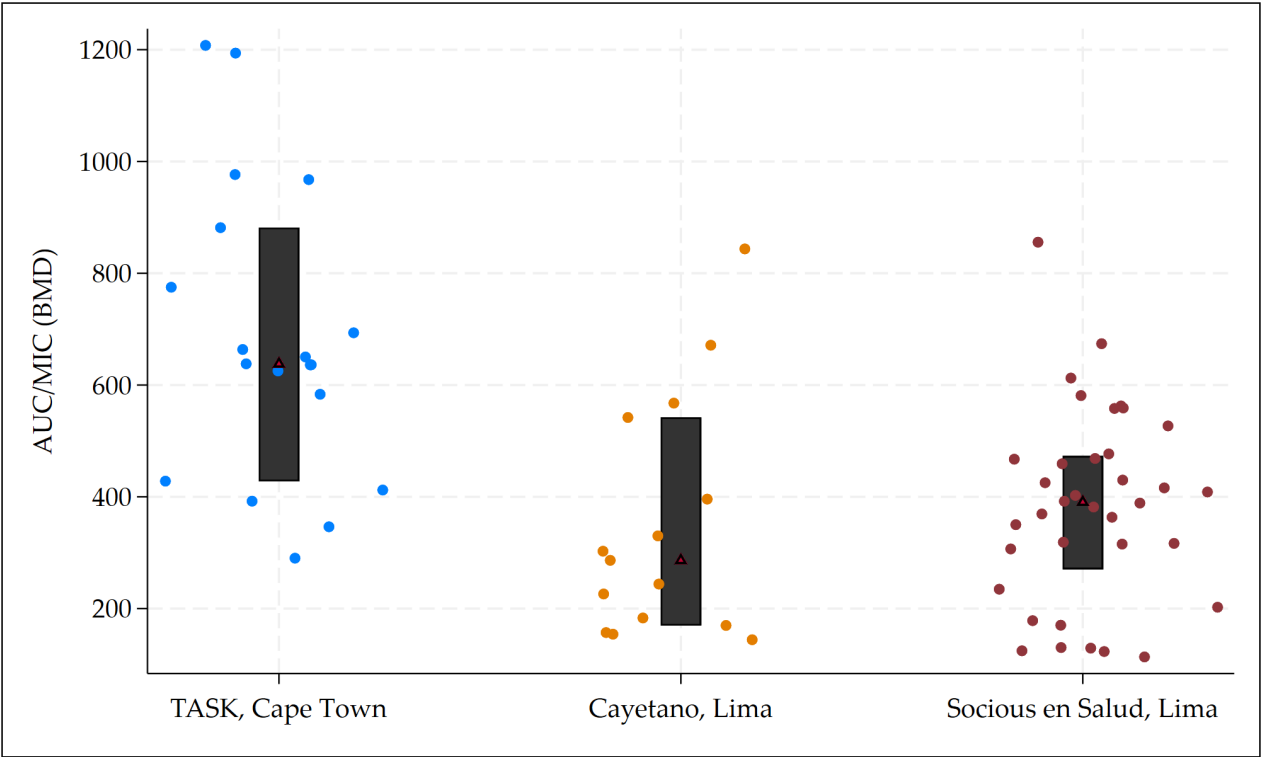


Table S7.1: Pharmacokinetic summary statistics by treatment arm

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
MIC (Agar Plate)					
Median (IQR)	0.25 (0.25, 0.38)	0.25 (0.25, 0.25)	0.25 (0.12, 0.25)	0.25 (0.25, 0.25)	0.25 (0.25, 0.25)
Min, Max	0.12, 0.50	0.12, 0.38	0.12, 0.38	0.12, 0.38	0.12, 0.50
Total non-missing	15	24	18	18	75
AUC					
Median (IQR)	187.04 (135.84, 212.62)	173.22 (157.10, 214.02)	250.61 (214.97, 312.99)	333.71 (279.49, 408.66)	230.99 (178.45, 318.05)
Min, Max	123.17, 305.86	117.36, 387.50	183.21, 603.87	202.44, 725.24	117.36, 725.24
Total non-missing	22	25	26	26	99
AU/MIC (Agar plate)					
Median (IQR)	572.76 (492.67, 967.55)	633.44 (605.45, 713.79)	918.28 (791.73, 1663.96)	1342.50 (1117.96, 1687.17)	855.05 (626.58, 1334.86)
Min, Max	332.06, 1569.00	469.44, 1550.01	624.77, 4830.99	744.16, 2250.71	332.06, 4830.99
Total non-missing	13	21	17	17	68
AU/MIC (Broth Micro Dilution)					
Median (IQR)	388.86 (129.24, 412.13)	316.09 (178.45, 381.82)	444.54 (369.33, 581.19)	612.50 (558.12, 674.03)	410.40 (290.27, 612.50)
Min, Max	113.51, 967.55	130.27, 775.00	183.21, 1207.75	202.44, 976.63	113.51, 1207.75
Total non-missing	13	22	18	17	70
MIC (Broth Micro Dilution)					
Median (IQR)	0.50 (0.50, 1.00)	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)
Min, Max	0.25, 2.00	0.50, 1.00	0.25, 1.00	0.50, 1.00	0.25, 2.00
Total non-missing	15	25	19	18	77
CMax					
Median (IQR)	10.79 (8.81, 13.06)	10.79 (8.94, 12.26)	14.84 (12.29, 17.12)	18.58 (15.18, 22.18)	13.47 (10.67, 17.59)
Min, Max	6.16, 16.46	6.38, 19.31	8.04, 24.96	13.20, 33.07	6.16, 33.07
Total non-missing	22	25	26	26	99

Table S7.2: Pharmacokinetic summary statistics by study site

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
MIC (Agar Plate)				
Median (IQR)	0.25 (0.19, 0.25)	0.25 (0.25, 0.25)	0.25 (0.25, 0.38)	0.25 (0.25, 0.25)
Min, Max	0.12, 0.25	0.12, 0.38	0.12, 0.50	0.12, 0.50
Total non-missing	22	16	37	75
AUC				
Median (IQR)	312.63 (228.85, 342.96)	169.87 (151.36, 235.37)	208.00 (175.09, 269.94)	230.99 (178.45, 318.05)
Min, Max	134.06, 725.24	121.97, 421.79	117.36, 427.82	117.36, 725.24
Total non-missing	41	21	37	99
AUC/MIC (Agar plate)				
Median (IQR)	1357.10 (1250.52, 1763.14)	732.85 (617.00, 975.75)	713.79 (521.09, 953.63)	855.05 (626.58, 1334.86)
Min, Max	692.88, 4830.99	572.76, 2167.73	332.06, 2250.71	332.06, 4830.99
Total non-missing	18	15	35	68
AUC/MIC (Broth Micro Dilution)				
Median (IQR)	638.00 (428.05, 881.57)	286.38 (169.87, 541.93)	390.49 (270.76, 472.70)	410.40 (290.27, 612.50)
Min, Max	290.27, 1207.75	144.31, 843.59	113.51, 855.64	113.51, 1207.75
Total non-missing	19	15	36	70
MIC (Broth Micro Dilution)				
Median (IQR)	0.50 (0.50, 0.50)	0.50 (0.50, 1.00)	0.50 (0.50, 1.00)	0.50 (0.50, 0.50)
Min, Max	0.25, 1.00	0.50, 1.00	0.50, 2.00	0.25, 2.00
Total non-missing	23	16	38	77
CMax				
Median (IQR)	15.20 (11.73, 19.00)	11.87 (8.94, 14.25)	13.06 (10.09, 15.18)	13.47 (10.67, 17.59)
Min, Max	7.61, 33.07	6.16, 22.51	6.38, 25.35	6.16, 33.07
Total non-missing	41	21	37	99

Table S7.3: Pharmacokinetic summary statistics by total daily dose received (mg).

	750mg	1000mg	1250mg	1500mg	Total
MIC (Agar Plate)					
Median (IQR)	0.25 (0.25, 0.29)	0.25 (0.25, 0.25)	0.25 (0.25, 0.25)	0.25 (0.19, 0.31)	0.25 (0.25, 0.25)
Min, Max	0.12, 0.50	0.12, 0.38	0.12, 0.38	0.12, 0.38	0.12, 0.50
Total non-missing	28	27	16	4	75
AUC					
Median (IQR)	175.09 (143.19, 212.62)	230.28 (187.76, 315.51)	318.14 (275.15, 404.10)	339.27 (280.20, 412.21)	230.99 (178.45, 318.05)
Min, Max	117.36, 312.63	130.27, 603.87	202.44, 725.24	235.37, 437.23	117.36, 725.24
Total non-missing	35	36	20	8	99
AUC/MIC (Agar plate)					
Median (IQR)	605.45 (492.67, 967.55)	850.23 (679.46, 1300.53)	1299.92 (934.72, 1634.65)	1526.88 (1043.33, 1980.99)	855.05 (626.58, 1334.86)
Min, Max	332.06, 1569.00	509.10, 4830.99	756.84, 2167.73	744.16, 2250.71	332.06, 4830.99
Total non-missing	23	27	14	4	68
AUC/MIC (Broth Micro Dilution)					
Median (IQR)	323.43 (202.51, 407.31)	405.93 (298.54, 608.65)	590.07 (467.36, 674.03)	616.96 (560.40, 763.44)	410.40 (290.27, 612.50)
Min, Max	113.51, 967.55	130.27, 1207.75	202.44, 976.63	558.12, 855.64	113.51, 1207.75
Total non-missing	24	28	14	4	70
MIC (Broth Micro Dilution)					
Median (IQR)	0.50 (0.50, 0.50)	0.50 (0.50, 1.00)	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)
Min, Max	0.25, 2.00	0.25, 1.00	0.50, 1.00	0.50, 0.50	0.25, 2.00
Total non-missing	29	28	16	4	77
CMax					
Median (IQR)	10.78 (8.81, 12.28)	13.72 (11.30, 16.47)	18.53 (15.76, 19.44)	19.14 (14.91, 23.71)	13.47 (10.67, 17.59)
Min, Max	6.16, 16.46	6.38, 24.96	13.20, 33.07	13.61, 25.63	6.16, 33.07
Total non-missing	35	36	20	8	99

3.8 Participant follow-up

Table S8.1: Final participant disposition by site (all participants enrolled).

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total enrolled	48	24	39	111
Total completed 24 weeks follow-up	31 (65%)	16 (67%)	32 (82%)	79 (71%)
Total not completed 24 weeks follow-up	17 (35%)	8 (33%)	7 (18%)	32 (29%)
Died during follow-up	1 (2%)	0	0	1 (1%)
Not completed follow-up to Week 24, with final visit				
Poor adherence	2 (4%)	0	1 (3%)	3 (3%)
AE	2 (4%)	1 (4%)	0	3 (3%)
Rifampin susceptible	1 (2%)	1 (4%)	0	2 (2%)
Concomitant fluoroquinolone	2 (4%)	0	0	2 (2%)
Withdrew consent	1 (2%)	0	1 (3%)	2 (2%)
Other	1 (2%)	0	0	1 (1%)
Treatment failure	0	1 (4%)	0	1 (1%)
XDR at baseline	1 (2%)	0	0	1 (1%)
In another trial	1 (2%)	0	0	1 (1%)
Moved away	0	0	1 (3%)	1 (1%)
Pregnancy	0	0	1 (3%)	1 (1%)
Not completed follow-up to Week 24, no final visit				
Lost to follow-up	2 (4%)	2 (8%)	0	4 (4%)
Withdrew consent	0	2 (8%)	2 (5%)	4 (4%)
Never started treatment	2 (4%)	1 (4%)	0	3 (3%)
Poor adherence	1 (2%)	0	1 (3%)	2 (2%)

Table S8.2: Final participant disposition by treatment arm (all participants enrolled).

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total enrolled					
	27	29	28	27	111
Total completed 24 weeks follow-up					
	17 (63%)	22 (76%)	20 (71%)	20 (74%)	79 (71%)
Total not completed 24 weeks follow-up					
	10 (37%)	7 (24%)	8 (29%)	7 (26%)	32 (29%)
Died during follow-up					
	0	0	1 (4%)	0	1 (1%)
Not completed follow-up to Week 24, with final visit					
Poor adherence	0	1 (3%)	2 (7%)	0	3 (3%)
AE	1 (4%)	1 (3%)	1 (4%)	0	3 (3%)
Concomitant fluoroquinolone	0	1 (3%)	0	1 (4%)	2 (2%)
Withdrew consent	0	0	1 (4%)	1 (4%)	2 (2%)
Rifampin susceptible	0	0	0	2 (7%)	2 (2%)
Pregnancy	1 (4%)	0	0	0	1 (1%)
In another trial	1 (4%)	0	0	0	1 (1%)
Moved away	0	1 (3%)	0	0	1 (1%)
XDR at baseline	0	0	1 (4%)	0	1 (1%)
Treatment failure	0	0	0	1 (4%)	1 (1%)
Other	0	0	1 (4%)	0	1 (1%)
Not completed follow-up to Week 24, no final visit					
Lost to follow-up	2 (7%)	0	1 (4%)	1 (4%)	4 (4%)
Withdrew consent	2 (7%)	2 (7%)	0	0	4 (4%)
Never started treatment	2 (7%)	1 (3%)	0	0	3 (3%)
Poor adherence	1 (4%)	0	0	1 (4%)	2 (2%)

Table S8.3: Final participant disposition by site (MITT analysis population).

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total enrolled	38	22	38	98
Total completed 24 weeks follow-up	27 (71%)	16 (73%)	31 (82%)	74 (76%)
Total not completed 24 weeks follow-up	11 (29%)	6 (27%)	7 (18%)	24 (24%)
Died during follow-up	1 (3%)	0	0	1 (1%)
Not completed follow-up to Week 24, with final visit				
AE	2 (5%)	1 (5%)	0	3 (3%)
Poor adherence	1 (3%)	0	1 (3%)	2 (2%)
Concomitant fluoroquinolone	2 (5%)	0	0	2 (2%)
Withdrew consent	1 (3%)	0	1 (3%)	2 (2%)
Pregnancy	0	0	1 (3%)	1 (1%)
Other	1 (3%)	0	0	1 (1%)
In another trial	1 (3%)	0	0	1 (1%)
Moved away	0	0	1 (3%)	1 (1%)
Treatment failure	0	1 (5%)	0	1 (1%)
Not completed follow-up to Week 24, no final visit				
Withdrew consent	0	2 (9%)	2 (5%)	4 (4%)
Lost to follow-up	1 (3%)	2 (9%)	0	3 (3%)
Poor adherence	1 (3%)	0	1 (3%)	2 (2%)

Table S8.4: Final participant disposition by treatment arm (MITT analysis population).

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total enrolled					
	27	29	28	27	111
Total completed 24 weeks follow-up					
	17 (63%)	22 (76%)	20 (71%)	20 (74%)	79 (71%)
Total not completed 24 weeks follow-up					
	10 (37%)	7 (24%)	8 (29%)	7 (26%)	32 (29%)
Died during follow-up					
	0	0	1 (4%)	0	1 (1%)
Not completed follow-up to Week 24, with final visit					
Poor adherence	0	1 (3%)	2 (7%)	0	3 (3%)
AE	1 (4%)	1 (3%)	1 (4%)	0	3 (3%)
Concomitant fluoroquinolone	0	1 (3%)	0	1 (4%)	2 (2%)
Withdrew consent	0	0	1 (4%)	1 (4%)	2 (2%)
Rifampin susceptible	0	0	0	2 (7%)	2 (2%)
Pregnancy	1 (4%)	0	0	0	1 (1%)
In another trial	1 (4%)	0	0	0	1 (1%)
Moved away	0	1 (3%)	0	0	1 (1%)
XDR at baseline	0	0	1 (4%)	0	1 (1%)
Treatment failure	0	0	0	1 (4%)	1 (1%)
Other	0	0	1 (4%)	0	1 (1%)
Not completed follow-up to Week 24, no final visit					
Lost to follow-up	2 (7%)	0	1 (4%)	1 (4%)	4 (4%)
Withdrew consent	2 (7%)	2 (7%)	0	0	4 (4%)
Never started treatment	2 (7%)	1 (3%)	0	0	3 (3%)
Poor adherence	1 (4%)	0	0	1 (4%)	2 (2%)

3.9 Occurrence of Adverse Events (AEs)

Table S9.1: Summary of AEs by treatment arm. Table shows numbers of participants and percentage of total.

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total participants	25	28	28	27	108
Any AE	24 (96.0%)	28 (100.0%)	28 (100.0%)	27 (100.0%)	107 (99.1%)
Any Grade 3-5 AE	4 (16.0%)	4 (14.3%)	7 (25.0%)	10 (37.0%)	25 (23.1%)
Any SAE	2 (8.0%)	1 (3.6%)	4 (14.3%)	3 (11.1%)	10 (9.3%)
Death	0	0	1 (3.6%)	0	1 (0.9%)

Table S9.2: Summary of AEs by total dose of levofloxacin received. Table shows numbers of participants and percentage of total.

	750mg	1000mg	1250mg	1500mg	Total
Total participants	41	37	22	8	108
Any AE	40 (97.6%)	37 (100.0%)	22 (100.0%)	8 (100.0%)	107 (99.1%)
Any Grade 3-5 AE	8 (19.5%)	7 (18.9%)	9 (40.9%)	1 (12.5%)	25 (23.1%)
Any SAE	3 (7.3%)	4 (10.8%)	2 (9.1%)	1 (12.5%)	10 (9.3%)
Death	0	1 (2.7%)	0	0	1 (0.9%)

Table S9.3: Summary of AEs by site. Table shows numbers of participants and percentage of total.

	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total participants	46	23	39	108
Any AE	46 (100.0%)	23 (100.0%)	38 (97.4%)	107 (99.1%)
Any Grade 3-5 AE	11 (23.9%)	2 (8.7%)	12 (30.8%)	25 (23.1%)
Any SAE	7 (15.2%)	2 (8.7%)	1 (2.6%)	10 (9.3%)
Death	1 (2.2%)	0	0	1 (0.9%)

Table S9.4: Summary of AEs by tertile of AUC. Table shows numbers of participants and percentage of total.

	Lower tertile	Middle tertile	Upper tertile	Total
Total participants	33	33	33	99
Any AE	33 (100.0%)	33 (100.0%)	33 (100.0%)	99 (100.0%)
Any Grade 3-5 AE	4 (12.1%)	8 (24.2%)	12 (36.4%)	24 (24.2%)
Any SAE	0	3 (9.1%)	6 (18.2%)	9 (9.1%)
Death	0	0	1 (3.0%)	1 (1.0%)

Table S9.5: Summary of AEs by tertile of CMax. Table shows numbers of participants and percentage of total.

	Lower tertile	Middle tertile	Upper tertile	Total
Total participants	33	33	33	99
Any AE	33 (100.0%)	33 (100.0%)	33 (100.0%)	99 (100.0%)
Any Grade 3-5 AE	5 (15.2%)	8 (24.2%)	11 (33.3%)	24 (24.2%)
Any SAE	1 (3.0%)	3 (9.1%)	5 (15.2%)	9 (9.1%)
Death	0	0	1 (3.0%)	1 (1.0%)

Table S9.6: Summary of AEs by tertile of baseline weight. Table shows numbers of participants and percentage of total.

	Lower tertile	Middle tertile	Upper tertile	Total
Total participants	37	37	34	108
Any AE	36 (97.3%)	37 (100.0%)	34 (100.0%)	107 (99.1%)
Any Grade 3-5 AE	14 (37.8%)	10 (27.0%)	1 (2.9%)	25 (23.1%)
Any SAE	6 (16.2%)	3 (8.1%)	1 (2.9%)	10 (9.3%)
Death	1 (2.7%)	0	0	1 (0.9%)

Table S9.7: Summary of AEs baseline weight (<60kg or ≥60kg) and randomized treatment arm. Table shows numbers of participants and percentage of total.

	Weight <60kg				Weight ≥60kg			
	11mg/kg (750mg)	14mg/kg (750mg)	17mg/kg (1000mg)	20mg/kg (1250mg)	11mg/kg (750mg)	14mg/kg (1000mg)	17mg/kg (1250mg)	20mg/kg (1500mg)
Total participants	16	16	25	19	9	12	3	8
Any AE	15 (93.8%)	16 (100.0%)	25 (100.0%)	19 (100.0%)	9 (100.0%)	12 (100.0%)	3 (100.0%)	8 (100.0%)
Any Grade 3-5 AE	4 (25.0%)	4 (25.0%)	7 (28.0%)	9 (47.4%)	0	0	0	1 (12.5%)
Any SAE	2 (12.5%)	1 (6.2%)	4 (16.0%)	2 (10.5%)	0	0	0	1 (12.5%)
Death	0	0	1 (4.0%)	0	0	0	0	0

Table S9.8: Listing of all adverse events reported for participant that died during the study. Only one participant, 32-33-008, died during the study on 9/May/2022.

Onset date	MedDRA SOC	MedDRA Preferred Term	Grade	SAE?
2015-03-21	Musculoskeletal And Connective Tissue Disorders	Buttock Pain Left	1	No
2015-03-22	Gastrointestinal Disorders	Intermittent Vomiting	1	No
2015-03-23	Ear And Labyrinth Disorders	Bilateral High Frequency Hearing Loss	1	No
2015-04-07	Investigations	Weight Loss	1	No
2015-04-13	Investigations	Weight Loss Grade 2	2	No
2015-04-13	Renal And Urinary Disorders	Renal Dysfunction	1	No
2015-04-21	Investigations	Weight Loss Grade 1	1	No
2015-04-25	Gastrointestinal Disorders	Diarrhoea	1	No
2015-05-07	Psychiatric Disorders	Delirium	3	Yes
2015-05-07	Infections And Infestations	Possible Tuberculosis Meningitis	3	No
2015-05-07	Immune System Disorders	Immune Reconstitution Inflammatory Syndrome	3	Yes
2015-05-07	Infections And Infestations	Disseminated Tuberculosis	3	No

Table S9.9: Listing of adverse events among participants not randomized

Participant	Site	Screening	MedDRA SOC	MedDRA Preferred Term	Grade	SAE?	Start	Stop	Action	Outcome
32-38-012	38	2015-05-21	Respiratory, thoracic and mediastinal disorders	Hemorrhage, pulmonary	2	Yes	2015-05-25	2015-06-10	Hospitalization or prolongation	Resolved

Table S9.10: Listing of adverse events among randomized participants not in ITT analysis population

Participant	Site	Screening	Randomization	MedDRA SOC	MedDRA Preferred Term	Grade	SAE?	Start	Stop	Action	Outcome
32-33-059	33	2016-03-23	2016-03-30	Gastrointestinal disorders	Constipation	1	No	2016-03-23	NA	None	Ongoing
32-33-059	33	2016-03-23	2016-03-30	Investigations	Decreasing creatine clearance	1	No	2016-03-29	NA	None	Ongoing
32-33-060	33	2016-03-23	2016-03-30	Respiratory, thoracic and mediastinal disorders	Sore throat (pharyngitis)	1	No	2016-03-27	NA	None	Unknown

Figure S9.1: Summary of AUC by weight-adjusted dose, highlighting grade 3-5 AEs and deaths.

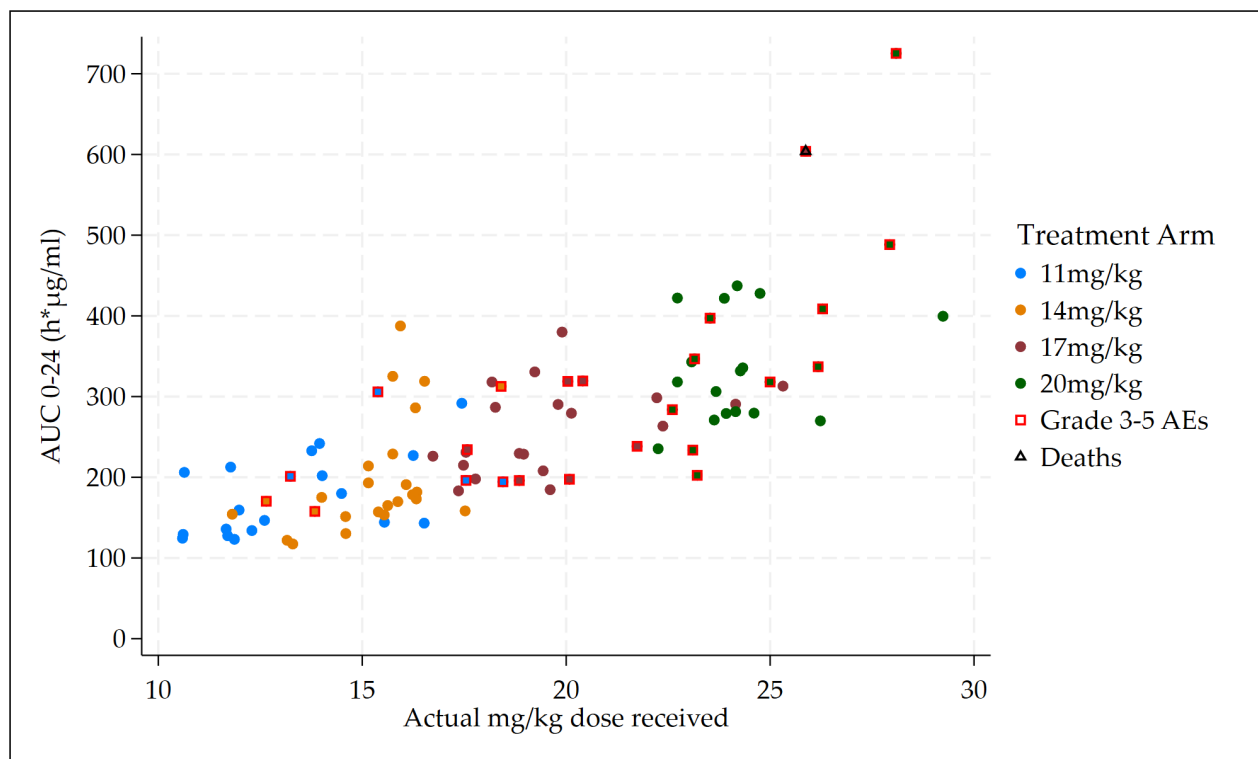
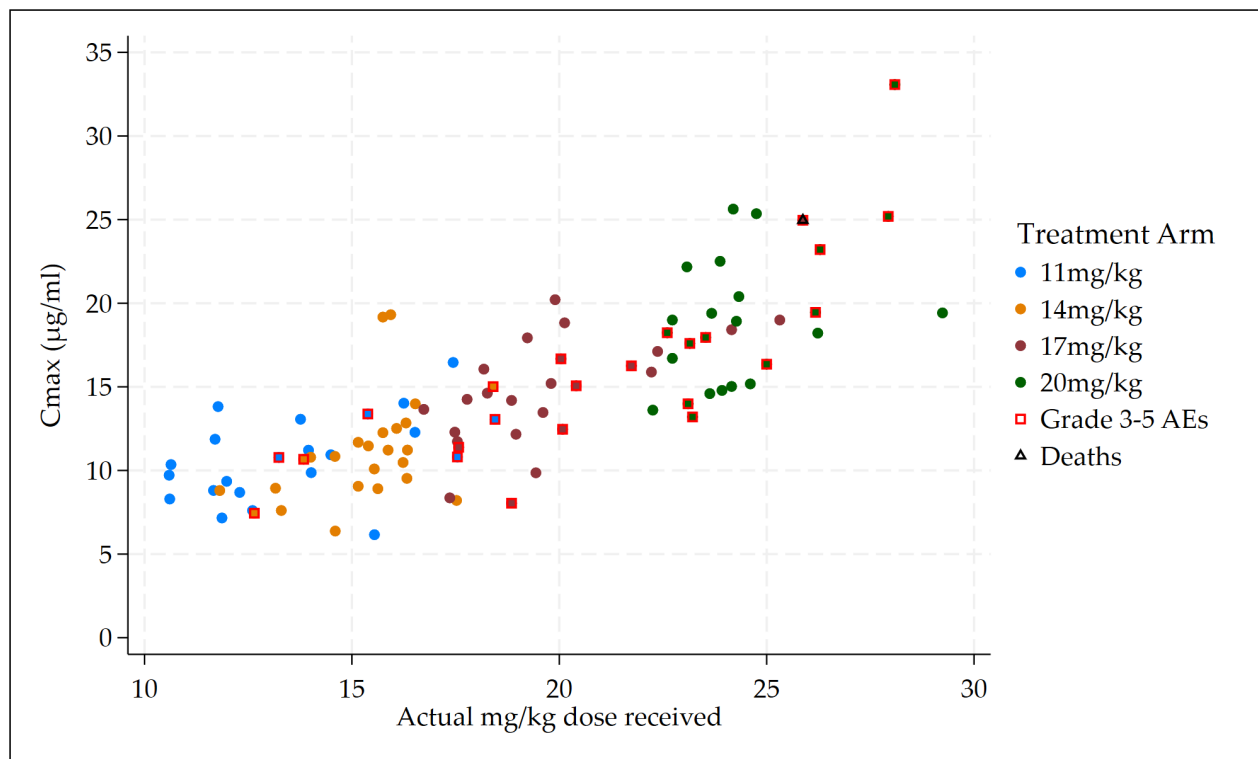


Figure S9.2: Summary of CMax by weight-adjusted dose, highlighting grade 3-5 AEs and deaths.



3.10 Summary of AEs and SAEs by MedDRA coding, severity, dose, AUC, and study site

3.10.1 Summary of AEs by MedDRA coding and study site

Table S10.1: Grade 1 AEs by System Organ Class (SOC) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Gastrointestinal disorders	43 (93.5%) [140]	23 (100.0%) [110]	37 (94.9%) [100]	103 (95.4%) [350]
Musculoskeletal and connective tissue disorders	39 (84.8%) [86]	21 (91.3%) [97]	36 (92.3%) [93]	96 (88.9%) [276]
Skin and subcutaneous tissue disorders	34 (73.9%) [88]	18 (78.3%) [88]	25 (64.1%) [55]	77 (71.3%) [231]
Nervous system disorders	33 (71.7%) [69]	20 (87.0%) [64]	30 (76.9%) [62]	83 (76.9%) [195]
Respiratory, thoracic and mediastinal disorders	20 (43.5%) [31]	15 (65.2%) [31]	12 (30.8%) [18]	47 (43.5%) [80]
General disorders and administration site conditions	33 (71.7%) [47]	7 (30.4%) [7]	18 (46.2%) [21]	58 (53.7%) [75]
Infections and infestations	15 (32.6%) [27]	10 (43.5%) [18]	16 (41.0%) [20]	41 (38.0%) [65]
Psychiatric disorders	13 (28.3%) [22]	10 (43.5%) [19]	8 (20.5%) [9]	31 (28.7%) [50]
Cardiac disorders	13 (28.3%) [17]	2 (8.7%) [2]	18 (46.2%) [25]	33 (30.6%) [44]
Ear and labyrinth disorders	10 (21.7%) [13]	4 (17.4%) [8]	13 (33.3%) [20]	27 (25.0%) [41]
Metabolism and nutrition disorders	14 (30.4%) [15]	9 (39.1%) [16]	4 (10.3%) [4]	27 (25.0%) [35]
Investigations	7 (15.2%) [9]	2 (8.7%) [3]	14 (35.9%) [19]	23 (21.3%) [31]
Blood and lymphatic system disorders	4 (8.7%) [4]	5 (21.7%) [10]	11 (28.2%) [12]	20 (18.5%) [26]
Eye disorders	8 (17.4%) [8]	0	7 (17.9%) [10]	15 (13.9%) [18]
Injury, poisoning and procedural complications	4 (8.7%) [5]	3 (13.0%) [5]	2 (5.1%) [2]	9 (8.3%) [12]
Renal and urinary disorders	2 (4.3%) [2]	3 (13.0%) [4]	5 (12.8%) [5]	10 (9.3%) [11]
Reproductive system and breast disorders	4 (8.7%) [5]	1 (4.3%) [2]	3 (7.7%) [3]	8 (7.4%) [10]
Endocrine disorders	4 (8.7%) [4]	0	1 (2.6%) [1]	5 (4.6%) [5]
Hepatobiliary disorders	2 (4.3%) [3]	1 (4.3%) [1]	1 (2.6%) [1]	4 (3.7%) [5]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (4.3%) [3]	1 (4.3%) [1]	1 (2.6%) [1]	4 (3.7%) [5]
Total Grade 1 AEs AEs	46 (100.0%) [598]	23 (100.0%) [486]	38 (97.4%) [481]	107 (99.1%) [1565]

Table S10.2: Grade 1 AEs by Preferred Term (PT) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Arthralgia	31 (67.4%) [42]	17 (73.9%) [39]	17 (43.6%) [23]	65 (60.2%) [104]
Musculoskeletal pain	11 (23.9%) [13]	10 (43.5%) [18]	34 (87.2%) [63]	55 (50.9%) [94]
Pruritus	22 (47.8%) [34]	15 (65.2%) [42]	13 (33.3%) [18]	50 (46.3%) [94]
Nausea	32 (69.6%) [36]	17 (73.9%) [22]	19 (48.7%) [21]	68 (63.0%) [79]
Vomiting	23 (50.0%) [30]	19 (82.6%) [31]	11 (28.2%) [14]	53 (49.1%) [75]
Dizziness	20 (43.5%) [25]	14 (60.9%) [19]	22 (56.4%) [28]	56 (51.9%) [72]
Abdominal pain	20 (43.5%) [23]	17 (73.9%) [30]	8 (20.5%) [9]	45 (41.7%) [62]
Rash	10 (21.7%) [10]	12 (52.2%) [30]	16 (41.0%) [20]	38 (35.2%) [60]
Headache	16 (34.8%) [18]	14 (60.9%) [19]	17 (43.6%) [18]	47 (43.5%) [55]
Diarrhoea	18 (39.1%) [24]	5 (21.7%) [12]	7 (17.9%) [12]	30 (27.8%) [48]
Pain in extremity	11 (23.9%) [13]	13 (56.5%) [25]	2 (5.1%) [2]	26 (24.1%) [40]
Insomnia	12 (26.1%) [18]	9 (39.1%) [14]	4 (10.3%) [5]	25 (23.1%) [37]
Hypoesthesia	4 (8.7%) [4]	7 (30.4%) [23]	6 (15.4%) [6]	17 (15.7%) [33]
Decreased appetite	13 (28.3%) [13]	9 (39.1%) [16]	3 (7.7%) [3]	25 (23.1%) [32]
Gastritis	1 (2.2%) [1]	0	21 (53.8%) [24]	22 (20.4%) [25]
Injection site pain	19 (41.3%) [24]	0	0	19 (17.6%) [24]
Bradycardia	1 (2.2%) [1]	0	17 (43.6%) [21]	18 (16.7%) [22]
Cough	4 (8.7%) [4]	10 (43.5%) [16]	1 (2.6%) [1]	15 (13.9%) [21]
Pyrexia	11 (23.9%) [12]	5 (21.7%) [5]	3 (7.7%) [3]	19 (17.6%) [20]
Constipation	9 (19.6%) [12]	2 (8.7%) [2]	4 (10.3%) [5]	15 (13.9%) [19]
Palpitations	12 (26.1%) [16]	2 (8.7%) [2]	1 (2.6%) [1]	15 (13.9%) [19]
Chest pain	1 (2.2%) [1]	2 (8.7%) [2]	13 (33.3%) [14]	16 (14.8%) [17]
Back pain	4 (8.7%) [5]	8 (34.8%) [8]	2 (5.1%) [2]	14 (13.0%) [15]
Hyperhidrosis	5 (10.9%) [5]	9 (39.1%) [9]	1 (2.6%) [1]	15 (13.9%) [15]
Nasopharyngitis	0	6 (26.1%) [8]	7 (17.9%) [7]	13 (12.0%) [15]
Pleuritic pain	12 (26.1%) [15]	0	0	12 (11.1%) [15]
Productive cough	2 (4.3%) [2]	7 (30.4%) [11]	2 (5.1%) [2]	11 (10.2%) [15]
Tinnitus	4 (8.7%) [4]	1 (4.3%) [1]	7 (17.9%) [9]	12 (11.1%) [14]
Haemoptysis	5 (10.9%) [5]	2 (8.7%) [2]	4 (10.3%) [6]	11 (10.2%) [13]
Ear pain	3 (6.5%) [3]	2 (8.7%) [4]	5 (12.8%) [5]	10 (9.3%) [12]
Night sweats	9 (19.6%) [11]	1 (4.3%) [1]	0	10 (9.3%) [12]
Dry skin	6 (13.0%) [10]	0	0	6 (5.6%) [10]
Neuropathy peripheral	10 (21.7%) [10]	0	0	10 (9.3%) [10]
Upper respiratory tract infection	7 (15.2%) [10]	0	0	7 (6.5%) [10]
Deafness	5 (10.9%) [5]	0	4 (10.3%) [4]	9 (8.3%) [9]
Eosinophilia	0	1 (4.3%) [1]	7 (17.9%) [8]	8 (7.4%) [9]
Abdominal pain upper	1 (2.2%) [1]	5 (21.7%) [5]	2 (5.1%) [2]	8 (7.4%) [8]
Acne	1 (2.2%) [1]	0	7 (17.9%) [7]	8 (7.4%) [8]
Paraesthesia	7 (15.2%) [8]	0	0	7 (6.5%) [8]
Anxiety	2 (4.3%) [2]	3 (13.0%) [5]	0	5 (4.6%) [7]

Table S10.2: Grade 1 AEs by Preferred Term (PT) and study site. (*continued*)

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Dyspepsia	2 (4.3%) [2]	3 (13.0%) [3]	2 (5.1%) [2]	7 (6.5%) [7]
Myalgia	4 (8.7%) [4]	2 (8.7%) [2]	1 (2.6%) [1]	7 (6.5%) [7]
Tremor	0	0	7 (17.9%) [7]	7 (6.5%) [7]
Vision blurred	0	0	5 (12.8%) [7]	5 (4.6%) [7]
Blood uric acid increased	0	0	6 (15.4%) [6]	6 (5.6%) [6]
Dysuria	1 (2.2%) [1]	3 (13.0%) [3]	2 (5.1%) [2]	6 (5.6%) [6]
Neutropenia	1 (2.2%) [1]	4 (17.4%) [5]	0	5 (4.6%) [6]
Gastroesophageal reflux disease	2 (4.3%) [2]	2 (8.7%) [2]	1 (2.6%) [1]	5 (4.6%) [5]
Hyperbilirubinaemia	2 (4.3%) [3]	1 (4.3%) [1]	1 (2.6%) [1]	4 (3.7%) [5]
Hypothyroidism	4 (8.7%) [4]	0	1 (2.6%) [1]	5 (4.6%) [5]
Leukopenia	0	3 (13.0%) [3]	2 (5.1%) [2]	5 (4.6%) [5]
Alanine aminotransferase increased	1 (2.2%) [1]	1 (4.3%) [1]	2 (5.1%) [2]	4 (3.7%) [4]
Contusion	0	2 (8.7%) [2]	2 (5.1%) [2]	4 (3.7%) [4]
Dermatitis acneiform	4 (8.7%) [4]	0	0	4 (3.7%) [4]
Fungal infection	0	2 (8.7%) [2]	2 (5.1%) [2]	4 (3.7%) [4]
Pharyngitis	0	0	4 (10.3%) [4]	4 (3.7%) [4]
Creatinine renal clearance decreased	1 (2.2%) [1]	0	2 (5.1%) [2]	3 (2.8%) [3]
Dry eye	2 (4.3%) [2]	0	1 (2.6%) [1]	3 (2.8%) [3]
Electrocardiogram qt prolonged	1 (2.2%) [1]	0	2 (5.1%) [2]	3 (2.8%) [3]
Fatigue	3 (6.5%) [3]	0	0	3 (2.8%) [3]
Haemorrhoids	2 (4.3%) [2]	0	1 (2.6%) [1]	3 (2.8%) [3]
Hypoacusis	0	2 (8.7%) [3]	0	2 (1.9%) [3]
Incision site pain	0	1 (4.3%) [3]	0	1 (0.9%) [3]
Joint swelling	2 (4.3%) [3]	0	0	2 (1.9%) [3]
Musculoskeletal chest pain	1 (2.2%) [1]	2 (8.7%) [2]	0	3 (2.8%) [3]
Odynophagia	1 (2.2%) [1]	2 (8.7%) [2]	0	3 (2.8%) [3]
Oedema peripheral	1 (2.2%) [1]	0	2 (5.1%) [2]	3 (2.8%) [3]
Oropharyngeal pain	0	1 (4.3%) [1]	2 (5.1%) [2]	3 (2.8%) [3]
Pollakiuria	0	1 (4.3%) [1]	2 (5.1%) [2]	3 (2.8%) [3]
Pruritus generalised	2 (4.3%) [2]	1 (4.3%) [1]	0	3 (2.8%) [3]
Rash pruritic	1 (2.2%) [1]	1 (4.3%) [2]	0	2 (1.9%) [3]
Rash pustular	1 (2.2%) [1]	2 (8.7%) [2]	0	3 (2.8%) [3]
Somnolence	0	1 (4.3%) [1]	2 (5.1%) [2]	3 (2.8%) [3]
Transaminases increased	0	1 (4.3%) [1]	2 (5.1%) [2]	3 (2.8%) [3]
Vaginal discharge	2 (4.3%) [2]	0	1 (2.6%) [1]	3 (2.8%) [3]
Vulvovaginitis	0	1 (4.3%) [2]	1 (2.6%) [1]	2 (1.9%) [3]
Weight decreased	2 (4.3%) [3]	0	0	2 (1.9%) [3]
Anaemia	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Blood bilirubin increased	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Body tinea	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Breast pain	0	1 (4.3%) [1]	1 (2.6%) [1]	2 (1.9%) [2]

Table S10.2: Grade 1 AEs by Preferred Term (PT) and study site. (*continued*)

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Conjunctivitis allergic	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Dysphagia	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Eye pruritus	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Flatulence	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Gastric disorder	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Gastroenteritis	1 (2.2%) [1]	0	1 (2.6%) [1]	2 (1.9%) [2]
Gynaecomastia	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Joint injury	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Lower respiratory tract infection	1 (2.2%) [2]	0	0	1 (0.9%) [2]
Oral candidiasis	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Otitis externa	1 (2.2%) [1]	1 (4.3%) [1]	0	2 (1.9%) [2]
Rash maculo-papular	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Rash papular	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Rhinitis	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Rhinorrhoea	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Skin exfoliation	0	1 (4.3%) [2]	0	1 (0.9%) [2]
Skin hyperpigmentation	1 (2.2%) [1]	1 (4.3%) [1]	0	2 (1.9%) [2]
Skin lesion	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Skin papilloma	1 (2.2%) [1]	0	1 (2.6%) [1]	2 (1.9%) [2]
Syncope	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Throat irritation	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Toothache	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Vessel puncture site bruise	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Abdominal discomfort	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Abdominal distension	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Abdominal pain lower	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Acariasis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Acarodermatitis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Adjustment disorder	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Anorectal disorder	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Arrhythmia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Aspartate aminotransferase increased	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Asthenia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Blister	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Blood folate decreased	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Blood glucose increased	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Breath sounds abnormal	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Bronchitis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Bronchospasm	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Chronic obstructive pulmonary disease	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Conjunctivitis bacterial	0	0	1 (2.6%) [1]	1 (0.9%) [1]

Table S10.2: Grade 1 AEs by Preferred Term (PT) and study site. (*continued*)

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Costochondritis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Deafness neurosensory	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Depression	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Diabetes mellitus	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Diplopia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Dizziness postural	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Dyspnoea	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Ear discomfort	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Eosinophil count increased	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Erectile dysfunction	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Excoriation	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Eye swelling	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Fall	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Fibroadenoma of breast	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Gestational trophoblastic tumour	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Grip strength decreased	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Heat rash	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Herpes simplex	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hyperkeratosis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Hypoaesthesia oral	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Hypoalbuminaemia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Injection site haematoma	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Joint effusion	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Laceration	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Leukocytosis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Libido increased	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Limb discomfort	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Lip swelling	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Lymphadenopathy	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Lymphopenia	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Muscle atrophy	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Musculoskeletal discomfort	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Myopia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Nasal congestion	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Nasal discomfort	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Neck pain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Neuritis	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Neurodermatitis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Nightmare	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Oedema	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Oral disorder	1 (2.2%) [1]	0	0	1 (0.9%) [1]

Table S10.2: Grade 1 AEs by Preferred Term (PT) and study site. (*continued*)

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Oral herpes	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Otitis media	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Ototoxicity	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Pain	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Papule	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Paronychia	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Pelvic pain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Peripheral sensory neuropathy	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Personality disorder	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Pharyngitis bacterial	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Pharyngotonsillitis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Photosensitivity reaction	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Pityriasis alba	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Polyarthrititis	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Polycythaemia vera	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Polydipsia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Polyuria	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Post inflammatory pigmentation change	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Presyncope	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Proctalgia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Pruritus genital	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Psychotic disorder	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Rales	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Rash generalised	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Renal impairment	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Rhinitis allergic	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Sensory loss	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Sinus tachycardia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Skin hypopigmentation	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Sneezing	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Subcutaneous abscess	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Synovial cyst	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Tachycardia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Tendon pain	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Tenosynovitis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Thrombocytopenia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Tooth abscess	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Upper-airway cough syndrome	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Urinary tract infection	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Urine analysis abnormal	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Urticaria	0	0	1 (2.6%) [1]	1 (0.9%) [1]

Table S10.2: Grade 1 AEs by Preferred Term (PT) and study site. (*continued*)

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Vessel puncture site pain	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Viral pharyngitis	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Visual acuity reduced	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Xeroderma	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Xerosis	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Total Grade 1 AEs AEs	46 (100.0%) [598]	23 (100.0%) [486]	38 (97.4%) [481]	107 (99.1%) [1565]

Table S10.3: Grade 2 AEs by System Organ Class (SOC) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Musculoskeletal and connective tissue disorders	17 (37.0%) [23]	2 (8.7%) [4]	15 (38.5%) [20]	34 (31.5%) [47]
Gastrointestinal disorders	8 (17.4%) [9]	3 (13.0%) [4]	15 (38.5%) [16]	26 (24.1%) [29]
Psychiatric disorders	7 (15.2%) [10]	3 (13.0%) [6]	8 (20.5%) [8]	18 (16.7%) [24]
Nervous system disorders	5 (10.9%) [5]	2 (8.7%) [5]	8 (20.5%) [10]	15 (13.9%) [20]
Skin and subcutaneous tissue disorders	2 (4.3%) [2]	3 (13.0%) [10]	3 (7.7%) [6]	8 (7.4%) [18]
General disorders and administration site conditions	11 (23.9%) [13]	0	3 (7.7%) [3]	14 (13.0%) [16]
Blood and lymphatic system disorders	5 (10.9%) [5]	1 (4.3%) [1]	3 (7.7%) [4]	9 (8.3%) [10]
Ear and labyrinth disorders	5 (10.9%) [5]	0	3 (7.7%) [3]	8 (7.4%) [8]
Respiratory, thoracic and mediastinal disorders	3 (6.5%) [4]	3 (13.0%) [3]	0	6 (5.6%) [7]
Hepatobiliary disorders	0	1 (4.3%) [2]	2 (5.1%) [2]	3 (2.8%) [4]
Infections and infestations	3 (6.5%) [3]	1 (4.3%) [1]	0	4 (3.7%) [4]
Metabolism and nutrition disorders	2 (4.3%) [4]	0	0	2 (1.9%) [4]
Injury, poisoning and procedural complications	0	0	3 (7.7%) [3]	3 (2.8%) [3]
Investigations	3 (6.5%) [3]	0	0	3 (2.8%) [3]
Reproductive system and breast disorders	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Cardiac disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Endocrine disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Immune system disorders	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Social circumstances	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Vascular disorders	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Total Grade 2 AEs AEs	36 (78.3%) [91]	14 (60.9%) [37]	29 (74.4%) [76]	79 (73.1%) [204]

Table S10.4: Grade 2 AEs by Preferred Term (PT) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Arthralgia	14 (30.4%) [14]	0	10 (25.6%) [10]	24 (22.2%) [24]
Musculoskeletal pain	3 (6.5%) [3]	1 (4.3%) [1]	9 (23.1%) [10]	13 (12.0%) [14]
Injection site pain	9 (19.6%) [9]	0	0	9 (8.3%) [9]
Insomnia	4 (8.7%) [4]	2 (8.7%) [3]	1 (2.6%) [1]	7 (6.5%) [8]
Pruritus	0	1 (4.3%) [4]	3 (7.7%) [3]	4 (3.7%) [7]
Gastritis	0	0	5 (12.8%) [6]	5 (4.6%) [6]
Headache	0	1 (4.3%) [1]	5 (12.8%) [5]	6 (5.6%) [6]
Hypoaesthesia	1 (2.2%) [1]	1 (4.3%) [4]	1 (2.6%) [1]	3 (2.8%) [6]
Pain in extremity	2 (4.3%) [3]	2 (8.7%) [3]	0	4 (3.7%) [6]
Eosinophilia	0	1 (4.3%) [1]	3 (7.7%) [4]	4 (3.7%) [5]
Rash	0	1 (4.3%) [5]	0	1 (0.9%) [5]
Vomiting	3 (6.5%) [3]	0	2 (5.1%) [2]	5 (4.6%) [5]
Abdominal pain	1 (2.2%) [1]	2 (8.7%) [2]	1 (2.6%) [1]	4 (3.7%) [4]
Anaemia	4 (8.7%) [4]	0	0	4 (3.7%) [4]
Deafness	3 (6.5%) [3]	0	1 (2.6%) [1]	4 (3.7%) [4]
Nausea	2 (4.3%) [2]	1 (4.3%) [1]	1 (2.6%) [1]	4 (3.7%) [4]
Depression	0	1 (4.3%) [1]	2 (5.1%) [2]	3 (2.8%) [3]
Dizziness	0	0	3 (7.7%) [3]	3 (2.8%) [3]
Hyperbilirubinaemia	0	1 (4.3%) [1]	2 (5.1%) [2]	3 (2.8%) [3]
Major depression	0	1 (4.3%) [1]	2 (5.1%) [2]	3 (2.8%) [3]
Neuropathy peripheral	2 (4.3%) [2]	0	1 (2.6%) [1]	3 (2.8%) [3]
Oedema peripheral	1 (2.2%) [3]	0	0	1 (0.9%) [3]
Psychotic disorder	3 (6.5%) [3]	0	0	3 (2.8%) [3]
Anxiety	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Chest pain	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Dermatitis acneiform	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Dyspepsia	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Hypokalaemia	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Productive cough	0	2 (8.7%) [2]	0	2 (1.9%) [2]
Tinnitus	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Urticaria	0	0	1 (2.6%) [2]	1 (0.9%) [2]
Weight decreased	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Abdominal pain upper	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Acne	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Affect lability	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Arthritis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Asthenia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Bicytopenia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Breast pain	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Bronchospasm	1 (2.2%) [1]	0	0	1 (0.9%) [1]

Table S10.4: Grade 2 AEs by Preferred Term (PT) and study site. (*continued*)

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Bulimia nervosa	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Chronic obstructive pulmonary disease	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Constipation	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Contusion	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Dental caries	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Dental discomfort	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Diarrhoea	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Dyspnoea exertional	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Electrocardiogram qt prolonged	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Erectile dysfunction	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Gastroenteritis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Gastrooesophageal reflux disease	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Gingival pain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Haemoptysis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hallucinations, mixed	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hearing impaired	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Herpes simplex	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Herpes virus infection	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hyperhidrosis	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Hypersensitivity	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Hypoacusis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hypomagnesaemia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hyponatraemia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hypothyroidism	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Influenza like illness	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Jaundice	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Joint instability	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Ligament sprain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Limb injury	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Mood altered	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Myalgia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Nightmare	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Pallor	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Palpitations	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Physical assault	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Pneumothorax	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Post herpetic neuralgia	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Presyncope	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Psoas abscess	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Toothache	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Total Grade 2 AEs AEs	36 (78.3%) [91]	14 (60.9%) [37]	29 (74.4%) [76]	79 (73.1%) [204]

Table S10.5: Grade 3 AEs by System Organ Class (SOC) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Investigations	2 (4.3%) [2]	0	4 (10.3%) [4]	6 (5.6%) [6]
Ear and labyrinth disorders	2 (4.3%) [2]	0	2 (5.1%) [2]	4 (3.7%) [4]
Nervous system disorders	2 (4.3%) [2]	0	1 (2.6%) [1]	3 (2.8%) [3]
Respiratory, thoracic and mediastinal disorders	2 (4.3%) [2]	1 (4.3%) [1]	0	3 (2.8%) [3]
Blood and lymphatic system disorders	0	0	2 (5.1%) [2]	2 (1.9%) [2]
General disorders and administration site conditions	1 (2.2%) [1]	0	1 (2.6%) [1]	2 (1.9%) [2]
Hepatobiliary disorders	1 (2.2%) [1]	1 (4.3%) [1]	0	2 (1.9%) [2]
Infections and infestations	1 (2.2%) [2]	0	0	1 (0.9%) [2]
Metabolism and nutrition disorders	1 (2.2%) [1]	0	1 (2.6%) [1]	2 (1.9%) [2]
Musculoskeletal and connective tissue disorders	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Psychiatric disorders	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Gastrointestinal disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Immune system disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Total Grade 3 AEs AEs	11 (23.9%) [17]	2 (8.7%) [2]	9 (23.1%) [13]	22 (20.4%) [32]

Table S10.6: Grade 3 AEs by Preferred Term (PT) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Blood uric acid increased	0	0	4 (10.3%) [4]	4 (3.7%) [4]
Bronchospasm	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Deafness	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Eosinophilia	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Hepatic function abnormal	1 (2.2%) [1]	1 (4.3%) [1]	0	2 (1.9%) [2]
Acute psychosis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Alanine aminotransferase increased	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Arthralgia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Chest pain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Decreased appetite	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Delirium	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Disseminated tuberculosis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Dizziness	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Electrocardiogram qt prolonged	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hyperuricaemia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Immune reconstitution inflammatory syndrome	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Ischaemic stroke	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Meningitis tuberculous	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Musculoskeletal pain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Nausea	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Neuropathy peripheral	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Oedema peripheral	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Ototoxicity	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Pulmonary fistula	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Vertigo	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Total Grade 3 AEs AEs	11 (23.9%) [17]	2 (8.7%) [2]	9 (23.1%) [13]	22 (20.4%) [32]

Table S10.7: Grade 4 AEs by System Organ Class (SOC) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Investigations	0	0	3 (7.7%) [3]	3 (2.8%) [3]
Total Grade 4 AEs AEs	0	0	3 (7.7%) [3]	3 (2.8%) [3]

Table S10.8: Grade 4 AEs by Preferred Term (PT) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Blood uric acid increased	0	0	3 (7.7%) [3]	3 (2.8%) [3]
Total Grade 4 AEs AEs	0	0	3 (7.7%) [3]	3 (2.8%) [3]

Table S10.9: Grade 3-5 AEs by System Organ Class (SOC) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Investigations	2 (4.3%) [2]	0	7 (17.9%) [7]	9 (8.3%) [9]
Ear and labyrinth disorders	2 (4.3%) [2]	0	2 (5.1%) [2]	4 (3.7%) [4]
Nervous system disorders	2 (4.3%) [2]	0	1 (2.6%) [1]	3 (2.8%) [3]
Respiratory, thoracic and mediastinal disorders	2 (4.3%) [2]	1 (4.3%) [1]	0	3 (2.8%) [3]
Blood and lymphatic system disorders	0	0	2 (5.1%) [2]	2 (1.9%) [2]
General disorders and administration site conditions	1 (2.2%) [1]	0	1 (2.6%) [1]	2 (1.9%) [2]
Hepatobiliary disorders	1 (2.2%) [1]	1 (4.3%) [1]	0	2 (1.9%) [2]
Infections and infestations	1 (2.2%) [2]	0	0	1 (0.9%) [2]
Metabolism and nutrition disorders	1 (2.2%) [1]	0	1 (2.6%) [1]	2 (1.9%) [2]
Musculoskeletal and connective tissue disorders	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Psychiatric disorders	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Gastrointestinal disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Immune system disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Total Grade 3-5 AEs AEs	11 (23.9%) [17]	2 (8.7%) [2]	12 (30.8%) [16]	25 (23.1%) [35]

Table S10.10: Grade 3-5 AEs by Preferred Term (PT) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Blood uric acid increased	0	0	7 (17.9%) [7]	7 (6.5%) [7]
Bronchospasm	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Deafness	2 (4.3%) [2]	0	0	2 (1.9%) [2]
Eosinophilia	0	0	2 (5.1%) [2]	2 (1.9%) [2]
Hepatic function abnormal	1 (2.2%) [1]	1 (4.3%) [1]	0	2 (1.9%) [2]
Acute psychosis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Alanine aminotransferase increased	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Arthralgia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Chest pain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Decreased appetite	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Delirium	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Disseminated tuberculosis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Dizziness	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Electrocardiogram qt prolonged	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hyperuricaemia	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Immune reconstitution inflammatory syndrome	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Ischaemic stroke	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Meningitis tuberculous	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Musculoskeletal pain	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Nausea	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Neuropathy peripheral	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Oedema peripheral	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Ototoxicity	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Pulmonary fistula	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Vertigo	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Total Grade 3-5 AEs AEs	11 (23.9%) [17]	2 (8.7%) [2]	12 (30.8%) [16]	25 (23.1%) [35]

Table S10.11: SAEs by System Organ Class (SOC) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Respiratory, thoracic and mediastinal disorders	2 (4.3%) [2]	1 (4.3%) [2]	0	3 (2.8%) [4]
Psychiatric disorders	2 (4.3%) [2]	0	0	2 (1.9%) [2]
General disorders and administration site conditions	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hepatobiliary disorders	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Immune system disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Infections and infestations	1 (2.2%) [1]	0	0	1 (0.9%) [1]

Table S10.11: SAEs by System Organ Class (SOC) and study site. (*continued*)

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Investigations	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Musculoskeletal and connective tissue disorders	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Nervous system disorders	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Total SAEs AEs	7 (15.2%) [9]	2 (8.7%) [3]	1 (2.6%) [1]	10 (9.3%) [13]

Table S10.12: SAEs by Preferred Term (PT) and study site.

N participants (%) [N events]	TASK, Cape Town	Cayetano, Lima	Socios en Salud, Lima	Total
Total in ITT analysis	46	23	39	108
Acute psychosis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Bronchospasm	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Chronic obstructive pulmonary disease	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Delirium	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Gastroenteritis	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Hepatic function abnormal	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Immune reconstitution inflammatory syndrome	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Ischaemic stroke	0	0	1 (2.6%) [1]	1 (0.9%) [1]
Oedema peripheral	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Pain in extremity	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Pneumothorax	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Pulmonary fistula	0	1 (4.3%) [1]	0	1 (0.9%) [1]
Weight decreased	1 (2.2%) [1]	0	0	1 (0.9%) [1]
Total SAEs AEs	7 (15.2%) [9]	2 (8.7%) [3]	1 (2.6%) [1]	10 (9.3%) [13]

3.10.2 Summary of AEs by MedDRA coding and allocated dose

Table S10.13: Grade 1 AEs by System Organ Class (SOC) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Gastrointestinal disorders	24 (96.0%) [80]	25 (89.3%) [83]	27 (96.4%) [82]	27 (100.0%) [105]	103 (95.4%) [350]
Musculoskeletal and connective tissue disorders	22 (88.0%) [64]	24 (85.7%) [59]	24 (85.7%) [71]	26 (96.3%) [82]	96 (88.9%) [276]
Skin and subcutaneous tissue disorders	13 (52.0%) [54]	17 (60.7%) [46]	23 (82.1%) [72]	24 (88.9%) [59]	77 (71.3%) [231]
Nervous system disorders	18 (72.0%) [54]	20 (71.4%) [40]	21 (75.0%) [40]	24 (88.9%) [61]	83 (76.9%) [195]
Respiratory, thoracic and mediastinal disorders	12 (48.0%) [19]	15 (53.6%) [27]	12 (42.9%) [19]	8 (29.6%) [15]	47 (43.5%) [80]
General disorders and administration site conditions	11 (44.0%) [17]	17 (60.7%) [22]	12 (42.9%) [13]	18 (66.7%) [23]	58 (53.7%) [75]
Infections and infestations	6 (24.0%) [9]	14 (50.0%) [29]	13 (46.4%) [19]	8 (29.6%) [8]	41 (38.0%) [65]
Psychiatric disorders	10 (40.0%) [14]	6 (21.4%) [6]	8 (28.6%) [12]	7 (25.9%) [18]	31 (28.7%) [50]
Cardiac disorders	6 (24.0%) [10]	9 (32.1%) [13]	6 (21.4%) [9]	12 (44.4%) [12]	33 (30.6%) [44]
Ear and labyrinth disorders	5 (20.0%) [9]	7 (25.0%) [11]	10 (35.7%) [12]	5 (18.5%) [9]	27 (25.0%) [41]
Metabolism and nutrition disorders	7 (28.0%) [10]	4 (14.3%) [4]	4 (14.3%) [5]	12 (44.4%) [16]	27 (25.0%) [35]
Investigations	3 (12.0%) [4]	9 (32.1%) [14]	6 (21.4%) [8]	5 (18.5%) [5]	23 (21.3%) [31]
Blood and lymphatic system disorders	8 (32.0%) [13]	4 (14.3%) [4]	6 (21.4%) [7]	2 (7.4%) [2]	20 (18.5%) [26]
Eye disorders	3 (12.0%) [3]	2 (7.1%) [3]	4 (14.3%) [6]	6 (22.2%) [6]	15 (13.9%) [18]
Injury, poisoning and procedural complications	3 (12.0%) [3]	3 (10.7%) [4]	2 (7.1%) [2]	1 (3.7%) [3]	9 (8.3%) [12]
Renal and urinary disorders	2 (8.0%) [3]	3 (10.7%) [3]	4 (14.3%) [4]	1 (3.7%) [1]	10 (9.3%) [11]
Reproductive system and breast disorders	2 (8.0%) [4]	2 (7.1%) [2]	0	4 (14.8%) [4]	8 (7.4%) [10]
Endocrine disorders	2 (8.0%) [2]	0	0	3 (11.1%) [3]	5 (4.6%) [5]
Hepatobiliary disorders	1 (4.0%) [1]	2 (7.1%) [3]	0	1 (3.7%) [1]	4 (3.7%) [5]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (8.0%) [2]	0	1 (3.6%) [1]	1 (3.7%) [2]	4 (3.7%) [5]
Total Grade 1 AEs AEs	24 (96.0%) [375]	28 (100.0%) [373]	28 (100.0%) [382]	27 (100.0%) [435]	107 (99.1%) [1565]

Table S10.14: Grade 1 AEs by Preferred Term (PT) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Arthralgia	14 (56.0%) [21]	17 (60.7%) [26]	16 (57.1%) [26]	18 (66.7%) [31]	65 (60.2%) [104]
Musculoskeletal pain	13 (52.0%) [21]	12 (42.9%) [22]	13 (46.4%) [27]	17 (63.0%) [24]	55 (50.9%) [94]
Pruritus	7 (28.0%) [18]	12 (42.9%) [18]	18 (64.3%) [35]	13 (48.1%) [23]	50 (46.3%) [94]
Nausea	16 (64.0%) [18]	14 (50.0%) [17]	19 (67.9%) [22]	19 (70.4%) [22]	68 (63.0%) [79]
Vomiting	12 (48.0%) [16]	14 (50.0%) [18]	14 (50.0%) [18]	13 (48.1%) [23]	53 (49.1%) [75]
Dizziness	14 (56.0%) [18]	13 (46.4%) [16]	13 (46.4%) [15]	16 (59.3%) [23]	56 (51.9%) [72]
Abdominal pain	11 (44.0%) [14]	14 (50.0%) [18]	7 (25.0%) [8]	13 (48.1%) [22]	45 (41.7%) [62]
Rash	7 (28.0%) [19]	9 (32.1%) [11]	10 (35.7%) [15]	12 (44.4%) [15]	38 (35.2%) [60]
Headache	10 (40.0%) [13]	13 (46.4%) [15]	13 (46.4%) [13]	11 (40.7%) [14]	47 (43.5%) [55]
Diarrhoea	6 (24.0%) [12]	6 (21.4%) [8]	8 (28.6%) [12]	10 (37.0%) [16]	30 (27.8%) [48]
Pain in extremity	6 (24.0%) [12]	5 (17.9%) [5]	7 (25.0%) [10]	8 (29.6%) [13]	26 (24.1%) [40]
Insomnia	8 (32.0%) [11]	5 (17.9%) [5]	6 (21.4%) [10]	6 (22.2%) [11]	25 (23.1%) [37]
Hypoaesthesia	6 (24.0%) [14]	2 (7.1%) [2]	2 (7.1%) [3]	7 (25.9%) [14]	17 (15.7%) [33]
Decreased appetite	5 (20.0%) [8]	4 (14.3%) [4]	4 (14.3%) [4]	12 (44.4%) [16]	25 (23.1%) [32]
Gastritis	5 (20.0%) [5]	5 (17.9%) [6]	5 (17.9%) [6]	7 (25.9%) [8]	22 (20.4%) [25]
Injection site pain	7 (28.0%) [9]	5 (17.9%) [5]	2 (7.1%) [3]	5 (18.5%) [7]	19 (17.6%) [24]
Bradycardia	4 (16.0%) [7]	4 (14.3%) [4]	4 (14.3%) [5]	6 (22.2%) [6]	18 (16.7%) [22]
Cough	4 (16.0%) [8]	5 (17.9%) [5]	4 (14.3%) [5]	2 (7.4%) [3]	15 (13.9%) [21]
Pyrexia	5 (20.0%) [5]	7 (25.0%) [8]	3 (10.7%) [3]	4 (14.8%) [4]	19 (17.6%) [20]
Constipation	4 (16.0%) [5]	6 (21.4%) [7]	2 (7.1%) [3]	3 (11.1%) [4]	15 (13.9%) [19]
Palpitations	2 (8.0%) [3]	6 (21.4%) [8]	2 (7.1%) [3]	5 (18.5%) [5]	15 (13.9%) [19]
Chest pain	2 (8.0%) [2]	6 (21.4%) [6]	4 (14.3%) [4]	4 (14.8%) [5]	16 (14.8%) [17]
Back pain	3 (12.0%) [3]	4 (14.3%) [4]	4 (14.3%) [5]	3 (11.1%) [3]	14 (13.0%) [15]
Hyperhidrosis	4 (16.0%) [4]	4 (14.3%) [4]	3 (10.7%) [3]	4 (14.8%) [4]	15 (13.9%) [15]
Nasopharyngitis	5 (20.0%) [5]	4 (14.3%) [6]	1 (3.6%) [1]	3 (11.1%) [3]	13 (12.0%) [15]
Pleuritic pain	5 (20.0%) [5]	4 (14.3%) [7]	2 (7.1%) [2]	1 (3.7%) [1]	12 (11.1%) [15]
Productive cough	2 (8.0%) [3]	4 (14.3%) [4]	2 (7.1%) [3]	3 (11.1%) [5]	11 (10.2%) [15]
Tinnitus	2 (8.0%) [2]	1 (3.6%) [3]	5 (17.9%) [5]	4 (14.8%) [4]	12 (11.1%) [14]
Haemoptysis	1 (4.0%) [1]	4 (14.3%) [6]	5 (17.9%) [5]	1 (3.7%) [1]	11 (10.2%) [13]
Ear pain	1 (4.0%) [2]	3 (10.7%) [4]	3 (10.7%) [3]	3 (11.1%) [3]	10 (9.3%) [12]
Night sweats	3 (12.0%) [4]	2 (7.1%) [2]	2 (7.1%) [2]	3 (11.1%) [4]	10 (9.3%) [12]
Dry skin	1 (4.0%) [1]	0	2 (7.1%) [6]	3 (11.1%) [3]	6 (5.6%) [10]
Neuropathy peripheral	1 (4.0%) [1]	2 (7.1%) [2]	4 (14.3%) [4]	3 (11.1%) [3]	10 (9.3%) [10]
Upper respiratory tract infection	0	3 (10.7%) [5]	2 (7.1%) [3]	2 (7.4%) [2]	7 (6.5%) [10]
Deafness	2 (8.0%) [2]	3 (10.7%) [3]	4 (14.3%) [4]	0	9 (8.3%) [9]
Eosinophilia	2 (8.0%) [2]	2 (7.1%) [2]	4 (14.3%) [5]	0	8 (7.4%) [9]
Abdominal pain upper	1 (4.0%) [1]	2 (7.1%) [2]	2 (7.1%) [2]	3 (11.1%) [3]	8 (7.4%) [8]
Acne	0	3 (10.7%) [3]	3 (10.7%) [3]	2 (7.4%) [2]	8 (7.4%) [8]
Paraesthesia	3 (12.0%) [3]	1 (3.6%) [2]	0	3 (11.1%) [3]	7 (6.5%) [8]
Anxiety	2 (8.0%) [2]	0	0	3 (11.1%) [5]	5 (4.6%) [7]

Table S10.14: Grade 1 AEs by Preferred Term (PT) and allocated dose. (*continued*)

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Dyspepsia	1 (4.0%) [1]	1 (3.6%) [1]	3 (10.7%) [3]	2 (7.4%) [2]	7 (6.5%) [7]
Myalgia	3 (12.0%) [3]	0	1 (3.6%) [1]	3 (11.1%) [3]	7 (6.5%) [7]
Tremor	2 (8.0%) [2]	1 (3.6%) [1]	2 (7.1%) [2]	2 (7.4%) [2]	7 (6.5%) [7]
Vision blurred	1 (4.0%) [1]	0	2 (7.1%) [4]	2 (7.4%) [2]	5 (4.6%) [7]
Blood uric acid increased	1 (4.0%) [1]	4 (14.3%) [4]	1 (3.6%) [1]	0	6 (5.6%) [6]
Dysuria	1 (4.0%) [1]	3 (10.7%) [3]	2 (7.1%) [2]	0	6 (5.6%) [6]
Neutropenia	4 (16.0%) [5]	0	1 (3.6%) [1]	0	5 (4.6%) [6]
Gastroesophageal reflux disease	2 (8.0%) [2]	1 (3.6%) [1]	1 (3.6%) [1]	1 (3.7%) [1]	5 (4.6%) [5]
Hyperbilirubinaemia	1 (4.0%) [1]	2 (7.1%) [3]	0	1 (3.7%) [1]	4 (3.7%) [5]
Hypothyroidism	2 (8.0%) [2]	0	0	3 (11.1%) [3]	5 (4.6%) [5]
Leukopenia	2 (8.0%) [2]	0	1 (3.6%) [1]	2 (7.4%) [2]	5 (4.6%) [5]
Alanine aminotransferase increased	1 (4.0%) [1]	2 (7.1%) [2]	0	1 (3.7%) [1]	4 (3.7%) [4]
Contusion	1 (4.0%) [1]	1 (3.6%) [1]	2 (7.1%) [2]	0	4 (3.7%) [4]
Dermatitis acneiform	1 (4.0%) [1]	1 (3.6%) [1]	1 (3.6%) [1]	1 (3.7%) [1]	4 (3.7%) [4]
Fungal infection	1 (4.0%) [1]	1 (3.6%) [1]	2 (7.1%) [2]	0	4 (3.7%) [4]
Pharyngitis	0	0	4 (14.3%) [4]	0	4 (3.7%) [4]
Creatinine renal clearance decreased	0	2 (7.1%) [2]	1 (3.6%) [1]	0	3 (2.8%) [3]
Dry eye	1 (4.0%) [1]	1 (3.6%) [1]	0	1 (3.7%) [1]	3 (2.8%) [3]
Electrocardiogram qt prolonged	0	1 (3.6%) [1]	1 (3.6%) [1]	1 (3.7%) [1]	3 (2.8%) [3]
Fatigue	0	0	1 (3.6%) [1]	2 (7.4%) [2]	3 (2.8%) [3]
Haemorrhoids	2 (8.0%) [2]	1 (3.6%) [1]	0	0	3 (2.8%) [3]
Hypoacusis	1 (4.0%) [2]	1 (3.6%) [1]	0	0	2 (1.9%) [3]
Incision site pain	0	0	0	1 (3.7%) [3]	1 (0.9%) [3]
Joint swelling	0	0	0	2 (7.4%) [3]	2 (1.9%) [3]
Musculoskeletal chest pain	0	0	1 (3.6%) [1]	2 (7.4%) [2]	3 (2.8%) [3]
Odynophagia	0	1 (3.6%) [1]	0	2 (7.4%) [2]	3 (2.8%) [3]
Oedema peripheral	0	1 (3.6%) [1]	1 (3.6%) [1]	1 (3.7%) [1]	3 (2.8%) [3]
Oropharyngeal pain	0	2 (7.1%) [2]	1 (3.6%) [1]	0	3 (2.8%) [3]
Pollakiuria	1 (4.0%) [1]	0	1 (3.6%) [1]	1 (3.7%) [1]	3 (2.8%) [3]
Pruritus generalised	2 (8.0%) [2]	1 (3.6%) [1]	0	0	3 (2.8%) [3]
Rash pruritic	1 (4.0%) [1]	0	1 (3.6%) [2]	0	2 (1.9%) [3]
Rash pustular	0	1 (3.6%) [1]	1 (3.6%) [1]	1 (3.7%) [1]	3 (2.8%) [3]
Somnolence	1 (4.0%) [1]	1 (3.6%) [1]	1 (3.6%) [1]	0	3 (2.8%) [3]
Transaminases increased	0	0	2 (7.1%) [2]	1 (3.7%) [1]	3 (2.8%) [3]
Vaginal discharge	0	1 (3.6%) [1]	0	2 (7.4%) [2]	3 (2.8%) [3]
Vulvovaginitis	0	0	2 (7.1%) [3]	0	2 (1.9%) [3]
Weight decreased	0	0	1 (3.6%) [2]	1 (3.7%) [1]	2 (1.9%) [3]
Anaemia	1 (4.0%) [1]	1 (3.6%) [1]	0	0	2 (1.9%) [2]
Blood bilirubin increased	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Body tinea	0	2 (7.1%) [2]	0	0	2 (1.9%) [2]
Breast pain	1 (4.0%) [1]	0	0	1 (3.7%) [1]	2 (1.9%) [2]

Table S10.14: Grade 1 AEs by Preferred Term (PT) and allocated dose. (*continued*)

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Conjunctivitis allergic	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Dysphagia	0	2 (7.1%) [2]	0	0	2 (1.9%) [2]
Eye pruritus	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Flatulence	0	1 (3.6%) [1]	0	1 (3.7%) [1]	2 (1.9%) [2]
Gastric disorder	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Gastroenteritis	0	2 (7.1%) [2]	0	0	2 (1.9%) [2]
Gynaecomastia	1 (4.0%) [1]	0	0	1 (3.7%) [1]	2 (1.9%) [2]
Joint injury	1 (4.0%) [1]	1 (3.6%) [1]	0	0	2 (1.9%) [2]
Lower respiratory tract infection	0	1 (3.6%) [2]	0	0	1 (0.9%) [2]
Oral candidiasis	1 (4.0%) [1]	1 (3.6%) [1]	0	0	2 (1.9%) [2]
Otitis externa	0	1 (3.6%) [1]	0	1 (3.7%) [1]	2 (1.9%) [2]
Rash maculo-papular	0	0	2 (7.1%) [2]	0	2 (1.9%) [2]
Rash papular	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Rhinitis	0	1 (3.6%) [1]	1 (3.6%) [1]	0	2 (1.9%) [2]
Rhinorrhoea	0	1 (3.6%) [1]	0	1 (3.7%) [1]	2 (1.9%) [2]
Skin exfoliation	0	1 (3.6%) [2]	0	0	1 (0.9%) [2]
Skin hyperpigmentation	1 (4.0%) [1]	0	0	1 (3.7%) [1]	2 (1.9%) [2]
Skin lesion	0	1 (3.6%) [1]	0	1 (3.7%) [1]	2 (1.9%) [2]
Skin papilloma	2 (8.0%) [2]	0	0	0	2 (1.9%) [2]
Syncope	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Throat irritation	0	1 (3.6%) [1]	1 (3.6%) [1]	0	2 (1.9%) [2]
Toothache	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Vessel puncture site bruise	0	1 (3.6%) [1]	1 (3.6%) [1]	0	2 (1.9%) [2]
Abdominal discomfort	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Abdominal distension	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Abdominal pain lower	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Acariasis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Acarodermatitis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Adjustment disorder	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Anorectal disorder	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Arrhythmia	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Aspartate aminotransferase increased	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Asthenia	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Blister	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Blood folate decreased	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Blood glucose increased	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Breath sounds abnormal	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Bronchitis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Bronchospasm	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Chronic obstructive pulmonary disease	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Conjunctivitis bacterial	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]

Table S10.14: Grade 1 AEs by Preferred Term (PT) and allocated dose. (*continued*)

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Costochondritis	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Deafness neurosensory	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Depression	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Diabetes mellitus	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Diplopia	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Dizziness postural	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Dyspnoea	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Ear discomfort	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Eosinophil count increased	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Erectile dysfunction	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Excoriation	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Eye swelling	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Fall	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Fibroadenoma of breast	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Gestational trophoblastic tumour	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Grip strength decreased	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Heat rash	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Herpes simplex	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Hyperkeratosis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Hypoaesthesia oral	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Hypoalbuminaemia	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Injection site haematoma	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Joint effusion	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Laceration	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Leukocytosis	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Libido increased	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Limb discomfort	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Lip swelling	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Lymphadenopathy	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Lymphopenia	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Muscle atrophy	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Musculoskeletal discomfort	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Myopia	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Nasal congestion	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Nasal discomfort	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Neck pain	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Neuritis	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Neurodermatitis	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Nightmare	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Oedema	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Oral disorder	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]

Table S10.14: Grade 1 AEs by Preferred Term (PT) and allocated dose. (*continued*)

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Oral herpes	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Otitis media	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Ototoxicity	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Pain	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Papule	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Paronychia	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Pelvic pain	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Peripheral sensory neuropathy	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Personality disorder	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Pharyngitis bacterial	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Pharyngotonsillitis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Photosensitivity reaction	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Pityriasis alba	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Polyarthrititis	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Polycythaemia vera	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Polydipsia	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Polyuria	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Post inflammatory pigmentation change	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Presyncope	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Proctalgia	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Pruritus genital	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Psychotic disorder	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Rales	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Rash generalised	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Renal impairment	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Rhinitis allergic	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Sensory loss	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Sinus tachycardia	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Skin hypopigmentation	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Sneezing	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Subcutaneous abscess	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Synovial cyst	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Tachycardia	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Tendon pain	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Tenosynovitis	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Thrombocytopenia	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Tooth abscess	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Upper-airway cough syndrome	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Urinary tract infection	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Urine analysis abnormal	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Urticaria	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]

Table S10.14: Grade 1 AEs by Preferred Term (PT) and allocated dose. (*continued*)

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Vessel puncture site pain	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Viral pharyngitis	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Visual acuity reduced	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Xeroderma	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Xerosis	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Total Grade 1 AEs AEs	24 (96.0%) [375]	28 (100.0%) [373]	28 (100.0%) [382]	27 (100.0%) [435]	107 (99.1%) [1565]

Table S10.15: Grade 2 AEs by System Organ Class (SOC) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Musculoskeletal and connective tissue disorders	6 (24.0%) [8]	10 (35.7%) [11]	8 (28.6%) [12]	10 (37.0%) [16]	34 (31.5%) [47]
Gastrointestinal disorders	5 (20.0%) [5]	5 (17.9%) [5]	9 (32.1%) [12]	7 (25.9%) [7]	26 (24.1%) [29]
Psychiatric disorders	4 (16.0%) [6]	3 (10.7%) [6]	3 (10.7%) [4]	8 (29.6%) [8]	18 (16.7%) [24]
Nervous system disorders	4 (16.0%) [5]	2 (7.1%) [2]	2 (7.1%) [2]	7 (25.9%) [11]	15 (13.9%) [20]
Skin and subcutaneous tissue disorders	0	1 (3.6%) [1]	3 (10.7%) [11]	4 (14.8%) [6]	8 (7.4%) [18]
General disorders and administration site conditions	5 (20.0%) [5]	4 (14.3%) [4]	2 (7.1%) [2]	3 (11.1%) [5]	14 (13.0%) [16]
Blood and lymphatic system disorders	1 (4.0%) [1]	3 (10.7%) [3]	4 (14.3%) [5]	1 (3.7%) [1]	9 (8.3%) [10]
Ear and labyrinth disorders	3 (12.0%) [3]	2 (7.1%) [2]	1 (3.6%) [1]	2 (7.4%) [2]	8 (7.4%) [8]
Respiratory, thoracic and mediastinal disorders	1 (4.0%) [2]	3 (10.7%) [3]	0	2 (7.4%) [2]	6 (5.6%) [7]
Hepatobiliary disorders	0	0	3 (10.7%) [4]	0	3 (2.8%) [4]
Infections and infestations	1 (4.0%) [1]	1 (3.6%) [1]	0	2 (7.4%) [2]	4 (3.7%) [4]
Metabolism and nutrition disorders	0	0	1 (3.6%) [2]	1 (3.7%) [2]	2 (1.9%) [4]
Injury, poisoning and procedural complications	1 (4.0%) [1]	1 (3.6%) [1]	1 (3.6%) [1]	0	3 (2.8%) [3]
Investigations	1 (4.0%) [1]	0	2 (7.1%) [2]	0	3 (2.8%) [3]
Reproductive system and breast disorders	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Cardiac disorders	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Endocrine disorders	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Immune system disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Social circumstances	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Vascular disorders	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Total Grade 2 AEs AEs	16 (64.0%) [40]	22 (78.6%) [40]	19 (67.9%) [60]	22 (81.5%) [64]	79 (73.1%) [204]

Table S10.16: Grade 2 AEs by Preferred Term (PT) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Arthralgia	5 (20.0%) [5]	5 (17.9%) [5]	5 (17.9%) [5]	9 (33.3%) [9]	24 (22.2%) [24]
Musculoskeletal pain	2 (8.0%) [2]	4 (14.3%) [4]	4 (14.3%) [4]	3 (11.1%) [4]	13 (12.0%) [14]
Injection site pain	3 (12.0%) [3]	2 (7.1%) [2]	2 (7.1%) [2]	2 (7.4%) [2]	9 (8.3%) [9]
Insomnia	3 (12.0%) [3]	1 (3.6%) [2]	0	3 (11.1%) [3]	7 (6.5%) [8]
Pruritus	0	0	2 (7.1%) [5]	2 (7.4%) [2]	4 (3.7%) [7]
Gastritis	0	1 (3.6%) [1]	1 (3.6%) [2]	3 (11.1%) [3]	5 (4.6%) [6]
Headache	1 (4.0%) [1]	1 (3.6%) [1]	1 (3.6%) [1]	3 (11.1%) [3]	6 (5.6%) [6]
Hypoaesthesia	2 (8.0%) [2]	0	0	1 (3.7%) [4]	3 (2.8%) [6]
Pain in extremity	1 (4.0%) [1]	1 (3.6%) [1]	1 (3.6%) [2]	1 (3.7%) [2]	4 (3.7%) [6]
Eosinophilia	0	1 (3.6%) [1]	2 (7.1%) [3]	1 (3.7%) [1]	4 (3.7%) [5]
Rash	0	0	1 (3.6%) [5]	0	1 (0.9%) [5]
Vomiting	1 (4.0%) [1]	1 (3.6%) [1]	1 (3.6%) [1]	2 (7.4%) [2]	5 (4.6%) [5]
Abdominal pain	1 (4.0%) [1]	0	2 (7.1%) [2]	1 (3.7%) [1]	4 (3.7%) [4]
Anaemia	0	2 (7.1%) [2]	2 (7.1%) [2]	0	4 (3.7%) [4]
Deafness	2 (8.0%) [2]	1 (3.6%) [1]	1 (3.6%) [1]	0	4 (3.7%) [4]
Nausea	2 (8.0%) [2]	0	2 (7.1%) [2]	0	4 (3.7%) [4]
Depression	0	1 (3.6%) [1]	1 (3.6%) [1]	1 (3.7%) [1]	3 (2.8%) [3]
Dizziness	2 (8.0%) [2]	0	0	1 (3.7%) [1]	3 (2.8%) [3]
Hyperbilirubinaemia	0	0	3 (10.7%) [3]	0	3 (2.8%) [3]
Major depression	0	0	1 (3.6%) [1]	2 (7.4%) [2]	3 (2.8%) [3]
Neuropathy peripheral	0	1 (3.6%) [1]	0	2 (7.4%) [2]	3 (2.8%) [3]
Oedema peripheral	0	0	0	1 (3.7%) [3]	1 (0.9%) [3]
Psychotic disorder	1 (4.0%) [1]	2 (7.1%) [2]	0	0	3 (2.8%) [3]
Anxiety	0	0	0	2 (7.4%) [2]	2 (1.9%) [2]
Chest pain	1 (4.0%) [1]	1 (3.6%) [1]	0	0	2 (1.9%) [2]
Dermatitis acneiform	0	1 (3.6%) [1]	0	1 (3.7%) [1]	2 (1.9%) [2]
Dyspepsia	0	0	2 (7.1%) [2]	0	2 (1.9%) [2]
Hypokalaemia	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Productive cough	0	1 (3.6%) [1]	0	1 (3.7%) [1]	2 (1.9%) [2]
Tinnitus	0	1 (3.6%) [1]	0	1 (3.7%) [1]	2 (1.9%) [2]
Urticaria	0	0	0	1 (3.7%) [2]	1 (0.9%) [2]
Weight decreased	0	0	2 (7.1%) [2]	0	2 (1.9%) [2]
Abdominal pain upper	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Acne	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Affect lability	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Arthritis	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Asthenia	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Bicytopenia	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Breast pain	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Bronchospasm	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]

Table S10.16: Grade 2 AEs by Preferred Term (PT) and allocated dose. (*continued*)

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Bulimia nervosa	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Chronic obstructive pulmonary disease	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Constipation	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Contusion	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Dental caries	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Dental discomfort	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Diarrhoea	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Dyspnoea exertional	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Electrocardiogram qt prolonged	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Erectile dysfunction	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Gastroenteritis	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Gastroesophageal reflux disease	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Gingival pain	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Haemoptysis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Hallucinations, mixed	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Hearing impaired	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Herpes simplex	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Herpes virus infection	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Hyperhidrosis	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Hypersensitivity	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Hypoacusis	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Hypomagnesaemia	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Hyponatraemia	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Hypothyroidism	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Influenza like illness	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Jaundice	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Joint instability	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Ligament sprain	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Limb injury	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Mood altered	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Myalgia	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Nightmare	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Pallor	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Palpitations	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Physical assault	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Pneumothorax	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Post herpetic neuralgia	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Presyncope	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Psoas abscess	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Toothache	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Total Grade 2 AEs AEs	16 (64.0%) [40]	22 (78.6%) [40]	19 (67.9%) [60]	22 (81.5%) [64]	79 (73.1%) [204]

Table S10.17: Grade 3 AEs by System Organ Class (SOC) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Investigations	0	1 (3.6%) [1]	1 (3.6%) [1]	4 (14.8%) [4]	6 (5.6%) [6]
Ear and labyrinth disorders	0	0	1 (3.6%) [1]	3 (11.1%) [3]	4 (3.7%) [4]
Nervous system disorders	0	0	2 (7.1%) [2]	1 (3.7%) [1]	3 (2.8%) [3]
Respiratory, thoracic and mediastinal disorders	1 (4.0%) [1]	1 (3.6%) [1]	0	1 (3.7%) [1]	3 (2.8%) [3]
Blood and lymphatic system disorders	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
General disorders and administration site conditions	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Hepatobiliary disorders	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Infections and infestations	0	0	1 (3.6%) [2]	0	1 (0.9%) [2]
Metabolism and nutrition disorders	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Musculoskeletal and connective tissue disorders	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Psychiatric disorders	0	1 (3.6%) [1]	1 (3.6%) [1]	0	2 (1.9%) [2]
Gastrointestinal disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Immune system disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Total Grade 3 AEs AEs	3 (12.0%) [3]	3 (10.7%) [3]	7 (25.0%) [14]	9 (33.3%) [12]	22 (20.4%) [32]

Table S10.18: Grade 3 AEs by Preferred Term (PT) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Blood uric acid increased	0	1 (3.6%) [1]	1 (3.6%) [1]	2 (7.4%) [2]	4 (3.7%) [4]
Bronchospasm	1 (4.0%) [1]	1 (3.6%) [1]	0	0	2 (1.9%) [2]
Deafness	0	0	0	2 (7.4%) [2]	2 (1.9%) [2]
Eosinophilia	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Hepatic function abnormal	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Acute psychosis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Alanine aminotransferase increased	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Arthralgia	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Chest pain	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Decreased appetite	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Delirium	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Disseminated tuberculosis	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Dizziness	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Electrocardiogram qt prolonged	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Hyperuricaemia	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Immune reconstitution inflammatory syndrome	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Ischaemic stroke	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Meningitis tuberculous	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Musculoskeletal pain	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Nausea	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Neuropathy peripheral	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Oedema peripheral	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Ototoxicity	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Pulmonary fistula	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Vertigo	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Total Grade 3 AEs AEs	3 (12.0%) [3]	3 (10.7%) [3]	7 (25.0%) [14]	9 (33.3%) [12]	22 (20.4%) [32]

Table S10.19: Grade 4 AEs by System Organ Class (SOC) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Investigations	1 (4.0%) [1]	1 (3.6%) [1]	0	1 (3.7%) [1]	3 (2.8%) [3]
Total Grade 4 AEs AEs	1 (4.0%) [1]	1 (3.6%) [1]	0	1 (3.7%) [1]	3 (2.8%) [3]

Table S10.20: Grade 4 AEs by Preferred Term (PT) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Blood uric acid increased	1 (4.0%) [1]	1 (3.6%) [1]	0	1 (3.7%) [1]	3 (2.8%) [3]
Total Grade 4 AEs AEs	1 (4.0%) [1]	1 (3.6%) [1]	0	1 (3.7%) [1]	3 (2.8%) [3]

Table S10.21: Grade 3-5 AEs by System Organ Class (SOC) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Investigations	1 (4.0%) [1]	2 (7.1%) [2]	1 (3.6%) [1]	5 (18.5%) [5]	9 (8.3%) [9]
Ear and labyrinth disorders	0	0	1 (3.6%) [1]	3 (11.1%) [3]	4 (3.7%) [4]
Nervous system disorders	0	0	2 (7.1%) [2]	1 (3.7%) [1]	3 (2.8%) [3]
Respiratory, thoracic and mediastinal disorders	1 (4.0%) [1]	1 (3.6%) [1]	0	1 (3.7%) [1]	3 (2.8%) [3]
Blood and lymphatic system disorders	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
General disorders and administration site conditions	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Hepatobiliary disorders	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Infections and infestations	0	0	1 (3.6%) [2]	0	1 (0.9%) [2]
Metabolism and nutrition disorders	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Musculoskeletal and connective tissue disorders	0	0	1 (3.6%) [1]	1 (3.7%) [1]	2 (1.9%) [2]
Psychiatric disorders	0	1 (3.6%) [1]	1 (3.6%) [1]	0	2 (1.9%) [2]
Gastrointestinal disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Immune system disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Total Grade 3-5 AEs AEs	4 (16.0%) [4]	4 (14.3%) [4]	7 (25.0%) [14]	10 (37.0%) [13]	25 (23.1%) [35]

Table S10.22: Grade 3-5 AEs by Preferred Term (PT) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Blood uric acid increased	1 (4.0%) [1]	2 (7.1%) [2]	1 (3.6%) [1]	3 (11.1%) [3]	7 (6.5%) [7]
Bronchospasm	1 (4.0%) [1]	1 (3.6%) [1]	0	0	2 (1.9%) [2]
Deafness	0	0	0	2 (7.4%) [2]	2 (1.9%) [2]
Eosinophilia	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Hepatic function abnormal	1 (4.0%) [1]	0	1 (3.6%) [1]	0	2 (1.9%) [2]
Acute psychosis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Alanine aminotransferase increased	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Arthralgia	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Chest pain	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Decreased appetite	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Delirium	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Disseminated tuberculosis	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Dizziness	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Electrocardiogram qt prolonged	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Hyperuricaemia	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Immune reconstitution inflammatory syndrome	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Ischaemic stroke	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Meningitis tuberculous	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Musculoskeletal pain	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Nausea	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Neuropathy peripheral	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Oedema peripheral	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Ototoxicity	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Pulmonary fistula	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Vertigo	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Total Grade 3-5 AEs AEs	4 (16.0%) [4]	4 (14.3%) [4]	7 (25.0%) [14]	10 (37.0%) [13]	25 (23.1%) [35]

Table S10.23: SAEs by System Organ Class (SOC) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Respiratory, thoracic and mediastinal disorders	2 (8.0%) [2]	0	0	1 (3.7%) [2]	3 (2.8%) [4]
Psychiatric disorders	0	1 (3.6%) [1]	1 (3.6%) [1]	0	2 (1.9%) [2]
General disorders and administration site conditions	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Hepatobiliary disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Immune system disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Infections and infestations	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]

Table S10.23: SAEs by System Organ Class (SOC) and allocated dose. (*continued*)

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Investigations	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Musculoskeletal and connective tissue disorders	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Nervous system disorders	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Total SAEs AEs	2 (8.0%) [2]	1 (3.6%) [1]	4 (14.3%) [5]	3 (11.1%) [5]	10 (9.3%) [13]

Table S10.24: SAEs by Preferred Term (PT) and allocated dose.

N participants (%) [N events]	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total in ITT analysis	25	28	28	27	108
Acute psychosis	0	1 (3.6%) [1]	0	0	1 (0.9%) [1]
Bronchospasm	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Chronic obstructive pulmonary disease	1 (4.0%) [1]	0	0	0	1 (0.9%) [1]
Delirium	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Gastroenteritis	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Hepatic function abnormal	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Immune reconstitution inflammatory syndrome	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Ischaemic stroke	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Oedema peripheral	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Pain in extremity	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Pneumothorax	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Pulmonary fistula	0	0	0	1 (3.7%) [1]	1 (0.9%) [1]
Weight decreased	0	0	1 (3.6%) [1]	0	1 (0.9%) [1]
Total SAEs AEs	2 (8.0%) [2]	1 (3.6%) [1]	4 (14.3%) [5]	3 (11.1%) [5]	10 (9.3%) [13]

3.10.3 Summary of AEs by MedDRA coding and tertiles of AUC

Table S10.25: Grade 1 AEs by System Organ Class (SOC) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Gastrointestinal disorders	32 (97.0%) [118]	32 (97.0%) [99]	31 (93.9%) [120]	95 (96.0%) [337]
Musculoskeletal and connective tissue disorders	30 (90.9%) [103]	31 (93.9%) [81]	31 (93.9%) [87]	92 (92.9%) [271]
Skin and subcutaneous tissue disorders	23 (69.7%) [87]	24 (72.7%) [69]	27 (81.8%) [69]	74 (74.7%) [225]
Nervous system disorders	27 (81.8%) [70]	26 (78.8%) [57]	28 (84.8%) [64]	81 (81.8%) [191]
Respiratory, thoracic and mediastinal disorders	19 (57.6%) [35]	11 (33.3%) [13]	15 (45.5%) [30]	45 (45.5%) [78]
General disorders and administration site conditions	17 (51.5%) [21]	15 (45.5%) [18]	23 (69.7%) [32]	55 (55.6%) [71]
Infections and infestations	16 (48.5%) [25]	11 (33.3%) [16]	12 (36.4%) [22]	39 (39.4%) [63]
Psychiatric disorders	9 (27.3%) [12]	10 (30.3%) [16]	12 (36.4%) [22]	31 (31.3%) [50]
Cardiac disorders	8 (24.2%) [10]	11 (33.3%) [16]	14 (42.4%) [18]	33 (33.3%) [44]
Ear and labyrinth disorders	9 (27.3%) [17]	8 (24.2%) [13]	9 (27.3%) [10]	26 (26.3%) [40]
Metabolism and nutrition disorders	9 (27.3%) [12]	7 (21.2%) [9]	11 (33.3%) [14]	27 (27.3%) [35]
Investigations	8 (24.2%) [13]	7 (21.2%) [8]	8 (24.2%) [10]	23 (23.2%) [31]
Blood and lymphatic system disorders	11 (33.3%) [16]	7 (21.2%) [8]	2 (6.1%) [2]	20 (20.2%) [26]
Eye disorders	4 (12.1%) [5]	4 (12.1%) [6]	7 (21.2%) [7]	15 (15.2%) [18]
Injury, poisoning and procedural complications	4 (12.1%) [5]	4 (12.1%) [6]	1 (3.0%) [1]	9 (9.1%) [12]
Renal and urinary disorders	5 (15.2%) [6]	3 (9.1%) [3]	2 (6.1%) [2]	10 (10.1%) [11]
Reproductive system and breast disorders	2 (6.1%) [3]	2 (6.1%) [3]	4 (12.1%) [4]	8 (8.1%) [10]
Endocrine disorders	0	1 (3.0%) [1]	4 (12.1%) [4]	5 (5.1%) [5]
Hepatobiliary disorders	1 (3.0%) [1]	1 (3.0%) [1]	2 (6.1%) [3]	4 (4.0%) [5]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.0%) [1]	2 (6.1%) [2]	1 (3.0%) [2]	4 (4.0%) [5]
Total Grade 1 AEs AEs	33 (100.0%) [560]	33 (100.0%) [445]	33 (100.0%) [523]	99 (100.0%) [1528]

Table S10.26: Grade 1 AEs by Preferred Term (PT) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Arthralgia	20 (60.6%) [33]	19 (57.6%) [30]	23 (69.7%) [37]	62 (62.6%) [100]
Musculoskeletal pain	22 (66.7%) [43]	16 (48.5%) [31]	16 (48.5%) [19]	54 (54.5%) [93]
Pruritus	15 (45.5%) [33]	14 (42.4%) [27]	19 (57.6%) [31]	48 (48.5%) [91]
Nausea	24 (72.7%) [29]	16 (48.5%) [18]	24 (72.7%) [28]	64 (64.6%) [75]
Dizziness	22 (66.7%) [28]	18 (54.5%) [20]	15 (45.5%) [23]	55 (55.6%) [71]
Vomiting	17 (51.5%) [20]	16 (48.5%) [25]	16 (48.5%) [26]	49 (49.5%) [71]
Abdominal pain	18 (54.5%) [24]	12 (36.4%) [15]	12 (36.4%) [20]	42 (42.4%) [59]
Rash	16 (48.5%) [31]	13 (39.4%) [18]	8 (24.2%) [10]	37 (37.4%) [59]
Headache	17 (51.5%) [20]	14 (42.4%) [15]	14 (42.4%) [18]	45 (45.5%) [53]
Diarrhoea	8 (24.2%) [18]	5 (15.2%) [7]	15 (45.5%) [21]	28 (28.3%) [46]
Pain in extremity	8 (24.2%) [14]	7 (21.2%) [11]	11 (33.3%) [15]	26 (26.3%) [40]
Insomnia	6 (18.2%) [9]	8 (24.2%) [11]	11 (33.3%) [17]	25 (25.3%) [37]
Hypoaesthesia	5 (15.2%) [13]	7 (21.2%) [12]	5 (15.2%) [8]	17 (17.2%) [33]
Decreased appetite	8 (24.2%) [11]	6 (18.2%) [8]	11 (33.3%) [13]	25 (25.3%) [32]
Gastritis	7 (21.2%) [8]	11 (33.3%) [12]	4 (12.1%) [5]	22 (22.2%) [25]
Bradycardia	7 (21.2%) [7]	9 (27.3%) [13]	2 (6.1%) [2]	18 (18.2%) [22]
Injection site pain	4 (12.1%) [5]	4 (12.1%) [4]	9 (27.3%) [13]	17 (17.2%) [22]
Cough	7 (21.2%) [12]	3 (9.1%) [3]	5 (15.2%) [6]	15 (15.2%) [21]
Constipation	5 (15.2%) [5]	4 (12.1%) [6]	6 (18.2%) [8]	15 (15.2%) [19]
Palpitations	2 (6.1%) [2]	2 (6.1%) [2]	11 (33.3%) [15]	15 (15.2%) [19]
Pyrexia	7 (21.2%) [7]	5 (15.2%) [5]	6 (18.2%) [7]	18 (18.2%) [19]
Chest pain	8 (24.2%) [8]	6 (18.2%) [7]	2 (6.1%) [2]	16 (16.2%) [17]
Back pain	8 (24.2%) [8]	3 (9.1%) [4]	3 (9.1%) [3]	14 (14.1%) [15]
Nasopharyngitis	9 (27.3%) [11]	4 (12.1%) [4]	0	13 (13.1%) [15]
Hyperhidrosis	6 (18.2%) [6]	6 (18.2%) [6]	2 (6.1%) [2]	14 (14.1%) [14]
Pleuritic pain	2 (6.1%) [2]	3 (9.1%) [3]	6 (18.2%) [9]	11 (11.1%) [14]
Productive cough	6 (18.2%) [8]	0	4 (12.1%) [6]	10 (10.1%) [14]
Tinnitus	2 (6.1%) [4]	6 (18.2%) [6]	4 (12.1%) [4]	12 (12.1%) [14]
Haemoptysis	4 (12.1%) [6]	3 (9.1%) [3]	4 (12.1%) [4]	11 (11.1%) [13]
Ear pain	4 (12.1%) [6]	3 (9.1%) [3]	3 (9.1%) [3]	10 (10.1%) [12]
Night sweats	1 (3.0%) [2]	4 (12.1%) [4]	5 (15.2%) [6]	10 (10.1%) [12]
Dry skin	0	1 (3.0%) [1]	4 (12.1%) [8]	5 (5.1%) [9]
Eosinophilia	4 (12.1%) [4]	4 (12.1%) [5]	0	8 (8.1%) [9]
Neuropathy peripheral	2 (6.1%) [2]	1 (3.0%) [1]	6 (18.2%) [6]	9 (9.1%) [9]
Upper respiratory tract infection	0	0	6 (18.2%) [9]	6 (6.1%) [9]
Abdominal pain upper	3 (9.1%) [3]	3 (9.1%) [3]	2 (6.1%) [2]	8 (8.1%) [8]
Acne	4 (12.1%) [4]	3 (9.1%) [3]	1 (3.0%) [1]	8 (8.1%) [8]
Deafness	3 (9.1%) [3]	2 (6.1%) [2]	3 (9.1%) [3]	8 (8.1%) [8]
Paraesthesia	1 (3.0%) [1]	1 (3.0%) [1]	5 (15.2%) [6]	7 (7.1%) [8]
Anxiety	1 (3.0%) [1]	2 (6.1%) [3]	2 (6.1%) [3]	5 (5.1%) [7]

Table S10.26: Grade 1 AEs by Preferred Term (PT) and tertiles of AUC. (*continued*)

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Dyspepsia	2 (6.1%) [2]	3 (9.1%) [3]	2 (6.1%) [2]	7 (7.1%) [7]
Myalgia	2 (6.1%) [2]	1 (3.0%) [1]	4 (12.1%) [4]	7 (7.1%) [7]
Tremor	2 (6.1%) [2]	5 (15.2%) [5]	0	7 (7.1%) [7]
Vision blurred	2 (6.1%) [2]	3 (9.1%) [5]	0	5 (5.1%) [7]
Blood uric acid increased	4 (12.1%) [4]	2 (6.1%) [2]	0	6 (6.1%) [6]
Dysuria	5 (15.2%) [5]	1 (3.0%) [1]	0	6 (6.1%) [6]
Neutropenia	4 (12.1%) [5]	1 (3.0%) [1]	0	5 (5.1%) [6]
Gastroesophageal reflux disease	3 (9.1%) [3]	0	2 (6.1%) [2]	5 (5.1%) [5]
Hyperbilirubinaemia	1 (3.0%) [1]	1 (3.0%) [1]	2 (6.1%) [3]	4 (4.0%) [5]
Hypothyroidism	0	1 (3.0%) [1]	4 (12.1%) [4]	5 (5.1%) [5]
Leukopenia	3 (9.1%) [3]	2 (6.1%) [2]	0	5 (5.1%) [5]
Alanine aminotransferase increased	3 (9.1%) [3]	0	1 (3.0%) [1]	4 (4.0%) [4]
Contusion	2 (6.1%) [2]	2 (6.1%) [2]	0	4 (4.0%) [4]
Dermatitis acneiform	1 (3.0%) [1]	1 (3.0%) [1]	2 (6.1%) [2]	4 (4.0%) [4]
Fungal infection	4 (12.1%) [4]	0	0	4 (4.0%) [4]
Pharyngitis	1 (3.0%) [1]	3 (9.1%) [3]	0	4 (4.0%) [4]
Creatinine renal clearance decreased	2 (6.1%) [2]	0	1 (3.0%) [1]	3 (3.0%) [3]
Dry eye	2 (6.1%) [2]	0	1 (3.0%) [1]	3 (3.0%) [3]
Electrocardiogram qt prolonged	0	2 (6.1%) [2]	1 (3.0%) [1]	3 (3.0%) [3]
Haemorrhoids	1 (3.0%) [1]	2 (6.1%) [2]	0	3 (3.0%) [3]
Hypoacusis	2 (6.1%) [3]	0	0	2 (2.0%) [3]
Incision site pain	0	1 (3.0%) [3]	0	1 (1.0%) [3]
Joint swelling	0	0	2 (6.1%) [3]	2 (2.0%) [3]
Musculoskeletal chest pain	1 (3.0%) [1]	1 (3.0%) [1]	1 (3.0%) [1]	3 (3.0%) [3]
Odynophagia	0	1 (3.0%) [1]	2 (6.1%) [2]	3 (3.0%) [3]
Oedema peripheral	0	1 (3.0%) [1]	2 (6.1%) [2]	3 (3.0%) [3]
Oropharyngeal pain	2 (6.1%) [2]	1 (3.0%) [1]	0	3 (3.0%) [3]
Pollakiuria	1 (3.0%) [1]	1 (3.0%) [1]	1 (3.0%) [1]	3 (3.0%) [3]
Pruritus generalised	2 (6.1%) [2]	0	1 (3.0%) [1]	3 (3.0%) [3]
Rash pruritic	0	2 (6.1%) [3]	0	2 (2.0%) [3]
Rash pustular	0	1 (3.0%) [1]	2 (6.1%) [2]	3 (3.0%) [3]
Somnolence	1 (3.0%) [1]	2 (6.1%) [2]	0	3 (3.0%) [3]
Transaminases increased	1 (3.0%) [1]	1 (3.0%) [1]	1 (3.0%) [1]	3 (3.0%) [3]
Vaginal discharge	0	1 (3.0%) [1]	2 (6.1%) [2]	3 (3.0%) [3]
Vulvovaginitis	0	1 (3.0%) [2]	1 (3.0%) [1]	2 (2.0%) [3]
Weight decreased	0	0	2 (6.1%) [3]	2 (2.0%) [3]
Anaemia	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Blood bilirubin increased	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Body tinea	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Breast pain	1 (3.0%) [1]	0	1 (3.0%) [1]	2 (2.0%) [2]
Conjunctivitis allergic	0	0	2 (6.1%) [2]	2 (2.0%) [2]

Table S10.26: Grade 1 AEs by Preferred Term (PT) and tertiles of AUC. (*continued*)

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Dysphagia	2 (6.1%) [2]	0	0	2 (2.0%) [2]
Eye pruritus	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Fatigue	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Flatulence	1 (3.0%) [1]	0	1 (3.0%) [1]	2 (2.0%) [2]
Gastric disorder	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Gastroenteritis	1 (3.0%) [1]	0	1 (3.0%) [1]	2 (2.0%) [2]
Gynaecomastia	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Joint injury	2 (6.1%) [2]	0	0	2 (2.0%) [2]
Lower respiratory tract infection	0	0	1 (3.0%) [2]	1 (1.0%) [2]
Oral candidiasis	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Otitis externa	1 (3.0%) [1]	0	1 (3.0%) [1]	2 (2.0%) [2]
Rash maculo-papular	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Rash papular	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Rhinitis	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Rhinorrhoea	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Skin exfoliation	1 (3.0%) [2]	0	0	1 (1.0%) [2]
Skin hyperpigmentation	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Skin lesion	1 (3.0%) [1]	0	1 (3.0%) [1]	2 (2.0%) [2]
Skin papilloma	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Syncope	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Throat irritation	2 (6.1%) [2]	0	0	2 (2.0%) [2]
Toothache	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Vessel puncture site bruise	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Abdominal discomfort	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Abdominal distension	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Abdominal pain lower	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Acariasis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Acarodermatitis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Adjustment disorder	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Anorectal disorder	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Arrhythmia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Aspartate aminotransferase increased	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Asthenia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Blister	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Blood folate decreased	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Blood glucose increased	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Breath sounds abnormal	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Bronchitis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Bronchospasm	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Chronic obstructive pulmonary disease	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Conjunctivitis bacterial	0	1 (3.0%) [1]	0	1 (1.0%) [1]

Table S10.26: Grade 1 AEs by Preferred Term (PT) and tertiles of AUC. (*continued*)

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Costochondritis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Deafness neurosensory	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Depression	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Diabetes mellitus	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Diplopia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Dizziness postural	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Dyspnoea	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Ear discomfort	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Eosinophil count increased	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Erectile dysfunction	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Excoriation	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Eye swelling	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Fall	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Fibroadenoma of breast	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Gestational trophoblastic tumour	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Grip strength decreased	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Heat rash	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Herpes simplex	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Hyperkeratosis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Hypoaesthesia oral	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Hypoalbuminaemia	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Injection site haematoma	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Joint effusion	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Laceration	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Leukocytosis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Libido increased	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Limb discomfort	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Lip swelling	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Lymphadenopathy	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Lymphopenia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Muscle atrophy	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Musculoskeletal discomfort	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Myopia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Nasal congestion	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Nasal discomfort	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Neck pain	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Neuritis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Neurodermatitis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Nightmare	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Oedema	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Oral disorder	0	1 (3.0%) [1]	0	1 (1.0%) [1]

Table S10.26: Grade 1 AEs by Preferred Term (PT) and tertiles of AUC. (*continued*)

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Oral herpes	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Ototoxicity	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pain	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Papule	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Paronychia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Pelvic pain	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Peripheral sensory neuropathy	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Personality disorder	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pharyngitis bacterial	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Pharyngotonsillitis	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Photosensitivity reaction	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pityriasis alba	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Polyarthritits	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Polycythaemia vera	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Polydipsia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Polyuria	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Post inflammatory pigmentation change	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Presyncope	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Proctalgia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pruritus genital	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Psychotic disorder	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Rales	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Rash generalised	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Renal impairment	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Rhinitis allergic	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Sensory loss	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Sinus tachycardia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Skin hypopigmentation	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Sneezing	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Subcutaneous abscess	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Synovial cyst	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Tachycardia	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Tendon pain	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Tenosynovitis	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Thrombocytopenia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Tooth abscess	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Upper-airway cough syndrome	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Urinary tract infection	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Urine analysis abnormal	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Urticaria	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Vessel puncture site pain	0	0	1 (3.0%) [1]	1 (1.0%) [1]

Table S10.26: Grade 1 AEs by Preferred Term (PT) and tertiles of AUC. (*continued*)

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Viral pharyngitis	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Visual acuity reduced	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Xeroderma	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Xerosis	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Total Grade 1 AEs AEs	33 (100.0%) [560]	33 (100.0%) [445]	33 (100.0%) [523]	99 (100.0%) [1528]

Table S10.27: Grade 2 AEs by System Organ Class (SOC) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Musculoskeletal and connective tissue disorders	10 (30.3%) [12]	11 (33.3%) [15]	13 (39.4%) [20]	34 (34.3%) [47]
Gastrointestinal disorders	10 (30.3%) [10]	11 (33.3%) [14]	5 (15.2%) [5]	26 (26.3%) [29]
Psychiatric disorders	4 (12.1%) [7]	7 (21.2%) [10]	6 (18.2%) [6]	17 (17.2%) [23]
Nervous system disorders	4 (12.1%) [5]	5 (15.2%) [5]	6 (18.2%) [10]	15 (15.2%) [20]
Skin and subcutaneous tissue disorders	0	4 (12.1%) [12]	4 (12.1%) [6]	8 (8.1%) [18]
General disorders and administration site conditions	3 (9.1%) [3]	4 (12.1%) [4]	7 (21.2%) [9]	14 (14.1%) [16]
Blood and lymphatic system disorders	2 (6.1%) [2]	2 (6.1%) [3]	4 (12.1%) [4]	8 (8.1%) [9]
Ear and labyrinth disorders	2 (6.1%) [2]	3 (9.1%) [3]	3 (9.1%) [3]	8 (8.1%) [8]
Respiratory, thoracic and mediastinal disorders	2 (6.1%) [2]	3 (9.1%) [4]	1 (3.0%) [1]	6 (6.1%) [7]
Hepatobiliary disorders	1 (3.0%) [1]	2 (6.1%) [3]	0	3 (3.0%) [4]
Infections and infestations	1 (3.0%) [1]	1 (3.0%) [1]	2 (6.1%) [2]	4 (4.0%) [4]
Metabolism and nutrition disorders	0	0	2 (6.1%) [4]	2 (2.0%) [4]
Injury, poisoning and procedural complications	1 (3.0%) [1]	2 (6.1%) [2]	0	3 (3.0%) [3]
Investigations	0	1 (3.0%) [1]	2 (6.1%) [2]	3 (3.0%) [3]
Reproductive system and breast disorders	1 (3.0%) [1]	0	1 (3.0%) [1]	2 (2.0%) [2]
Cardiac disorders	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Endocrine disorders	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Immune system disorders	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Social circumstances	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Vascular disorders	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Total Grade 2 AEs AEs	24 (72.7%) [47]	26 (78.8%) [81]	28 (84.8%) [74]	78 (78.8%) [202]

Table S10.28: Grade 2 AEs by Preferred Term (PT) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Arthralgia	5 (15.2%) [5]	9 (27.3%) [9]	10 (30.3%) [10]	24 (24.2%) [24]
Musculoskeletal pain	6 (18.2%) [6]	4 (12.1%) [4]	3 (9.1%) [4]	13 (13.1%) [14]
Injection site pain	1 (3.0%) [1]	2 (6.1%) [2]	6 (18.2%) [6]	9 (9.1%) [9]
Insomnia	2 (6.1%) [3]	3 (9.1%) [3]	2 (6.1%) [2]	7 (7.1%) [8]
Pruritus	0	3 (9.1%) [6]	1 (3.0%) [1]	4 (4.0%) [7]
Gastritis	1 (3.0%) [1]	3 (9.1%) [4]	1 (3.0%) [1]	5 (5.1%) [6]
Headache	2 (6.1%) [2]	4 (12.1%) [4]	0	6 (6.1%) [6]
Hypoaesthesia	2 (6.1%) [2]	0	1 (3.0%) [4]	3 (3.0%) [6]
Pain in extremity	1 (3.0%) [1]	1 (3.0%) [2]	2 (6.1%) [3]	4 (4.0%) [6]
Eosinophilia	1 (3.0%) [1]	2 (6.1%) [3]	1 (3.0%) [1]	4 (4.0%) [5]
Rash	0	1 (3.0%) [5]	0	1 (1.0%) [5]
Vomiting	2 (6.1%) [2]	1 (3.0%) [1]	2 (6.1%) [2]	5 (5.1%) [5]
Abdominal pain	1 (3.0%) [1]	3 (9.1%) [3]	0	4 (4.0%) [4]
Deafness	1 (3.0%) [1]	1 (3.0%) [1]	2 (6.1%) [2]	4 (4.0%) [4]
Nausea	1 (3.0%) [1]	2 (6.1%) [2]	1 (3.0%) [1]	4 (4.0%) [4]
Anaemia	0	0	3 (9.1%) [3]	3 (3.0%) [3]
Depression	1 (3.0%) [1]	1 (3.0%) [1]	1 (3.0%) [1]	3 (3.0%) [3]
Dizziness	1 (3.0%) [1]	1 (3.0%) [1]	1 (3.0%) [1]	3 (3.0%) [3]
Hyperbilirubinaemia	1 (3.0%) [1]	2 (6.1%) [2]	0	3 (3.0%) [3]
Major depression	0	2 (6.1%) [2]	1 (3.0%) [1]	3 (3.0%) [3]
Neuropathy peripheral	0	0	3 (9.1%) [3]	3 (3.0%) [3]
Oedema peripheral	0	0	1 (3.0%) [3]	1 (1.0%) [3]
Anxiety	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Chest pain	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Dermatitis acneiform	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Dyspepsia	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Hypokalaemia	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Productive cough	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Psychotic disorder	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Tinnitus	1 (3.0%) [1]	1 (3.0%) [1]	0	2 (2.0%) [2]
Urticaria	0	0	1 (3.0%) [2]	1 (1.0%) [2]
Weight decreased	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Abdominal pain upper	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Acne	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Affect lability	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Arthritis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Asthenia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Bicytopenia	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Breast pain	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Bronchospasm	1 (3.0%) [1]	0	0	1 (1.0%) [1]

Table S10.28: Grade 2 AEs by Preferred Term (PT) and tertiles of AUC. (*continued*)

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Bulimia nervosa	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Chronic obstructive pulmonary disease	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Constipation	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Contusion	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Dental caries	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Dental discomfort	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Diarrhoea	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Dyspnoea exertional	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Electrocardiogram qt prolonged	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Erectile dysfunction	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Gastroenteritis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Gastrooesophageal reflux disease	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Gingival pain	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Haemoptysis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hallucinations, mixed	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Hearing impaired	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Herpes simplex	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Herpes virus infection	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hyperhidrosis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hypersensitivity	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Hypoacusis	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Hypomagnesaemia	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hyponatraemia	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hypothyroidism	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Influenza like illness	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Jaundice	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Joint instability	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Ligament sprain	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Limb injury	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Mood altered	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Myalgia	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Nightmare	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pallor	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Palpitations	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Physical assault	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Pneumothorax	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Post herpetic neuralgia	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Presyncope	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Psoas abscess	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Toothache	1 (3.0%) [1]	0	0	1 (1.0%) [1]
Total Grade 2 AEs AEs	24 (72.7%) [47]	26 (78.8%) [81]	28 (84.8%) [74]	78 (78.8%) [202]

Table S10.29: Grade 3 AEs by System Organ Class (SOC) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Investigations	2 (6.1%) [2]	1 (3.0%) [1]	3 (9.1%) [3]	6 (6.1%) [6]
Ear and labyrinth disorders	0	1 (3.0%) [1]	3 (9.1%) [3]	4 (4.0%) [4]
Nervous system disorders	0	0	3 (9.1%) [3]	3 (3.0%) [3]
Respiratory, thoracic and mediastinal disorders	0	1 (3.0%) [1]	2 (6.1%) [2]	3 (3.0%) [3]
Blood and lymphatic system disorders	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
General disorders and administration site conditions	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Hepatobiliary disorders	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Infections and infestations	0	0	1 (3.0%) [2]	1 (1.0%) [2]
Metabolism and nutrition disorders	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Musculoskeletal and connective tissue disorders	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Gastrointestinal disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Immune system disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Psychiatric disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Total Grade 3 AEs AEs	2 (6.1%) [2]	8 (24.2%) [10]	11 (33.3%) [19]	21 (21.2%) [31]

Table S10.30: Grade 3 AEs by Preferred Term (PT) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Blood uric acid increased	2 (6.1%) [2]	1 (3.0%) [1]	1 (3.0%) [1]	4 (4.0%) [4]
Bronchospasm	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Deafness	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Eosinophilia	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Hepatic function abnormal	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Alanine aminotransferase increased	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Arthralgia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Chest pain	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Decreased appetite	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Delirium	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Disseminated tuberculosis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Dizziness	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Electrocardiogram qt prolonged	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hyperuricaemia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Immune reconstitution inflammatory syndrome	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Ischaemic stroke	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Meningitis tuberculous	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Musculoskeletal pain	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Nausea	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Neuropathy peripheral	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Oedema peripheral	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Ototoxicity	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pulmonary fistula	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Vertigo	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Total Grade 3 AEs AEs	2 (6.1%) [2]	8 (24.2%) [10]	11 (33.3%) [19]	21 (21.2%) [31]

Table S10.31: Grade 4 AEs by System Organ Class (SOC) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Investigations	2 (6.1%) [2]	0	1 (3.0%) [1]	3 (3.0%) [3]
Total Grade 4 AEs AEs	2 (6.1%) [2]	0	1 (3.0%) [1]	3 (3.0%) [3]

Table S10.32: Grade 4 AEs by Preferred Term (PT) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Blood uric acid increased	2 (6.1%) [2]	0	1 (3.0%) [1]	3 (3.0%) [3]
Total Grade 4 AEs AEs	2 (6.1%) [2]	0	1 (3.0%) [1]	3 (3.0%) [3]

Table S10.33: Grade 3-5 AEs by System Organ Class (SOC) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Investigations	4 (12.1%) [4]	1 (3.0%) [1]	4 (12.1%) [4]	9 (9.1%) [9]
Ear and labyrinth disorders	0	1 (3.0%) [1]	3 (9.1%) [3]	4 (4.0%) [4]
Nervous system disorders	0	0	3 (9.1%) [3]	3 (3.0%) [3]
Respiratory, thoracic and mediastinal disorders	0	1 (3.0%) [1]	2 (6.1%) [2]	3 (3.0%) [3]
Blood and lymphatic system disorders	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
General disorders and administration site conditions	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Hepatobiliary disorders	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Infections and infestations	0	0	1 (3.0%) [2]	1 (1.0%) [2]
Metabolism and nutrition disorders	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Musculoskeletal and connective tissue disorders	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Gastrointestinal disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Immune system disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Psychiatric disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Total Grade 3-5 AEs AEs	4 (12.1%) [4]	8 (24.2%) [10]	12 (36.4%) [20]	24 (24.2%) [34]

Table S10.34: Grade 3-5 AEs by Preferred Term (PT) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Blood uric acid increased	4 (12.1%) [4]	1 (3.0%) [1]	2 (6.1%) [2]	7 (7.1%) [7]
Bronchospasm	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Deafness	0	0	2 (6.1%) [2]	2 (2.0%) [2]
Eosinophilia	0	1 (3.0%) [1]	1 (3.0%) [1]	2 (2.0%) [2]
Hepatic function abnormal	0	2 (6.1%) [2]	0	2 (2.0%) [2]
Alanine aminotransferase increased	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Arthralgia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Chest pain	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Decreased appetite	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Delirium	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Disseminated tuberculosis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Dizziness	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Electrocardiogram qt prolonged	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hyperuricaemia	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Immune reconstitution inflammatory syndrome	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Ischaemic stroke	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Meningitis tuberculous	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Musculoskeletal pain	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Nausea	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Neuropathy peripheral	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Oedema peripheral	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Ototoxicity	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pulmonary fistula	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Vertigo	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Total Grade 3-5 AEs AEs	4 (12.1%) [4]	8 (24.2%) [10]	12 (36.4%) [20]	24 (24.2%) [34]

Table S10.35: SAEs by System Organ Class (SOC) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Respiratory, thoracic and mediastinal disorders	0	2 (6.1%) [3]	1 (3.0%) [1]	3 (3.0%) [4]
General disorders and administration site conditions	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hepatobiliary disorders	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Immune system disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Infections and infestations	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Investigations	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Musculoskeletal and connective tissue disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]

Table S10.35: SAEs by System Organ Class (SOC) and tertiles of AUC. (*continued*)

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Nervous system disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Psychiatric disorders	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Total SAEs AEs	0	3 (9.1%) [4]	6 (18.2%) [8]	9 (9.1%) [12]

Table S10.36: SAEs by Preferred Term (PT) and tertiles of AUC.

N participants (%) [N events]	Lower tertile	Middle tertile	Upper tertile	Total
Total in ITT analysis	33	33	33	99
Bronchospasm	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Chronic obstructive pulmonary disease	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Delirium	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Gastroenteritis	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Hepatic function abnormal	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Immune reconstitution inflammatory syndrome	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Ischaemic stroke	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Oedema peripheral	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Pain in extremity	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Pneumothorax	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Pulmonary fistula	0	1 (3.0%) [1]	0	1 (1.0%) [1]
Weight decreased	0	0	1 (3.0%) [1]	1 (1.0%) [1]
Total SAEs AEs	0	3 (9.1%) [4]	6 (18.2%) [8]	9 (9.1%) [12]

3.11 Tolerability

Table S11.1: Tolerability by treatment arm: Primary tolerability analysis population

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total Randomised					
	27	29	28	27	111
Total ITT Population					
	25	28	28	27	108
Excluded from Tolerability Population					
Rifampin susceptible	0	0	0	2	2
In another trial	1	0	0	0	1
Moved away	0	1	0	0	1
Pregnancy	1	0	0	0	1
XDR at baseline	0	0	1	0	1
Total Tolerability Population					
	23	27	27	25	102
Completed 168 doses within 200 days					
	14 (61%)	21 (78%)	18 (67%)	18 (72%)	71 (70%)
Not completed treatment					
Other	1 (4%)	1 (4%)	3 (11%)	2 (8%)	7 (7%)
Poor adherence	2 (9%)	1 (4%)	3 (11%)	1 (4%)	7 (7%)
Withdrew consent	2 (9%)	2 (7%)	1 (4%)	1 (4%)	6 (6%)
AE	2 (9%)	1 (4%)	1 (4%)	0	4 (4%)
Concomitant fluoroquinolone	0	1 (4%)	0	1 (4%)	2 (2%)
Withdrawn from treatment in error	1 (4%)	0	0	1 (4%)	2 (2%)
Died	0	0	1 (4%)	0	1 (1%)
Lost to follow-up	1 (4%)	0	0	0	1 (1%)
Treatment failure	0	0	0	1 (4%)	1 (1%)

Table S11.2: Tolerability by treatment arm: Secondary MITT analysis population

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total MITT Population					
	24	27	24	23	98
Completed 168 doses within 200 days					
	13 (54%)	20 (74%)	17 (71%)	16 (70%)	66 (67%)
Not completed treatment					
Other	1 (4%)	1 (4%)	2 (8%)	2 (9%)	6 (6%)
Poor adherence	2 (8%)	1 (4%)	2 (8%)	1 (4%)	6 (6%)
Withdrew consent	2 (8%)	2 (7%)	1 (4%)	1 (4%)	6 (6%)
AE	2 (8%)	1 (4%)	1 (4%)	0	4 (4%)
Concomitant fluoroquinolone	0	1 (4%)	0	1 (4%)	2 (2%)
Withdrawn from treatment in error	1 (4%)	0	0	1 (4%)	2 (2%)
Died	0	0	1 (4%)	0	1 (1%)
In another trial	1 (4%)	0	0	0	1 (1%)
Lost to follow-up	1 (4%)	0	0	0	1 (1%)
Moved away	0	1 (4%)	0	0	1 (1%)
Pregnancy	1 (4%)	0	0	0	1 (1%)
Treatment failure	0	0	0	1 (4%)	1 (1%)

Table S11.3: Tolerability by treatment arm: Secondary ITT analysis population

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total ITT Population					
	25	28	28	27	108
Completed 168 doses within 200 days					
	14 (56%)	21 (75%)	18 (64%)	18 (67%)	71 (66%)
Not completed treatment					
Other	1 (4%)	1 (4%)	3 (11%)	2 (7%)	7 (6%)
Poor adherence	2 (8%)	1 (4%)	3 (11%)	1 (4%)	7 (6%)
Withdrew consent	2 (8%)	2 (7%)	1 (4%)	1 (4%)	6 (6%)
AE	2 (8%)	1 (4%)	1 (4%)	0	4 (4%)
Concomitant fluoroquinolone	0	1 (4%)	0	1 (4%)	2 (2%)
Rifampin susceptible	0	0	0	2 (7%)	2 (2%)
Withdrawn from treatment in error	1 (4%)	0	0	1 (4%)	2 (2%)
Died	0	0	1 (4%)	0	1 (1%)
In another trial	1 (4%)	0	0	0	1 (1%)
Lost to follow-up	1 (4%)	0	0	0	1 (1%)
Moved away	0	1 (4%)	0	0	1 (1%)
Pregnancy	1 (4%)	0	0	0	1 (1%)
Treatment failure	0	0	0	1 (4%)	1 (1%)
XDR at baseline	0	0	1 (4%)	0	1 (1%)

Table S11.4: Duration of treatment: Tolerability analysis population

	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Total	23	27	27	25	102
<2 weeks	2 (9%)	2 (7%)	1 (4%)	0	5 (5%)
2-<8 weeks	0	2 (7%)	2 (7%)	2 (8%)	6 (6%)
8-<16wks	3 (13%)	1 (4%)	0	2 (8%)	6 (6%)
16wks- <167 doses	4 (17%)	1 (4%)	6 (22%)	3 (12%)	14 (14%)
168+ doses	14 (61%)	21 (78%)	18 (67%)	18 (72%)	71 (70%)

Table S11.5: Tolerability by tertile of AUC: Primary tolerability analysis population

	Lower tertile	Middle tertile	Upper tertile	Total
Total Randomised				
	33	33	33	99
Total ITT Population				
	33	33	33	99
Excluded from Tolerability Population				
Rifampin susceptible	0	1	1	2
Moved away	1	0	0	1
Pregnancy	1	0	0	1
XDR at baseline	0	1	0	1
Total Tolerability Population				
	31	31	32	94
Completed 168 doses within 200 days				
	25 (81%)	19 (61%)	27 (84%)	71 (76%)
Not completed treatment				
Other	2 (6%)	3 (10%)	2 (6%)	7 (7%)
Poor adherence	2 (6%)	3 (10%)	1 (3%)	6 (6%)
AE	0	3 (10%)	0	3 (3%)
Withdrawn from treatment in error	1 (3%)	0	1 (3%)	2 (2%)
Withdrew consent	1 (3%)	1 (3%)	0	2 (2%)
Died	0	0	1 (3%)	1 (1%)
Lost to follow-up	0	1 (3%)	0	1 (1%)
Treatment failure	0	1 (3%)	0	1 (1%)

Table S11.6: Tolerability by tertile of AUC: Secondary MITT analysis population

	Lower tertile	Middle tertile	Upper tertile	Total
Total MITT Population				
	33	27	29	89
Completed 168 doses within 200 days				
	25 (76%)	16 (59%)	25 (86%)	66 (74%)
Not completed treatment				
Other	2 (6%)	3 (11%)	1 (3%)	6 (7%)
Poor adherence	2 (6%)	2 (7%)	1 (3%)	5 (6%)
AE	0	3 (11%)	0	3 (3%)
Withdrawn from treatment in error	1 (3%)	0	1 (3%)	2 (2%)
Withdrew consent	1 (3%)	1 (4%)	0	2 (2%)
Died	0	0	1 (3%)	1 (1%)
Lost to follow-up	0	1 (4%)	0	1 (1%)
Moved away	1 (3%)	0	0	1 (1%)
Pregnancy	1 (3%)	0	0	1 (1%)
Treatment failure	0	1 (4%)	0	1 (1%)

Table S11.7: Tolerability by tertile of AUC: Secondary ITT analysis population

	Lower tertile	Middle tertile	Upper tertile	Total
Total ITT Population				
	33	33	33	99
Completed 168 doses within 200 days				
	25 (76%)	19 (58%)	27 (82%)	71 (72%)
Not completed treatment				
Other	2 (6%)	3 (9%)	2 (6%)	7 (7%)
Poor adherence	2 (6%)	3 (9%)	1 (3%)	6 (6%)
AE	0	3 (9%)	0	3 (3%)
Rifampin susceptible	0	1 (3%)	1 (3%)	2 (2%)
Withdrawn from treatment in error	1 (3%)	0	1 (3%)	2 (2%)
Withdrew consent	1 (3%)	1 (3%)	0	2 (2%)
Died	0	0	1 (3%)	1 (1%)
Lost to follow-up	0	1 (3%)	0	1 (1%)
Moved away	1 (3%)	0	0	1 (1%)
Pregnancy	1 (3%)	0	0	1 (1%)
Treatment failure	0	1 (3%)	0	1 (1%)
XDR at baseline	0	1 (3%)	0	1 (1%)

Table S11.8: Duration of treatment: Tolerability analysis population

	Lower tertile	Middle tertile	Upper tertile	Total
Total	31	31	32	94
2-<8 weeks	1 (3%)	3 (10%)	1 (3%)	5 (5%)
8-<16wks	1 (3%)	2 (6%)	1 (3%)	4 (4%)
16wks- <167 doses	4 (13%)	7 (23%)	3 (9%)	14 (15%)
168+ doses	25 (81%)	19 (61%)	27 (84%)	71 (76%)

3.12 Cardiac toxicity

Figure S12.1: Summary of QTcF over time.

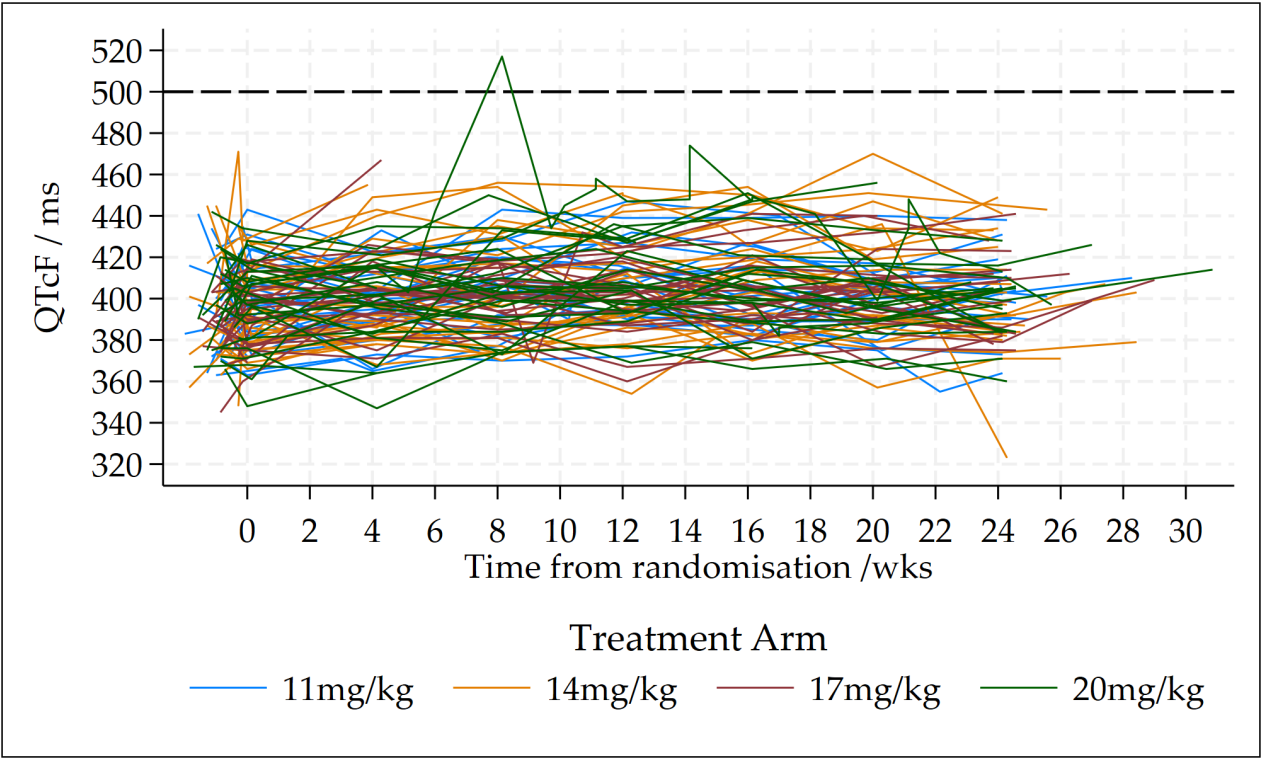


Figure S12.2: Summary of QTcF by AUC (all measurements).

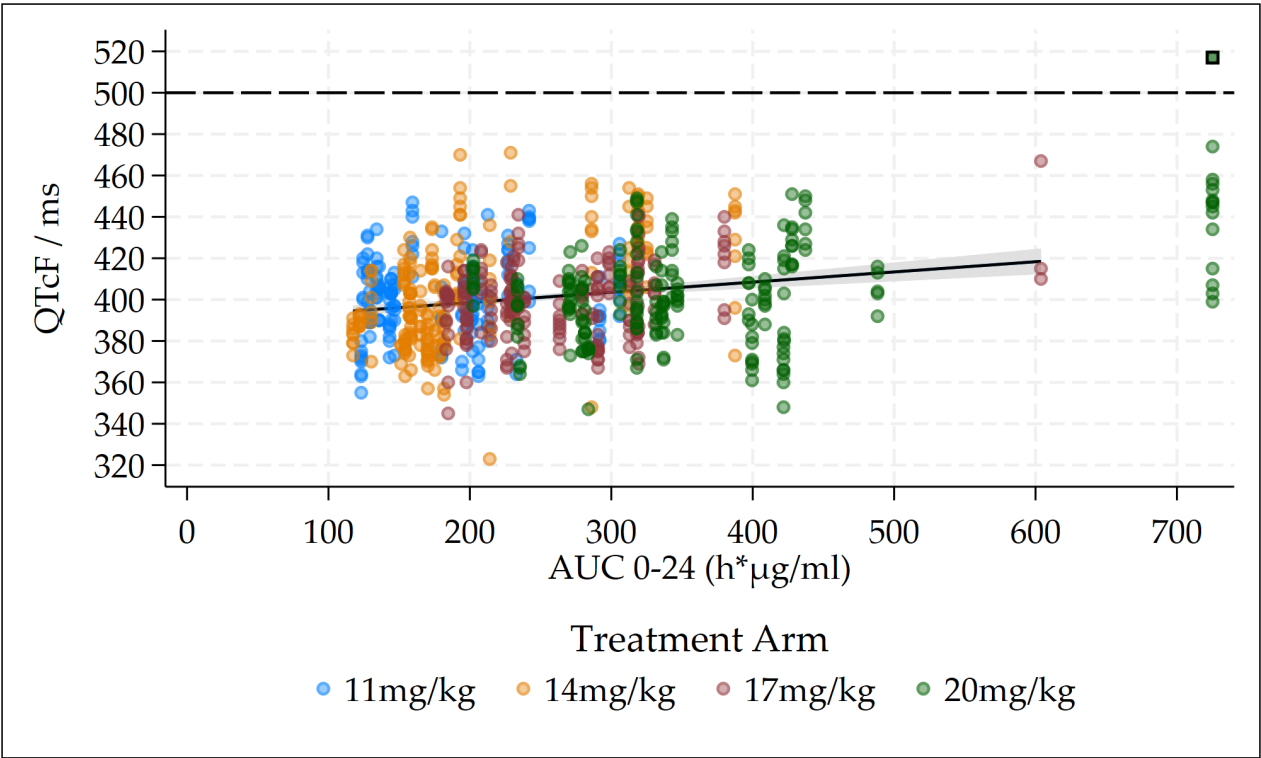


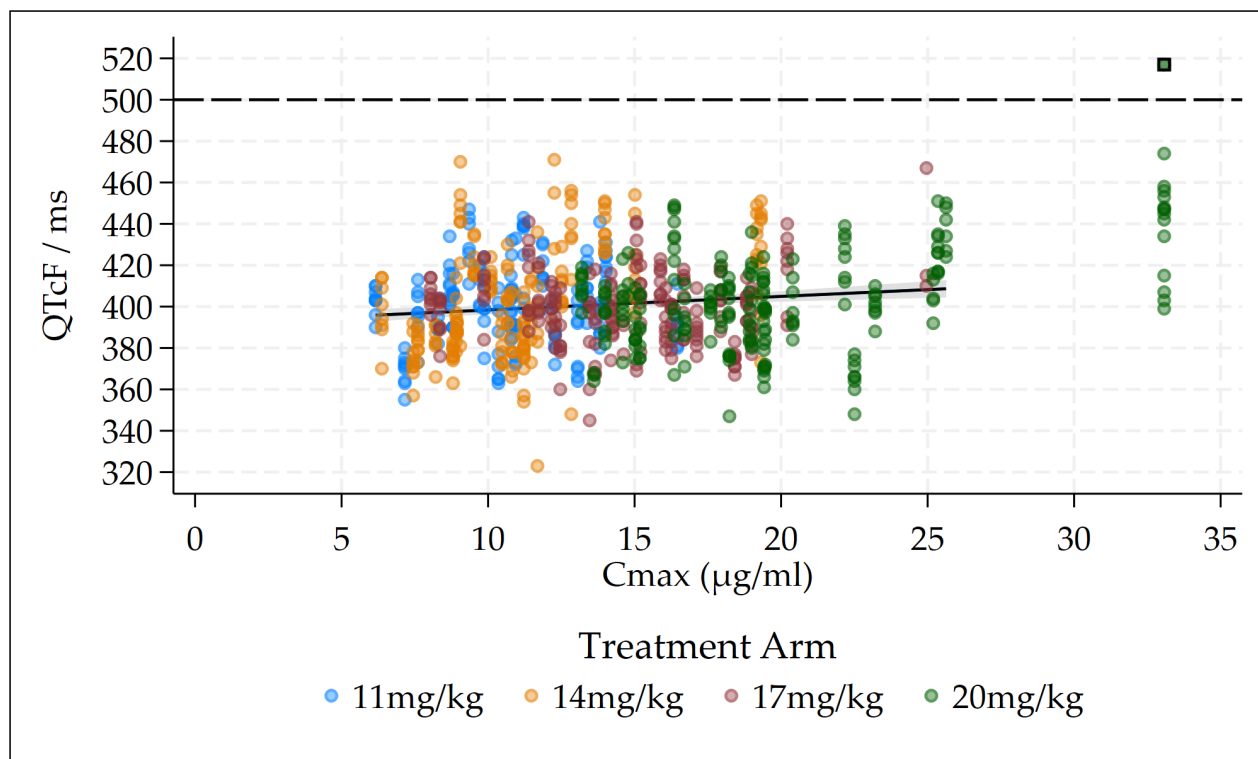
Figure S12.3: Summary of QTcF by C_{max} (all measurements).

Figure S12.4: Summary of QTcF by AUC (only showing each participants maximum post-baseline measurement). The black square shows a single participant had a QTcF exceeding 500ms (Grade 3) who received azithromycin. Line of best fit is shown (excluding participant that received azithromycin) as solid black line with 95% confidence region (gray shaded area).

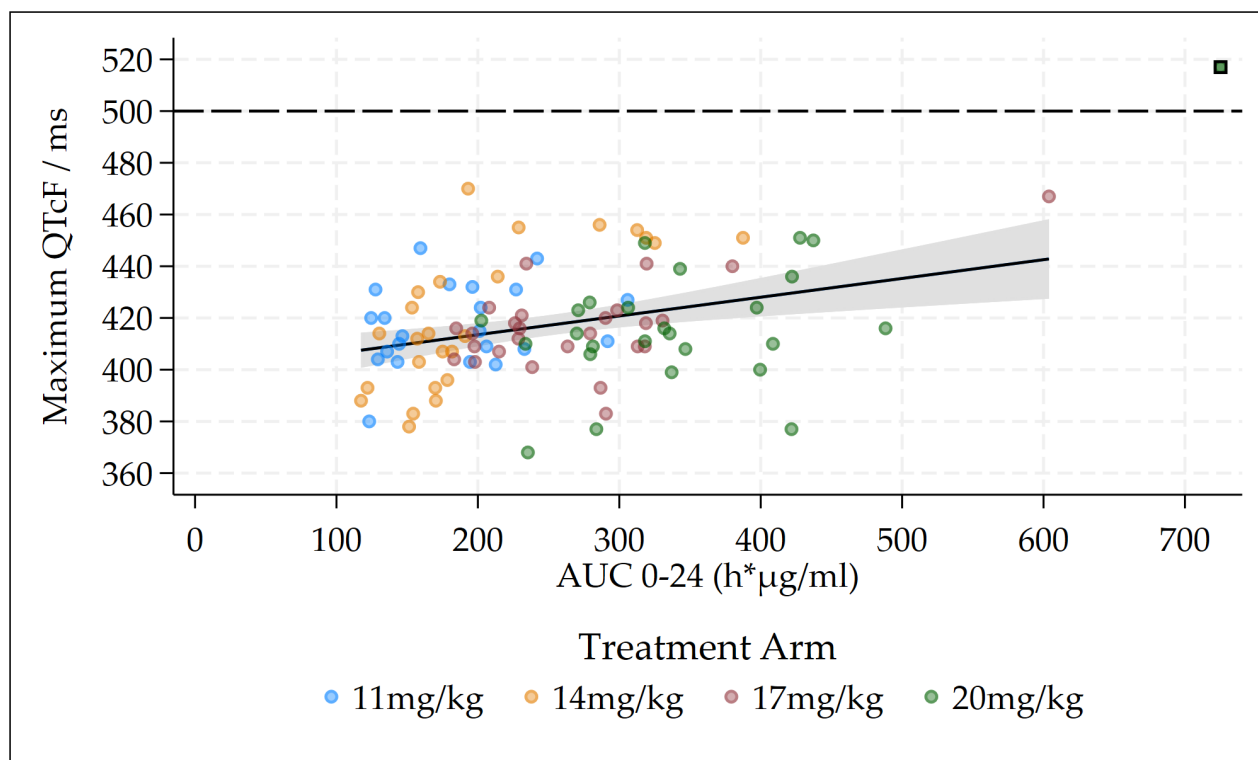


Figure S12.5: Summary of QTcF by C_{max} (only showing each participants maximum post-baseline measurement). The black square shows a single participant had a QTcF exceeding 500ms (Grade 3) who received azithromycin. Line of best fit is shown (excluding participant that received azithromycin) as solid black line with 95% confidence region (gray shaded area).

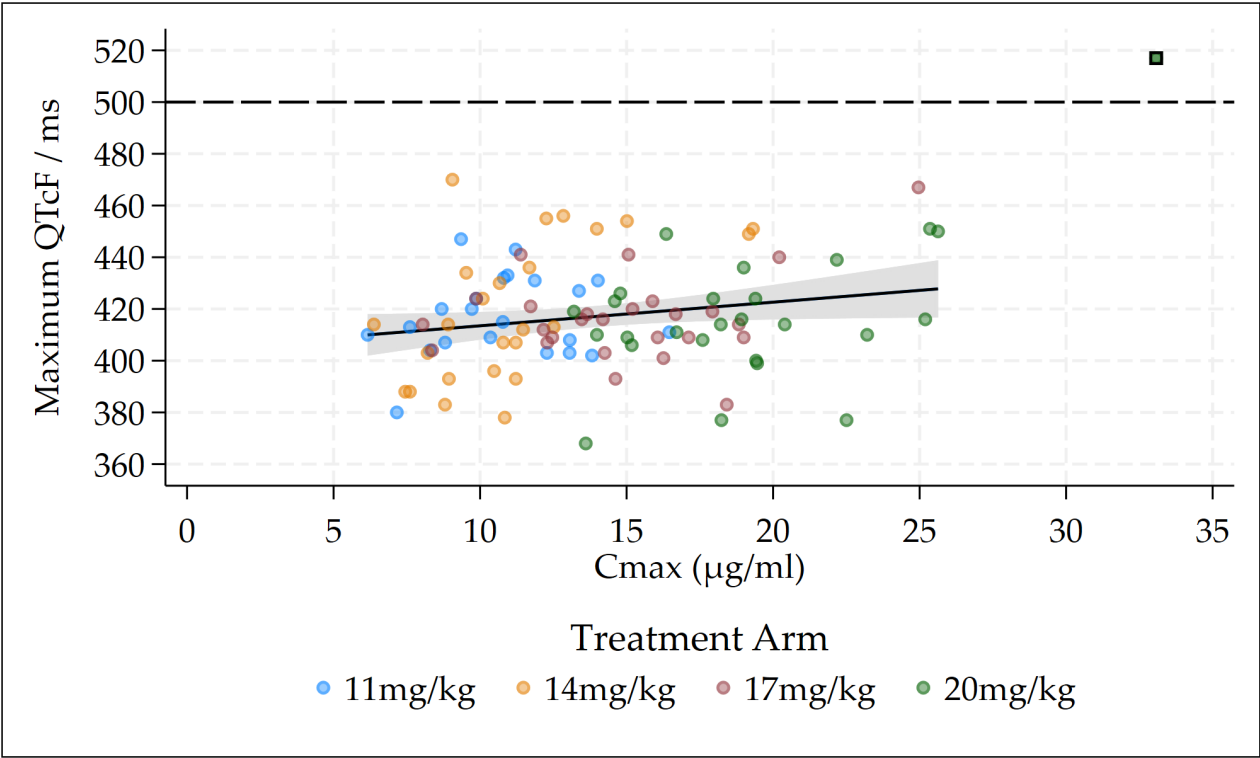


Figure S12.6: Mean of change in QTcF from baseline by tertile of AUC (bars show 95% confidence interval).

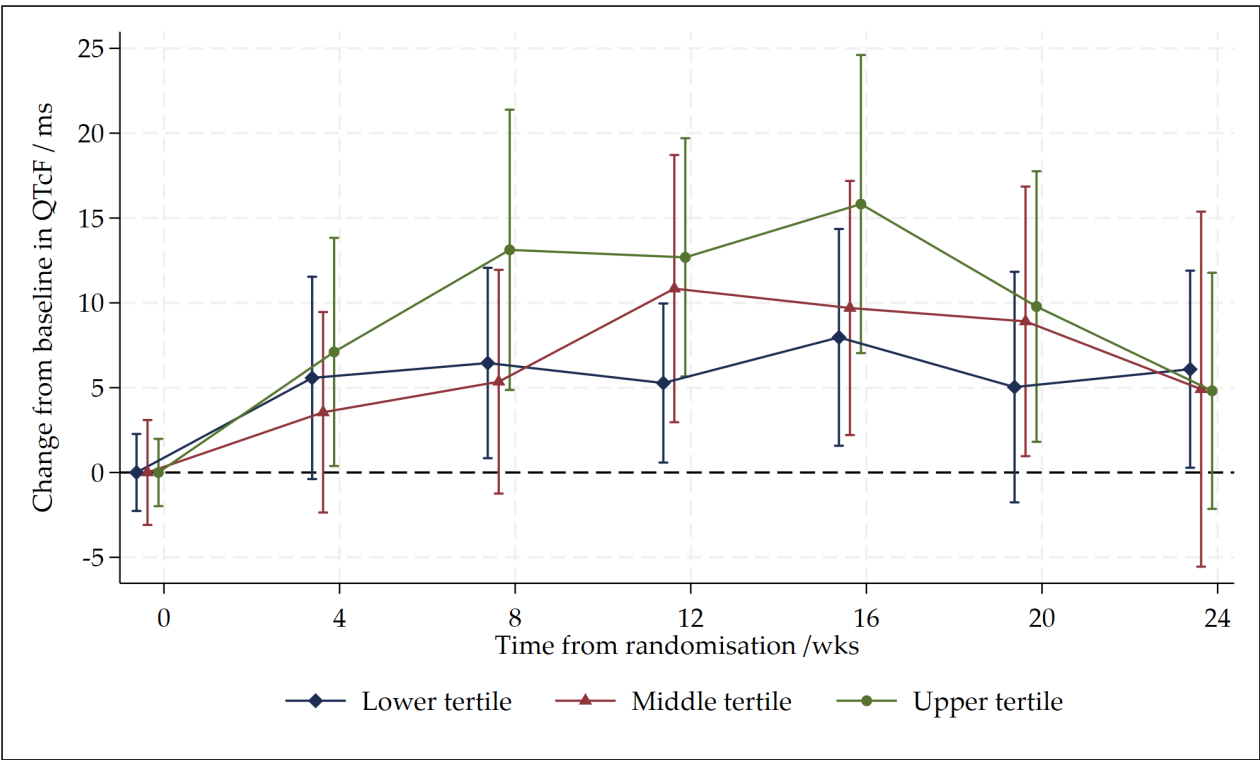


Figure S12.7: Mean of change in QTcF from baseline by tertile of CMax (bars show 95% confidence interval).

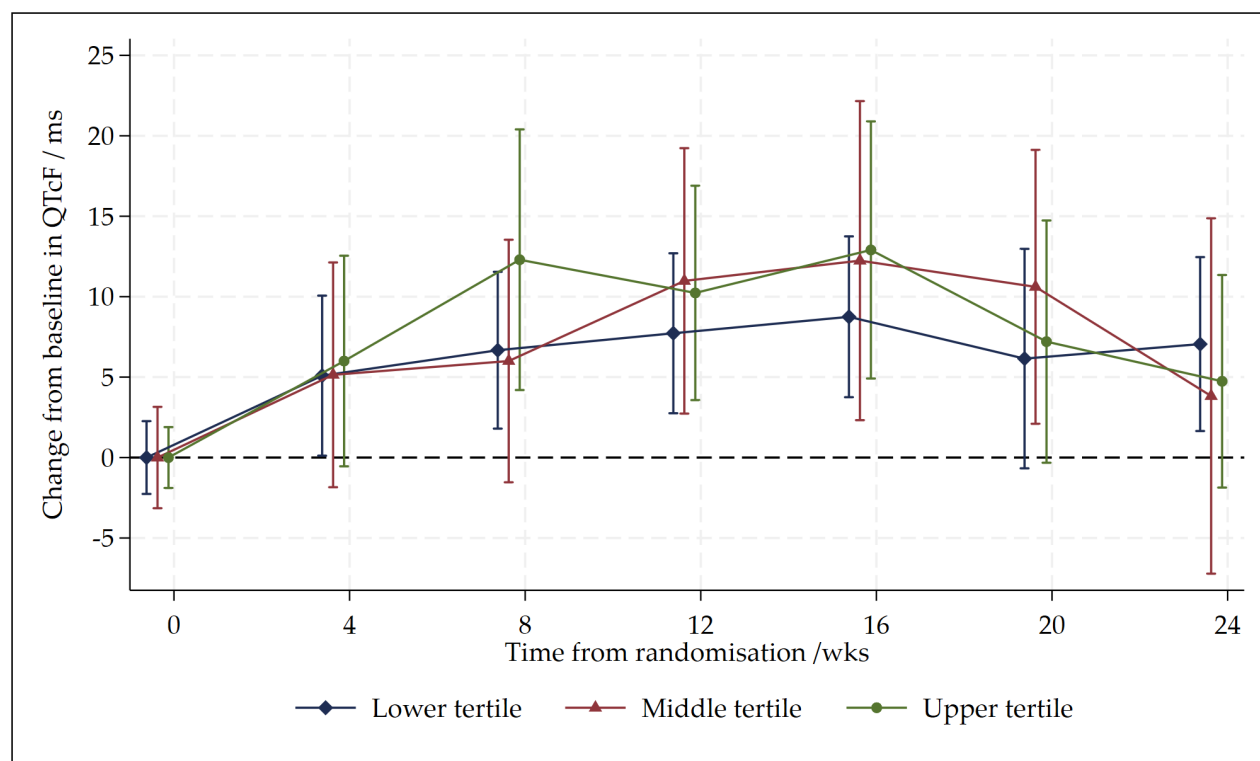


Figure S12.8: Mean of change in QTcF from baseline by tertile of AUC excluding participant that received azithromycin (bars show 95% confidence interval).

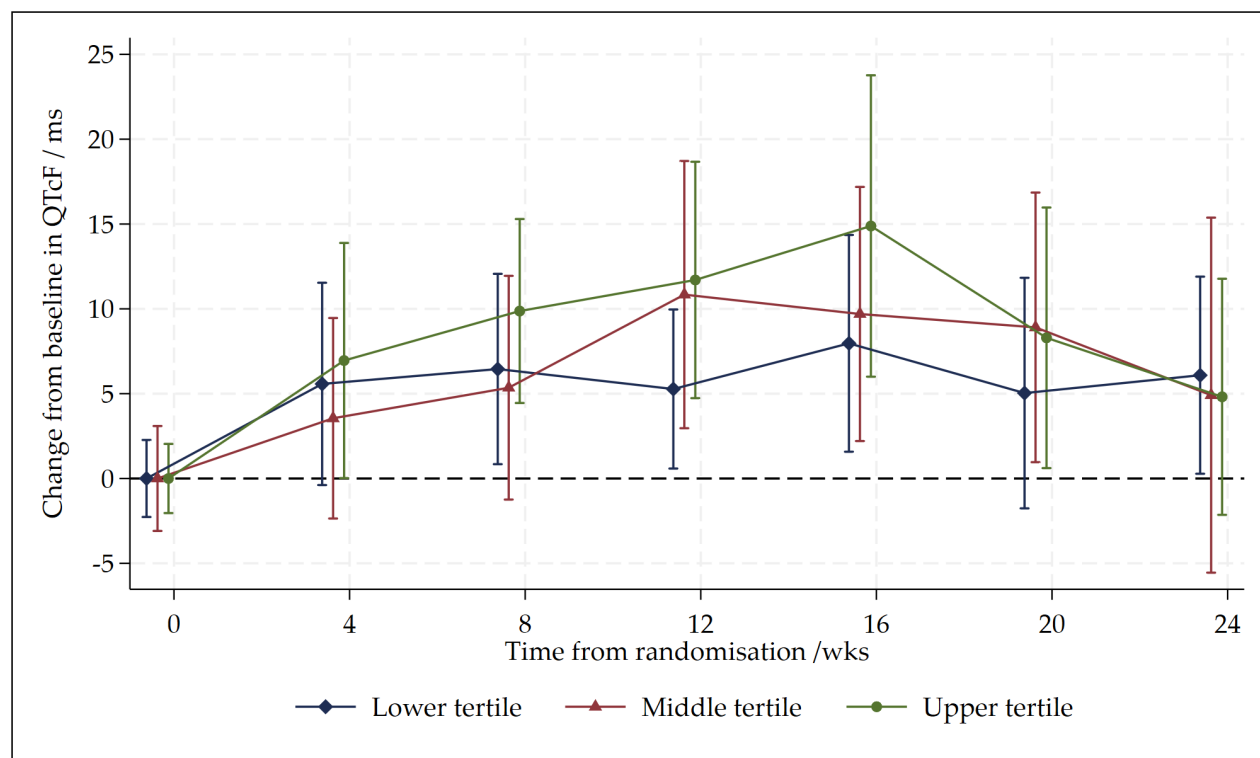
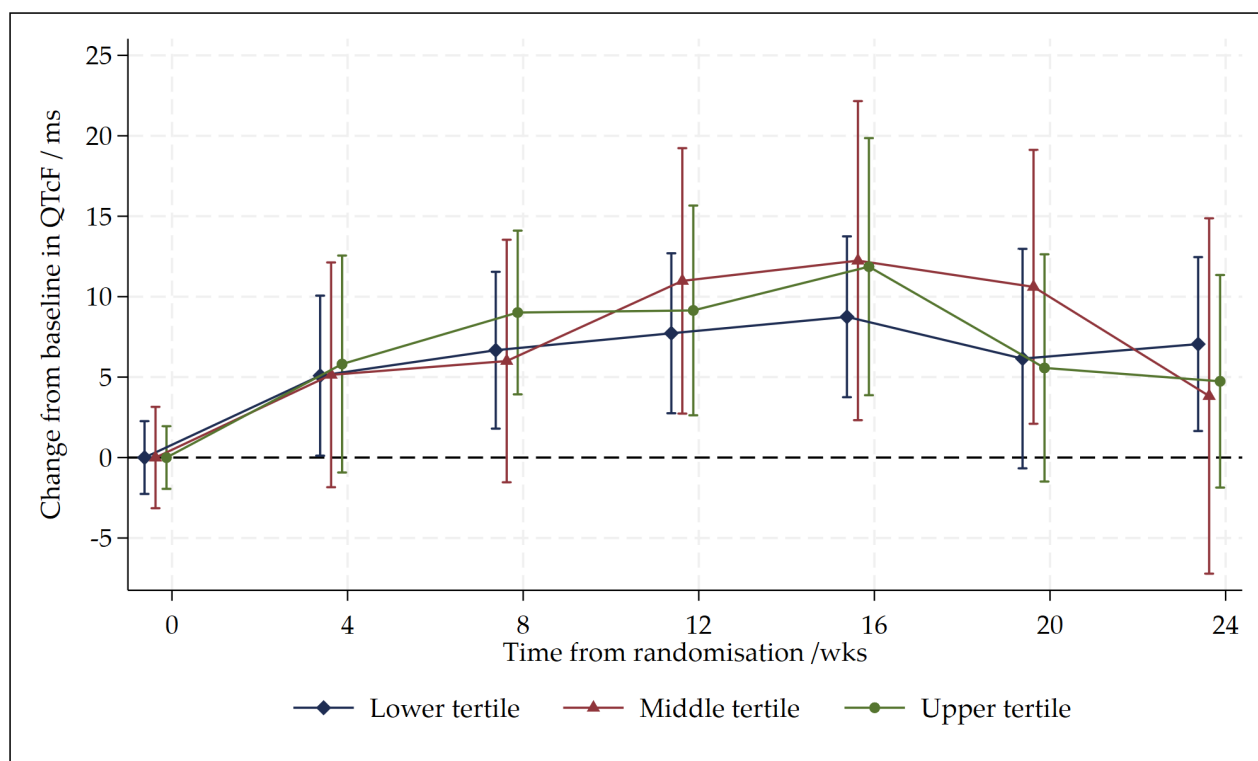


Figure S12.9: Mean of change in QTcF from baseline by tertile of CMax excluding participant that received azithromycin (bars show 95% confidence interval).



3.13 Weight Gain

Figure S13.1: Individual participant Weight over time.

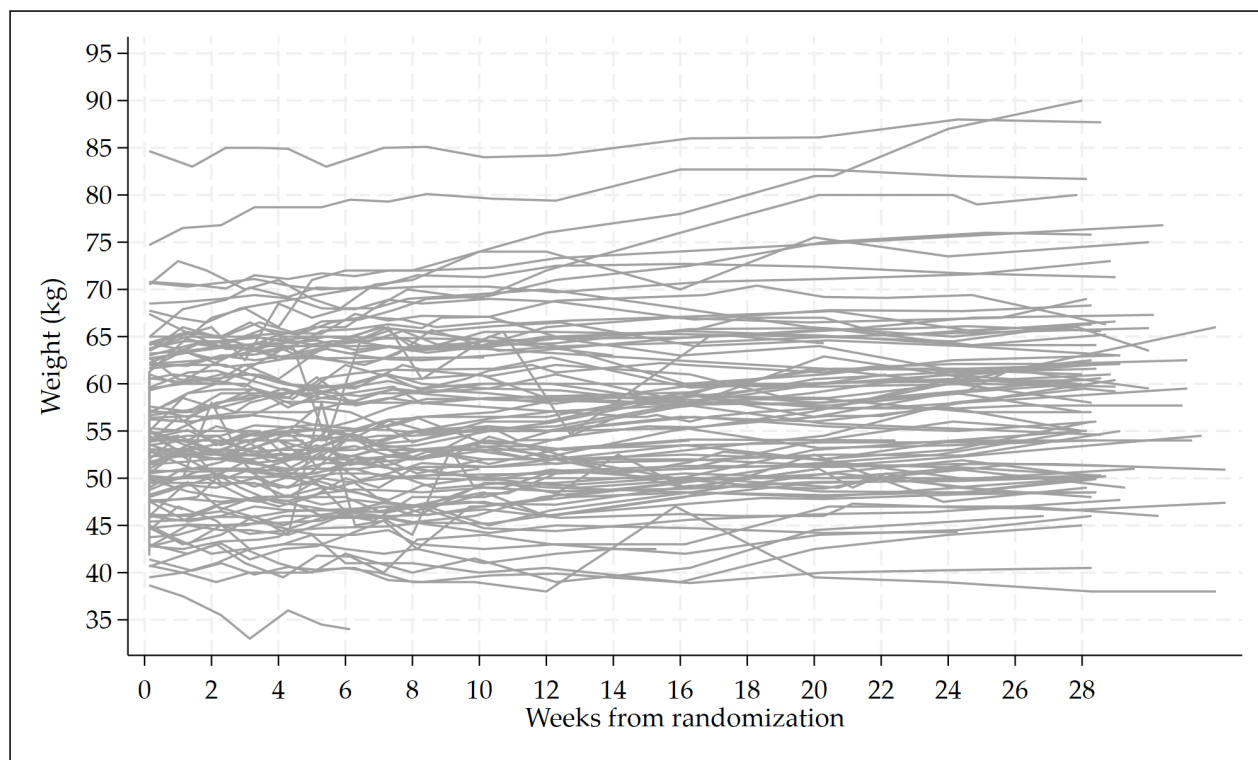


Figure S13.2: Individual participant change in Weight from baseline over time.

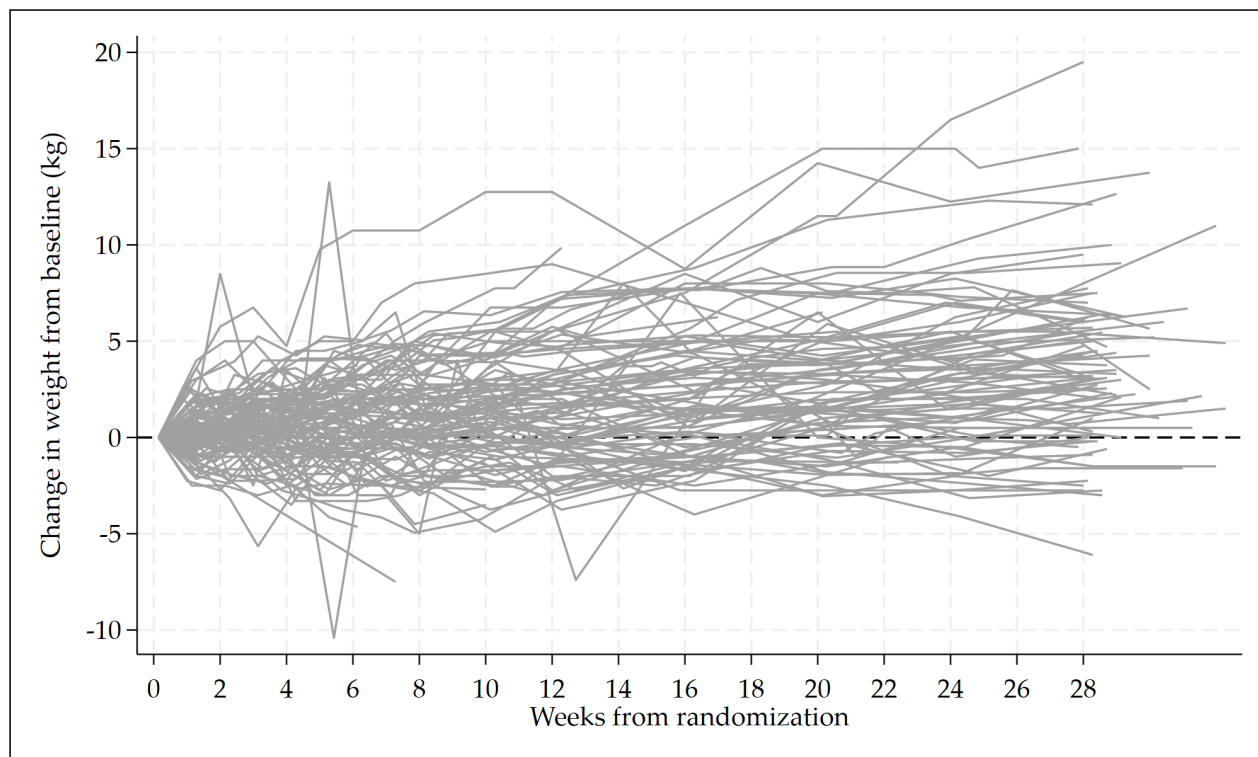


Figure S13.3: Mean weight gain from baseline by allocated treatment arm (kg)

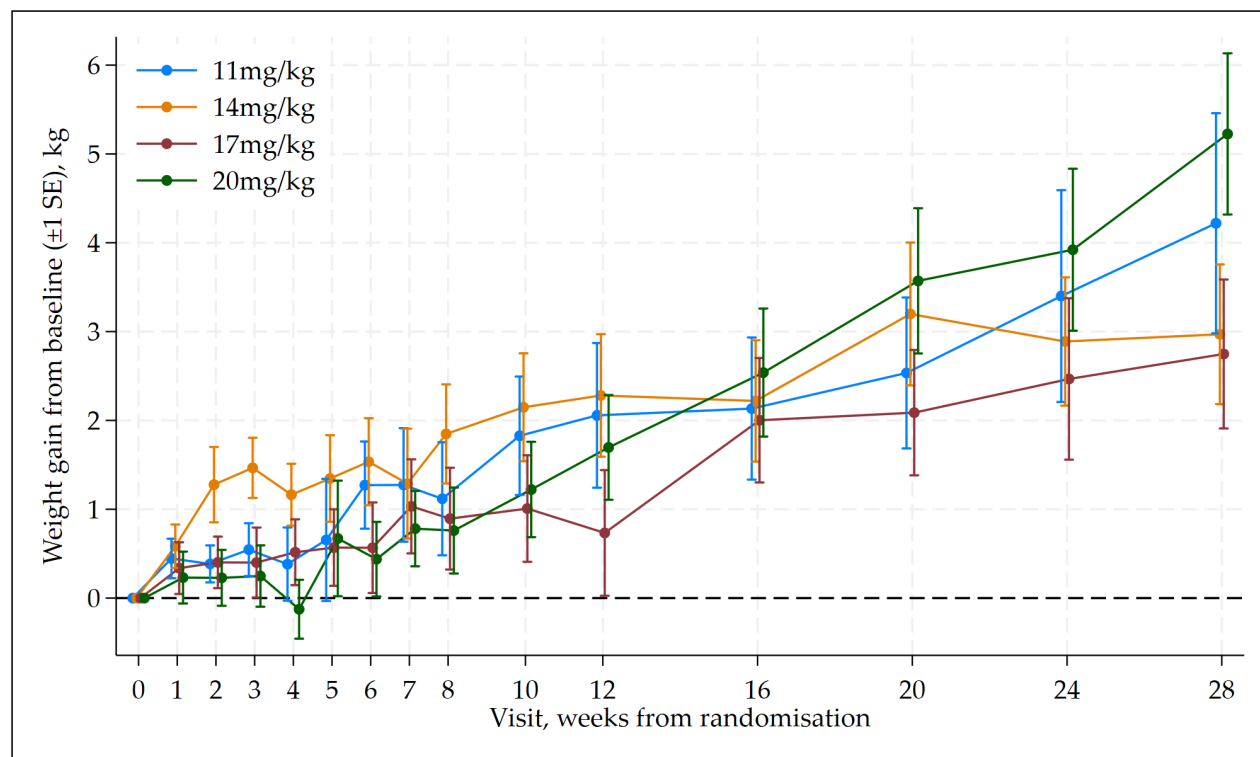


Figure S13.4: Mean percentage weight gain from baseline by allocated treatment arm (kg)

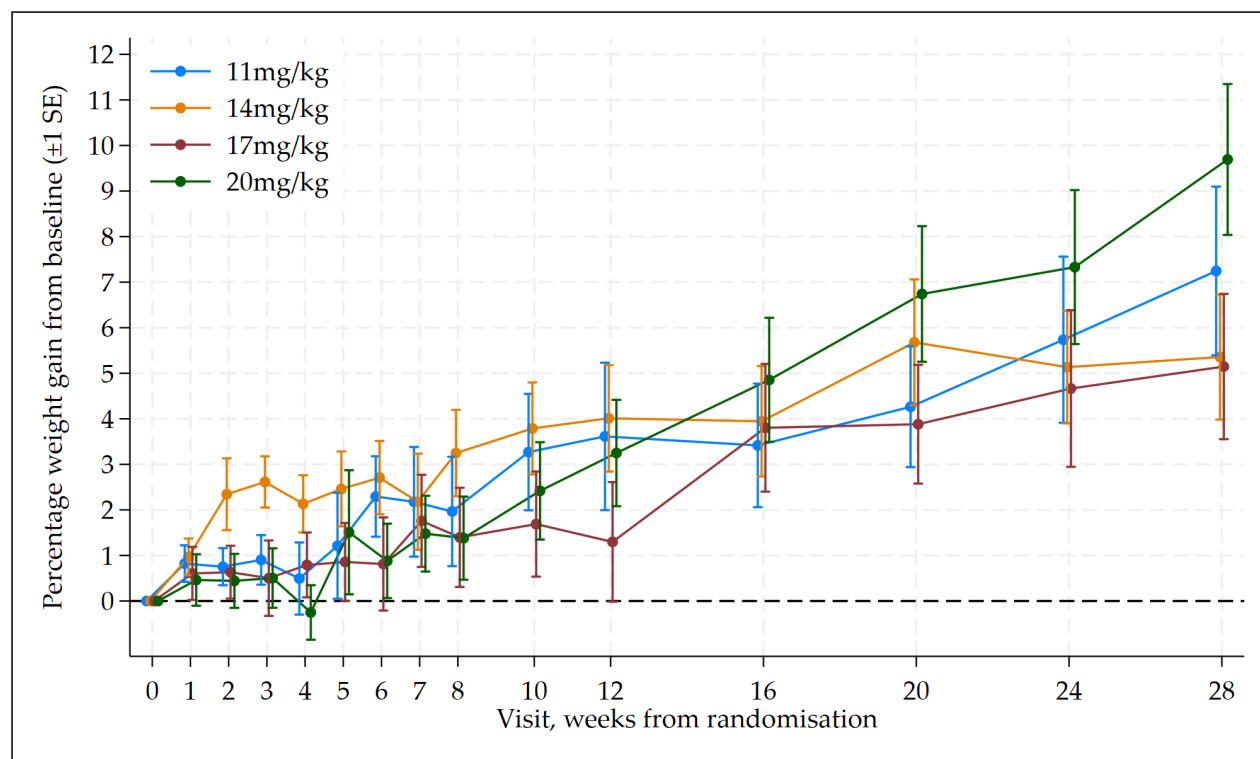


Figure S13.5: Mean weight gain from baseline by tertile of AUC

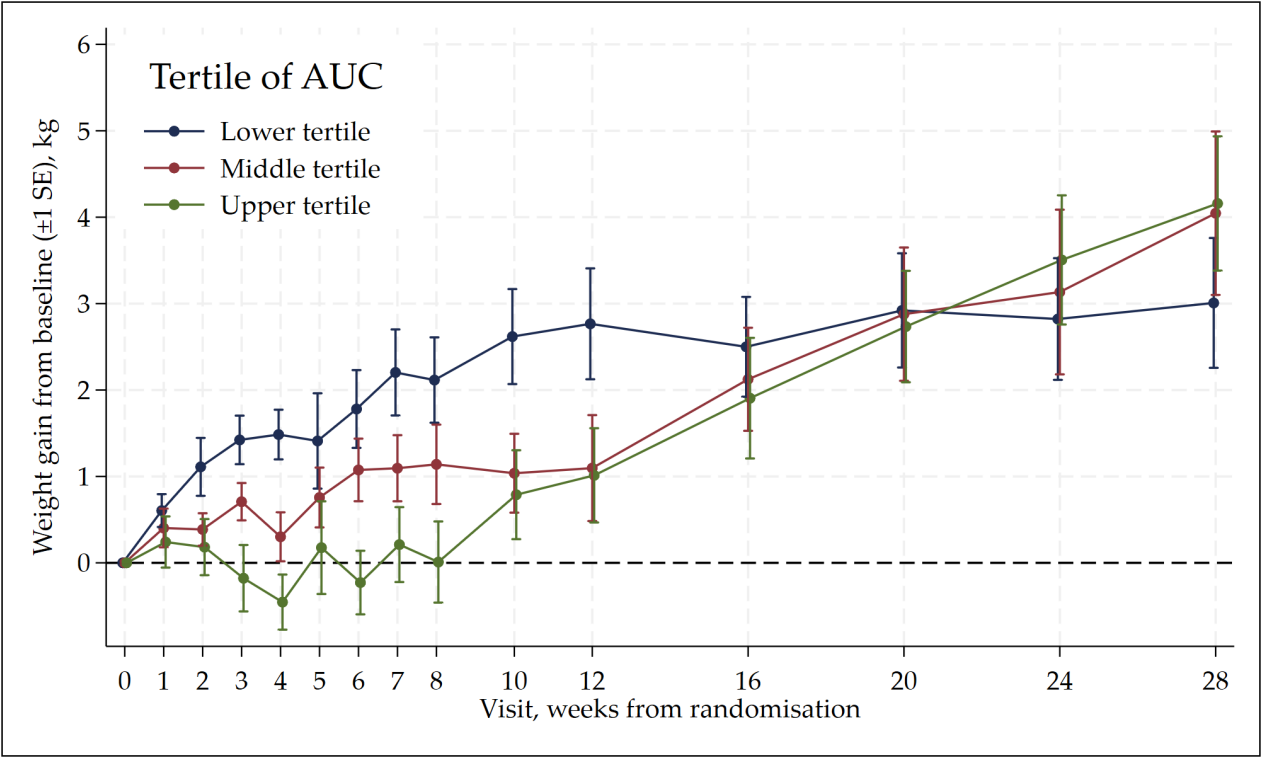
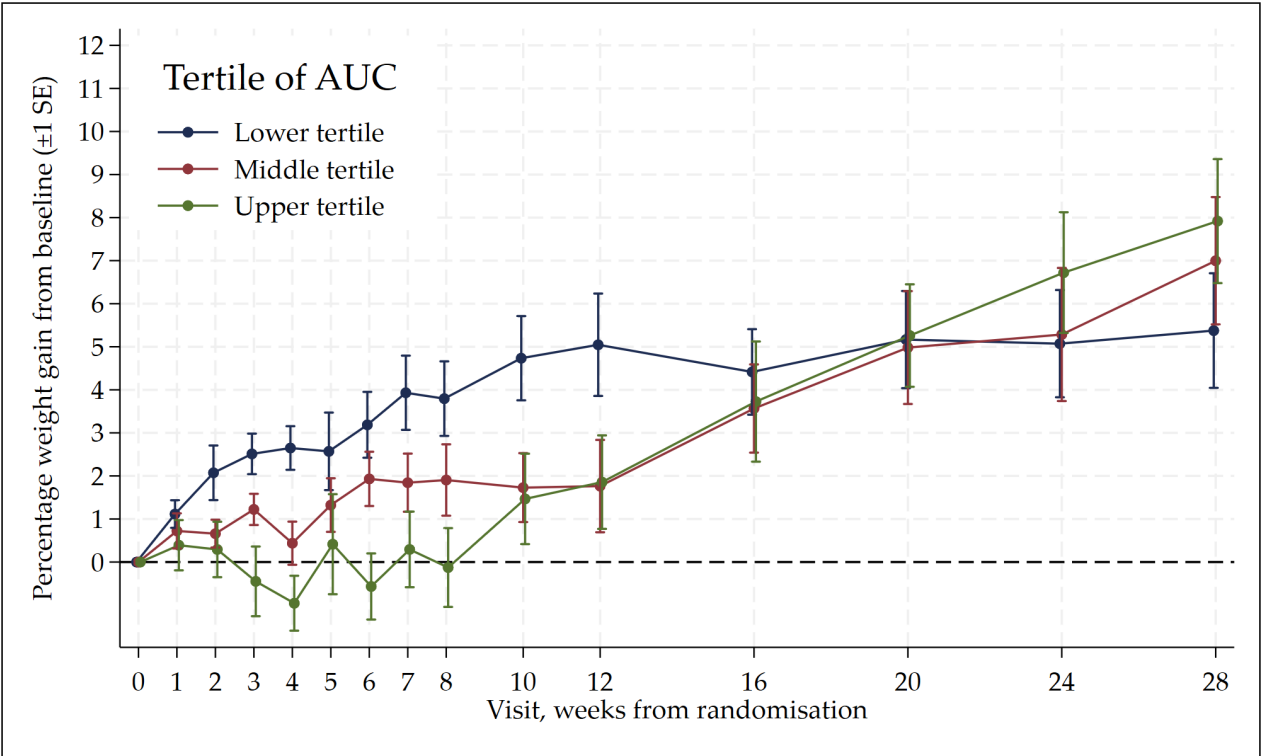


Figure S13.6: Mean percentage weight gain from baseline by tertile of AUC



3.14 Primary Efficacy Analyses: Time to culture conversion

Figure S14.1: Overall time to culture conversion (7H11).

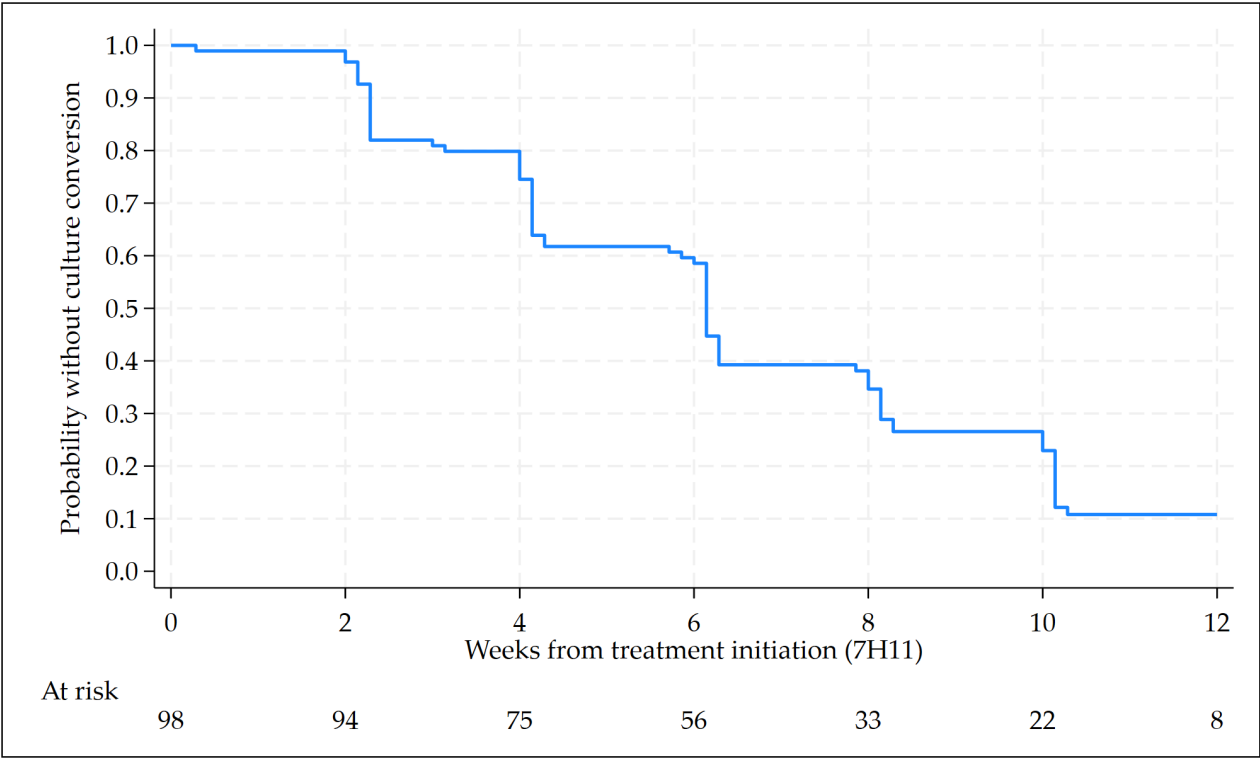


Table S14.1: Time to culture conversion summary (7H11).

Participants	Median (wks)	25th, 75th centile (wks)
98	6.1	4.0, 10.0
98		

Figure S14.2: Overall time to culture conversion (MGIT).

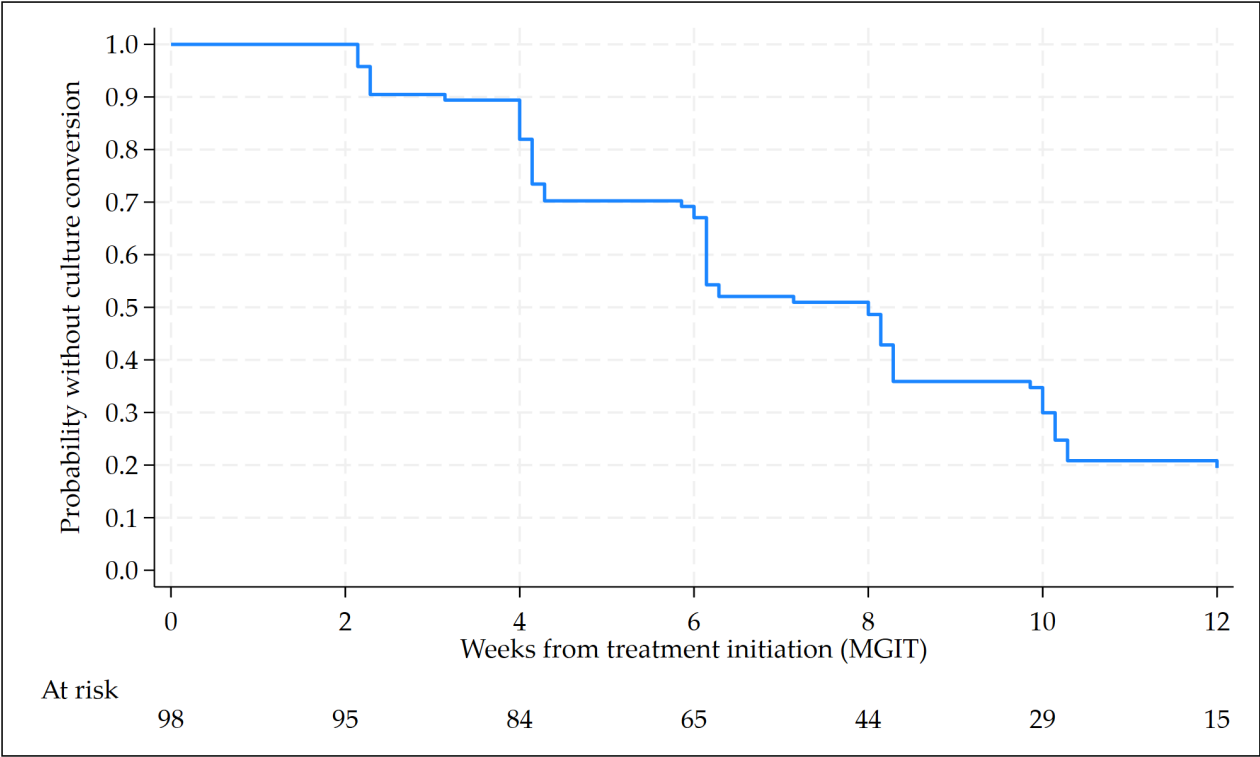


Table S14.2: Time to culture conversion summary (MGIT).

Participants	Median (wks)	25th, 75th centile (wks)
98	8.0	4.1, 10.1
98		

Figure S14.3: Time to culture conversion by treatment arm (7H11).

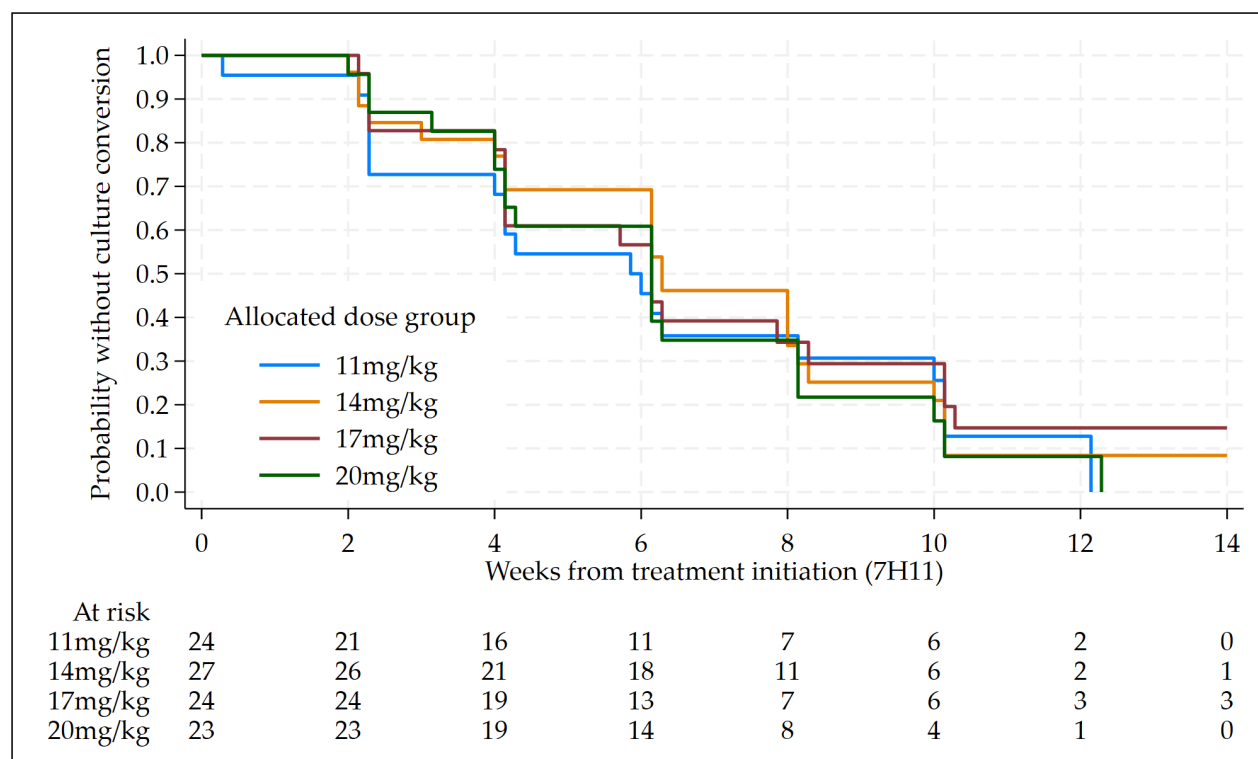


Table S14.3: Time to culture conversion by treatment arm (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
11mg/kg	24	5.9	2.3, 10.1	1.00 (1.00, 1.00)
14mg/kg	27	6.3	4.1, 10.0	0.79 (0.41, 1.51)
17mg/kg	24	6.1	4.1, 10.1	0.68 (0.34, 1.35)
20mg/kg	23	6.1	4.0, 8.1	0.92 (0.47, 1.81)
Overall	98			Log-rank test, p = 0.282
Adjusted phtest				
	NA			PH test, p = 0.689
Unadjusted				
11mg/kg	24	5.9	2.3, 10.1	1.00 (1.00, 1.00)
14mg/kg	27	6.3	4.1, 10.0	0.87 (0.48, 1.57)
17mg/kg	24	6.1	4.1, 10.1	0.74 (0.39, 1.39)
20mg/kg	23	6.1	4.0, 8.1	1.00 (0.54, 1.85)
Overall	98			Log-rank test, p = 0.236
Unadjusted phtest				
	NA			PH test, p = 0.480

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.4: Time to culture conversion by treatment arm (MGIT).

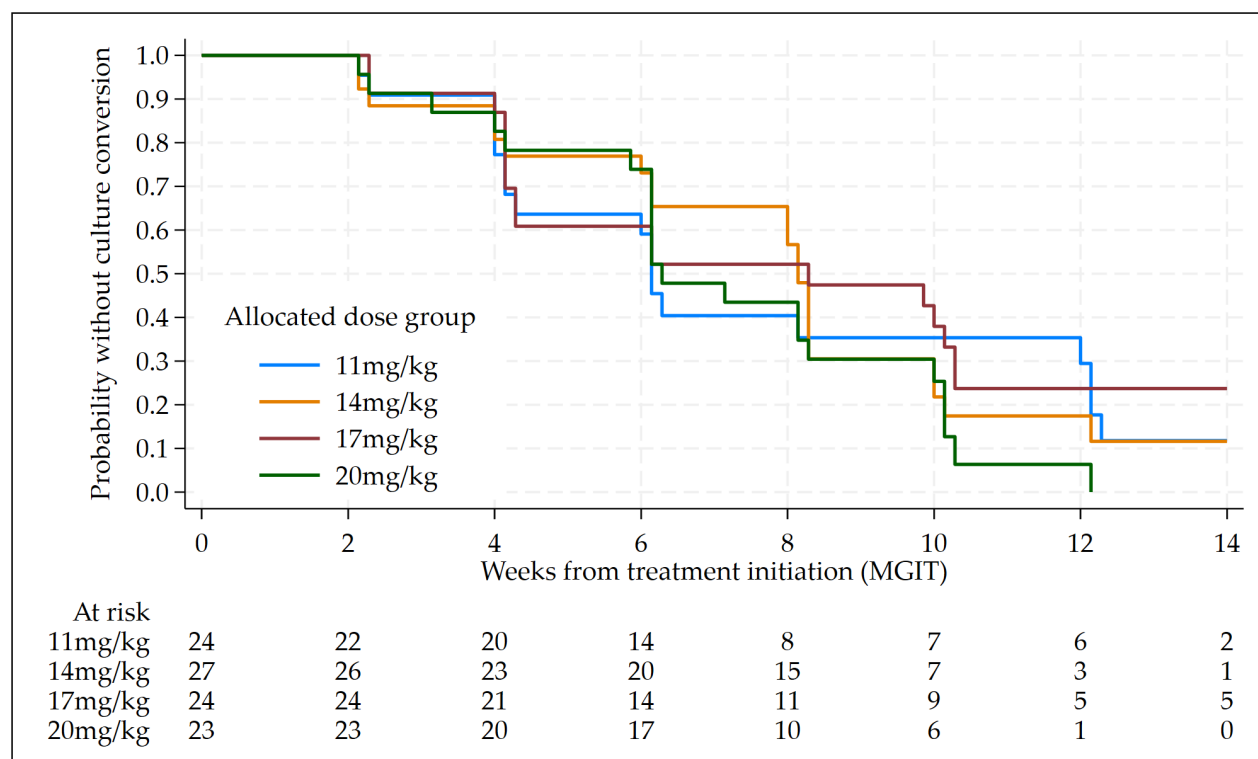


Table S14.4: Time to culture conversion by treatment arm (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
11mg/kg	24	6.1	4.1, 12.1	1.00 (1.00, 1.00)
14mg/kg	27	8.1	6.0, 10.0	1.00 (0.52, 1.92)
17mg/kg	24	8.3	4.1, 10.3	0.76 (0.38, 1.53)
20mg/kg	23	6.3	5.9, 10.1	1.14 (0.58, 2.24)
Overall	98			Log-rank test, p = 0.313
Adjusted phtest				
	NA			PH test, p = 0.648
Unadjusted				
11mg/kg	24	6.1	4.1, 12.1	1.00 (1.00, 1.00)
14mg/kg	27	8.1	6.0, 10.0	1.06 (0.57, 1.98)
17mg/kg	24	8.3	4.1, 10.3	0.83 (0.44, 1.56)
20mg/kg	23	6.3	5.9, 10.1	1.29 (0.68, 2.43)
Overall	98			Log-rank test, p = 0.151
Unadjusted phtest				
	NA			PH test, p = 0.319

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.5: Time to culture conversion by total dose (7H11).

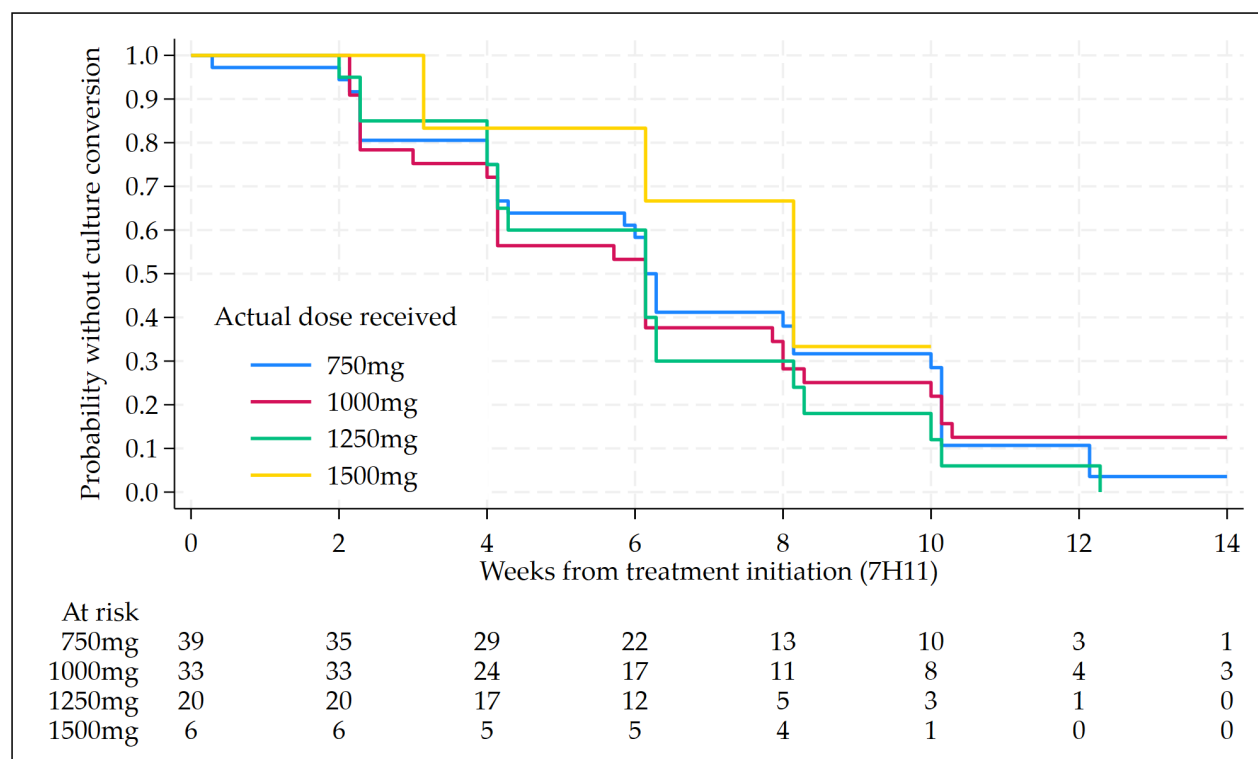


Table S14.5: Time to culture conversion by total dose (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
750mg	39	6.1	4.0, 10.1	1.00 (1.00, 1.00)
1000mg	33	6.1	4.0, 10.0	0.90 (0.52, 1.57)
1250mg	20	6.1	4.0, 8.1	1.12 (0.61, 2.06)
1500mg	6	8.1	6.1, .	0.51 (0.18, 1.51)
Overall	98			Log-rank test, p = 0.061
Adjusted phtest				
	NA			PH test, p = 0.381
Unadjusted				
750mg	39	6.1	4.0, 10.1	1.00 (1.00, 1.00)
1000mg	33	6.1	4.0, 10.0	0.96 (0.58, 1.59)
1250mg	20	6.1	4.0, 8.1	1.20 (0.68, 2.11)
1500mg	6	8.1	6.1, .	0.68 (0.24, 1.92)
Overall	98			Log-rank test, p = 0.228
Unadjusted phtest				
	NA			PH test, p = 0.322

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.6: Time to culture conversion by total dose (MGIT).

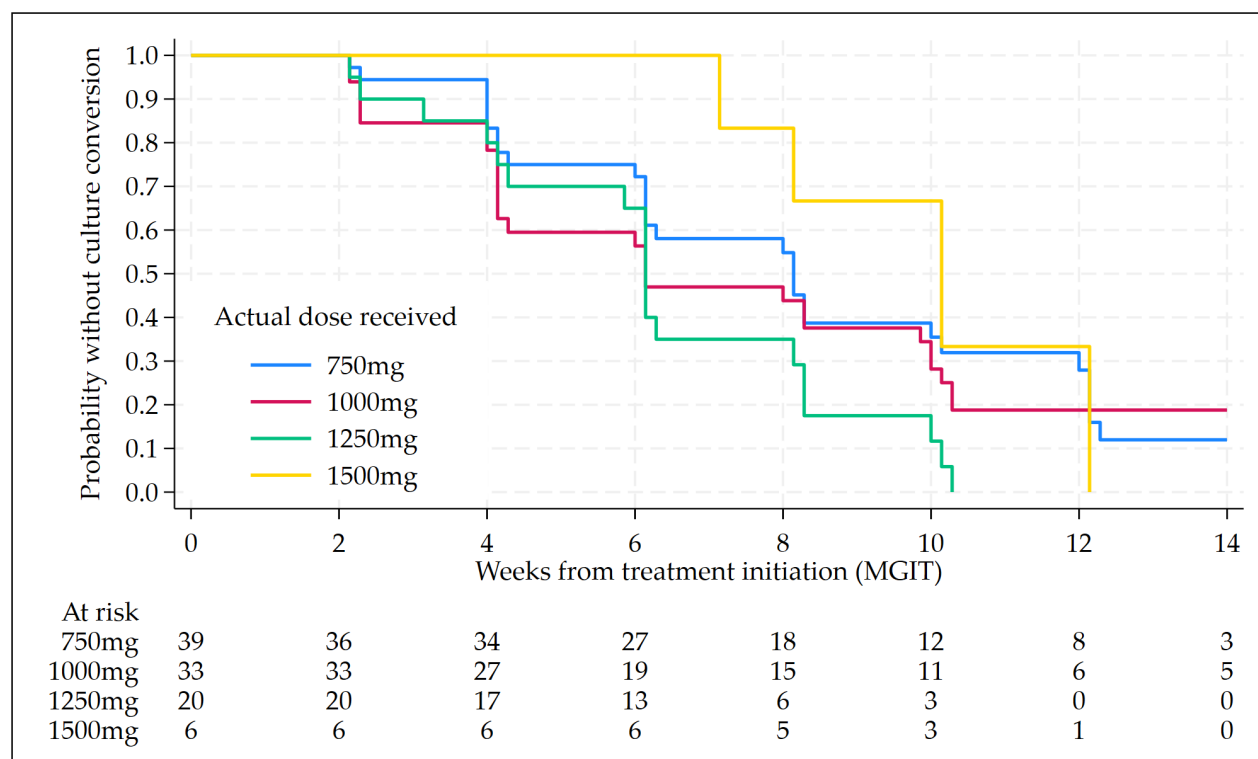


Table S14.6: Time to culture conversion by total dose (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
750mg	39	8.1	4.3, 12.1	1.00 (1.00, 1.00)
1000mg	33	6.1	4.1, 10.3	0.96 (0.55, 1.66)
1250mg	20	6.1	4.1, 8.3	1.57 (0.85, 2.88)
1500mg	6	10.1	8.1, 12.1	0.51 (0.17, 1.49)
Overall	98			Log-rank test, p = 0.008
Adjusted phtest				
	NA			PH test, p = 0.233
Unadjusted				
750mg	39	8.1	4.3, 12.1	1.00 (1.00, 1.00)
1000mg	33	6.1	4.1, 10.3	1.08 (0.65, 1.81)
1250mg	20	6.1	4.1, 8.3	1.77 (0.98, 3.20)
1500mg	6	10.1	8.1, 12.1	0.67 (0.23, 1.90)
Overall	98			Log-rank test, p = 0.015
Unadjusted phtest				
	NA			PH test, p = 0.167

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.7: Time to culture conversion by tertiles of AUC (7H11).

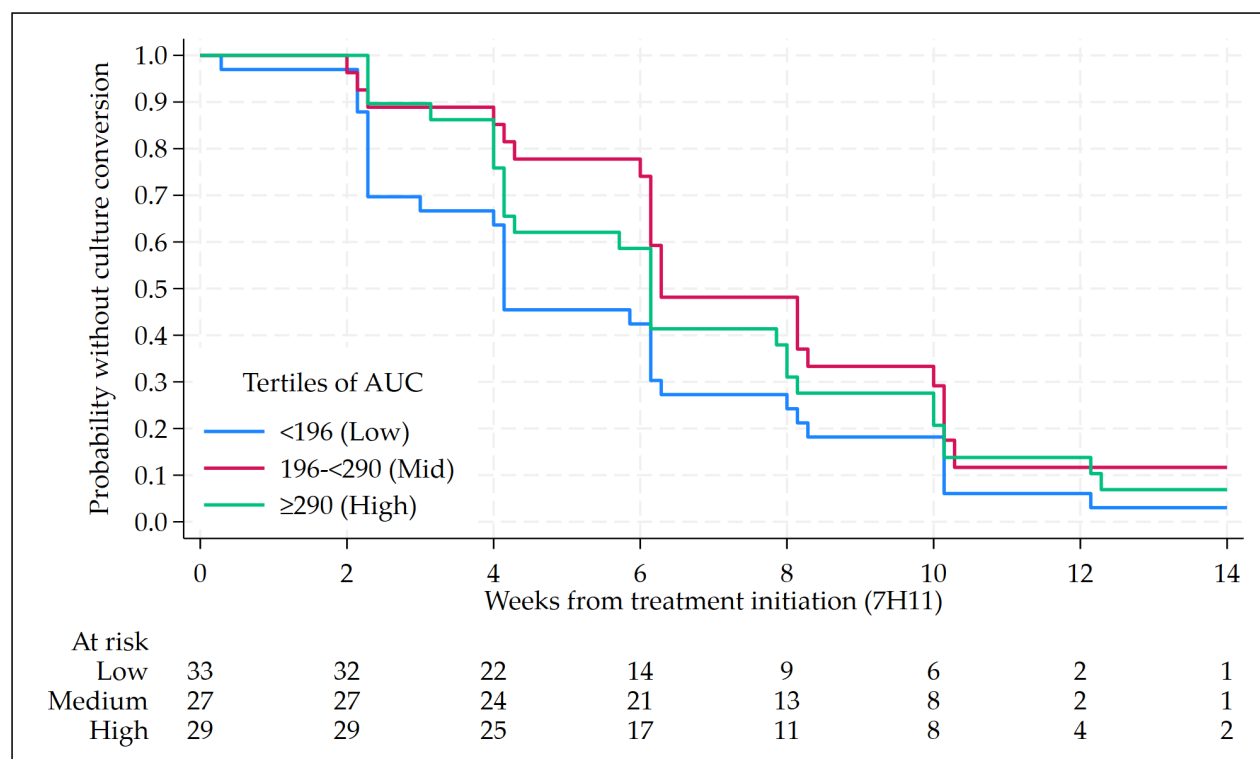


Table S14.7: Time to culture conversion by tertiles of AUC (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
<196 (Low)	33	4.1	2.3, 8.0	1.00 (1.00, 1.00)
196-290 (Mid)	27	6.3	6.0, 10.1	0.63 (0.36, 1.10)
≥290 (High)	29	6.1	4.1, 10.0	0.73 (0.39, 1.36)
Overall	89			Log-rank test, p = 0.153
Adjusted phtest				
	NA			PH test, p = 0.644
Unadjusted				
<196 (Low)	33	4.1	2.3, 8.0	1.00 (1.00, 1.00)
196-290 (Mid)	27	6.3	6.0, 10.1	0.59 (0.34, 1.01)
≥290 (High)	29	6.1	4.1, 10.0	0.69 (0.42, 1.16)
Overall	89			Log-rank test, p = 0.027
Unadjusted phtest				
	NA			PH test, p = 0.446

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.8: Time to culture conversion by tertiles of AUC (MGIT).

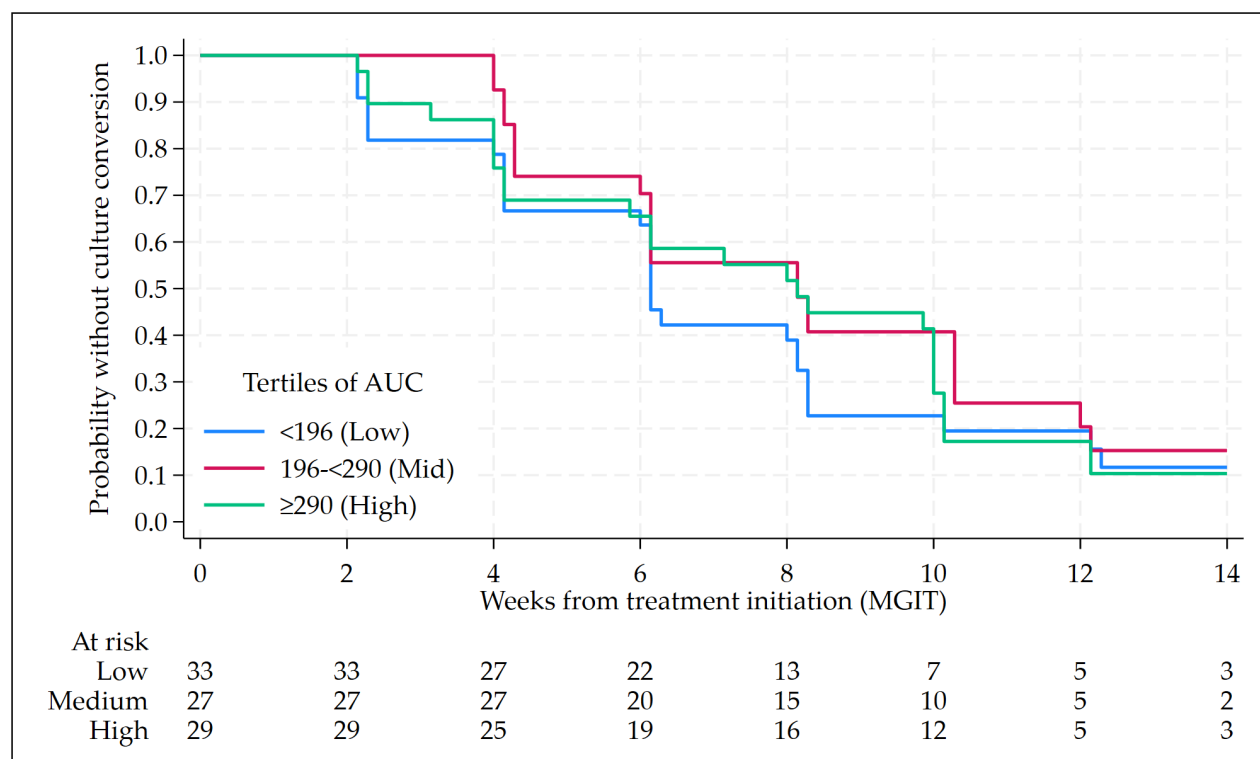


Table S14.8: Time to culture conversion by tertiles of AUC (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
<196 (Low)	33	6.1	4.1, 8.3	1.00 (1.00, 1.00)
196-<290 (Mid)	27	8.1	4.3, 12.0	0.64 (0.37, 1.13)
≥290 (High)	29	8.1	4.1, 10.1	0.99 (0.54, 1.82)
Overall	89			Log-rank test, p = 0.067
Adjusted phtest				
	NA			PH test, p = 0.288
Unadjusted				
<196 (Low)	33	6.1	4.1, 8.3	1.00 (1.00, 1.00)
196-<290 (Mid)	27	8.1	4.3, 12.0	0.76 (0.44, 1.31)
≥290 (High)	29	8.1	4.1, 10.1	0.87 (0.52, 1.47)
Overall	89			Log-rank test, p = 0.296
Unadjusted phtest				
	NA			PH test, p = 0.437

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.9: Time to culture conversion by tertiles of CMax (7H11).

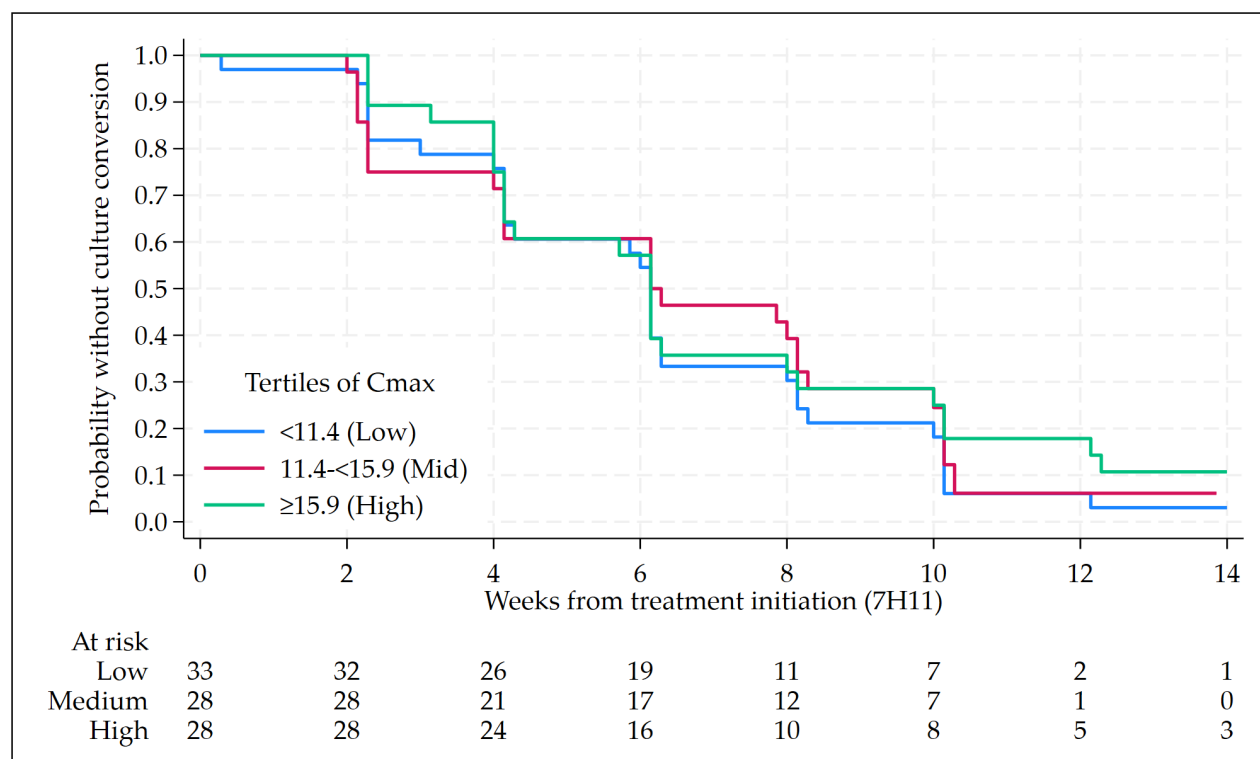


Table S14.9: Time to culture conversion by tertiles of CMax (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
<11.4 (Low)	33	6.1	4.1, 8.1	1.00 (1.00, 1.00)
11.4-15.9 (Mid)	28	6.1	2.3, 10.0	0.84 (0.48, 1.46)
≥15.9 (High)	28	6.1	4.0, 10.0	0.78 (0.44, 1.39)
Overall	89			Log-rank test, p = 0.504
Adjusted phtest				
	NA			PH test, p = 0.726
Unadjusted				
<11.4 (Low)	33	6.1	4.1, 8.1	1.00 (1.00, 1.00)
11.4-15.9 (Mid)	28	6.1	2.3, 10.0	0.84 (0.50, 1.43)
≥15.9 (High)	28	6.1	4.0, 10.0	0.76 (0.45, 1.28)
Overall	89			Log-rank test, p = 0.247
Unadjusted phtest				
	NA			PH test, p = 0.624

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.10: Time to culture conversion by tertiles of CMax (MGIT).

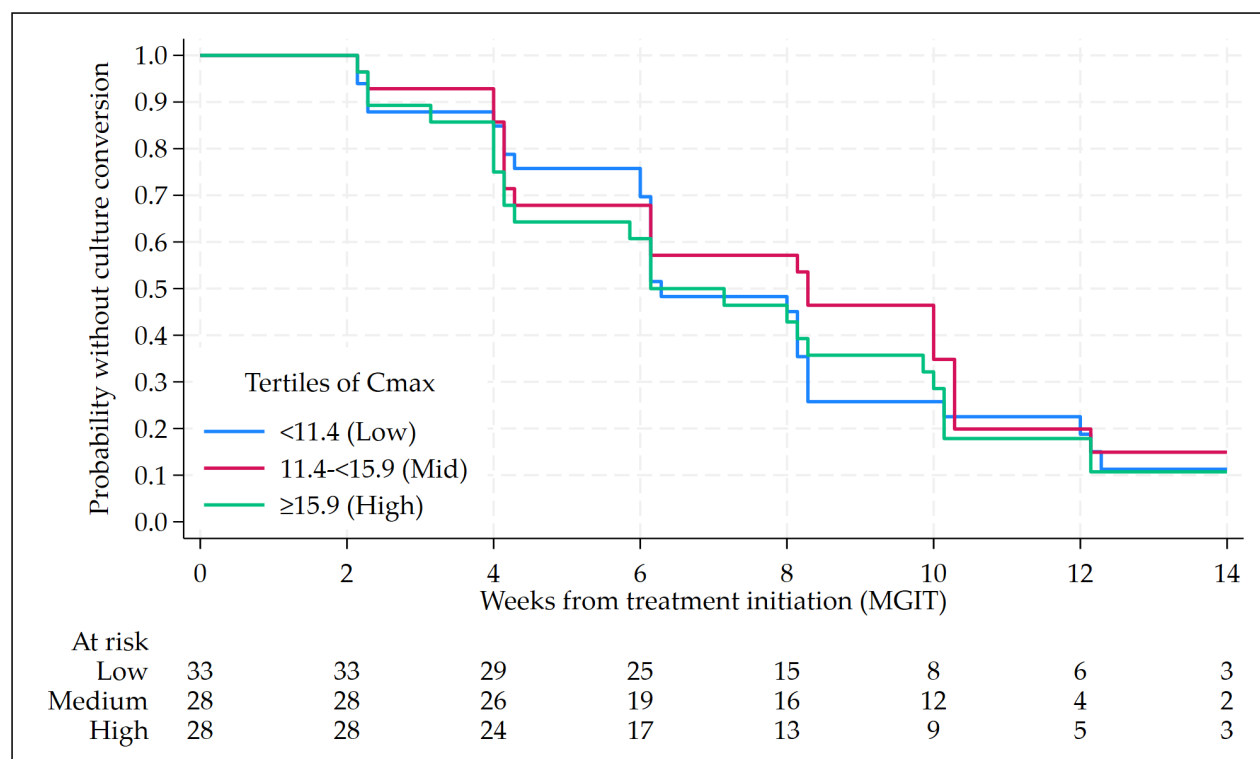


Table S14.10: Time to culture conversion by tertiles of CMax (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
<11.4 (Low)	33	6.3	6.0, 10.1	1.00 (1.00, 1.00)
11.4-15.9 (Mid)	28	8.3	4.1, 10.3	0.82 (0.47, 1.46)
≥15.9 (High)	28	6.1	4.0, 10.1	1.11 (0.62, 1.97)
Overall	89			Log-rank test, p = 0.638
Adjusted phtest				
	NA			PH test, p = 0.284
Unadjusted				
<11.4 (Low)	33	6.3	6.0, 10.1	1.00 (1.00, 1.00)
11.4-15.9 (Mid)	28	8.3	4.1, 10.3	0.88 (0.51, 1.51)
≥15.9 (High)	28	6.1	4.0, 10.1	0.98 (0.58, 1.67)
Overall	89			Log-rank test, p = 0.602
Unadjusted phtest				
	NA			PH test, p = 0.497

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.11: Time to culture conversion by tertiles of AUC/MIC (AP, 7H11).

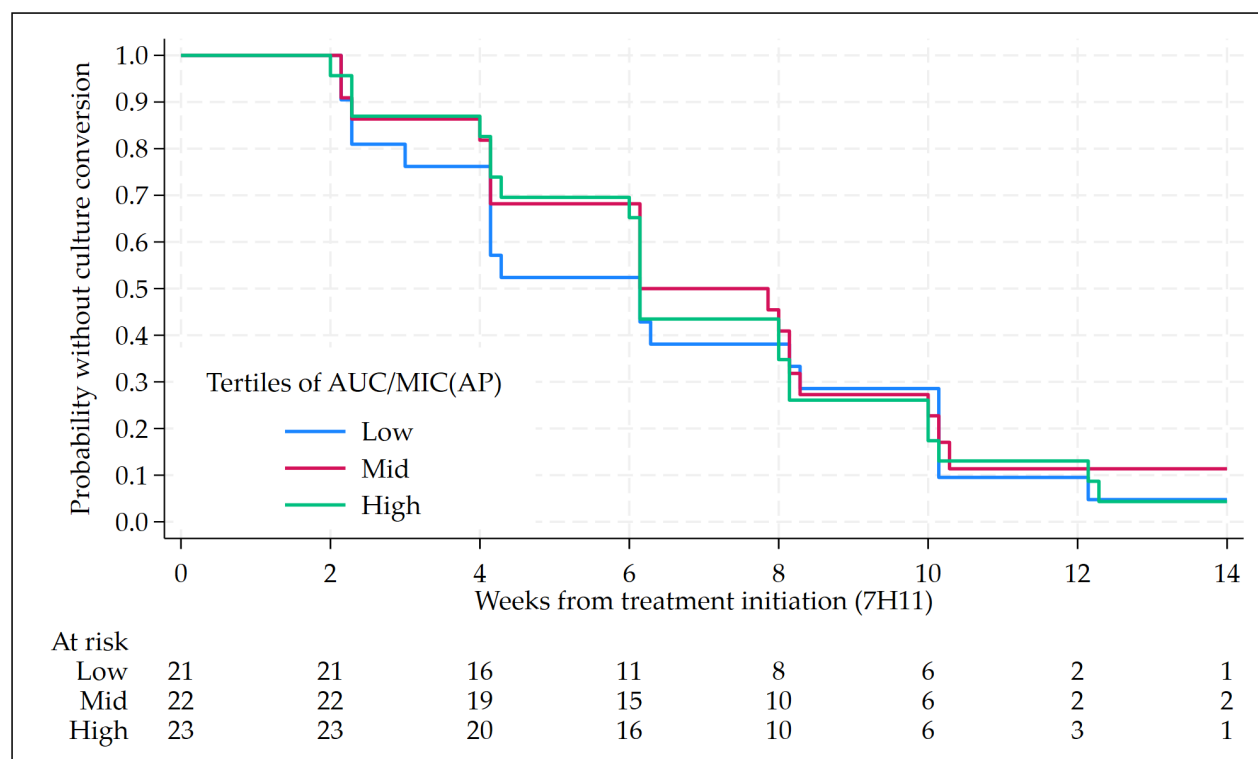


Table S14.11: Time to culture conversion by tertiles of AUC/MIC (AP, 7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
Low	21	6.1	4.1, 10.1	1.00 (1.00, 1.00)
Mid	22	6.1	4.1, 10.0	0.82 (0.42, 1.61)
High	23	6.1	4.1, 10.0	0.98 (0.43, 2.25)
Overall	66			Log-rank test, p = 0.350
Adjusted phtest				
	NA			PH test, p = 0.526
Unadjusted				
Low	21	6.1	4.1, 10.1	1.00 (1.00, 1.00)
Mid	22	6.1	4.1, 10.0	0.82 (0.44, 1.53)
High	23	6.1	4.1, 10.0	0.91 (0.50, 1.67)
Overall	66			Log-rank test, p = 0.505
Unadjusted phtest				
	NA			PH test, p = 0.995

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.12: Time to culture conversion by tertiles of AUC/MIC (AP, MGIT).

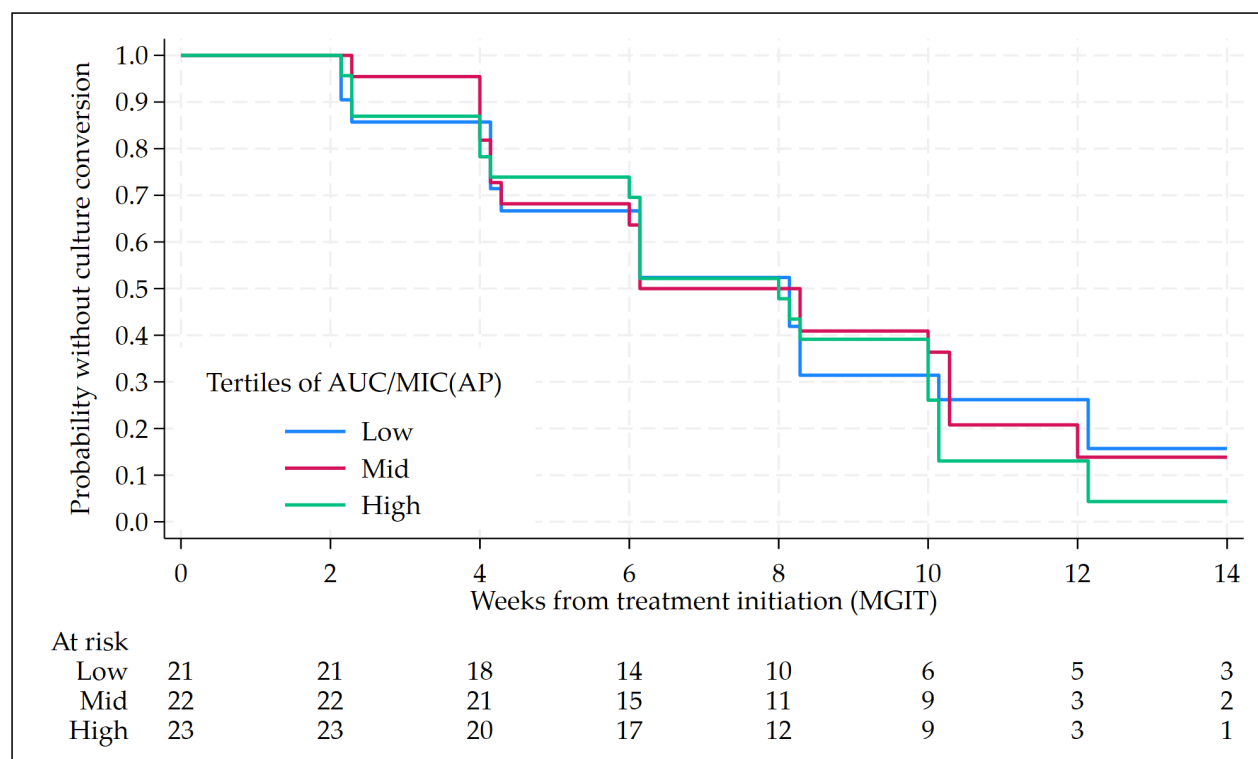


Table S14.12: Time to culture conversion by tertiles of AUC/MIC (AP, MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
Low	21	8.1	4.1, 12.1	1.00 (1.00, 1.00)
Mid	22	6.1	4.1, 10.3	0.66 (0.33, 1.29)
High	23	8.0	4.1, 10.1	1.01 (0.46, 2.25)
Overall	66			Log-rank test, p = 0.121
Adjusted phtest				
	NA			PH test, p = 0.681
Unadjusted				
Low	21	8.1	4.1, 12.1	1.00 (1.00, 1.00)
Mid	22	6.1	4.1, 10.3	0.87 (0.46, 1.65)
High	23	8.0	4.1, 10.1	1.07 (0.58, 1.97)
Overall	66			Log-rank test, p = 0.484
Unadjusted phtest				
	NA			PH test, p = 0.868

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.13: Time to culture conversion by tertiles of AUC/MIC (BMD, 7H11).

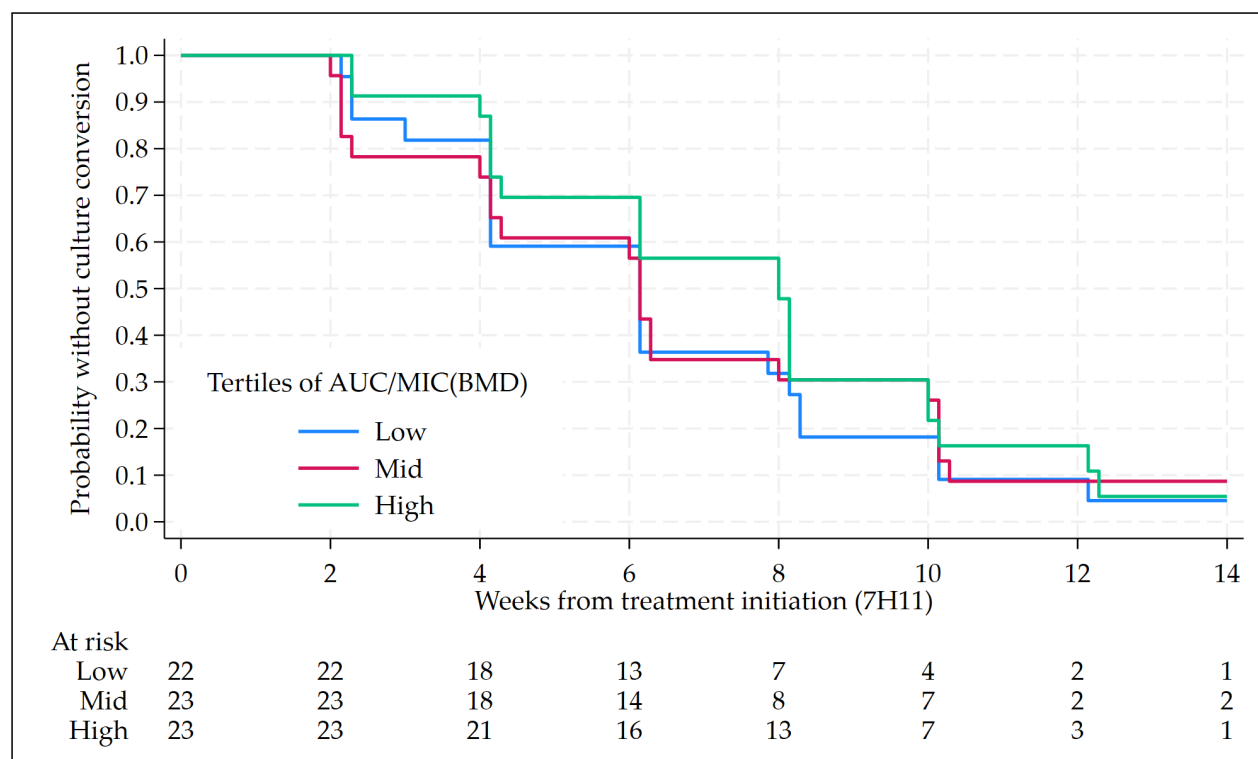


Table S14.13: Time to culture conversion by tertiles of AUC/MIC (BMD, 7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
Low	22	6.1	4.1, 8.3	1.00 (1.00, 1.00)
Mid	23	6.1	4.0, 10.1	1.13 (0.60, 2.13)
High	23	8.0	4.1, 10.0	0.73 (0.33, 1.63)
Overall	68			Log-rank test, p = 0.004
Adjusted phtest				
	NA			PH test, p = 0.354
Unadjusted				
Low	22	6.1	4.1, 8.3	1.00 (1.00, 1.00)
Mid	23	6.1	4.0, 10.1	0.99 (0.55, 1.80)
High	23	8.0	4.1, 10.0	0.80 (0.43, 1.46)
Overall	68			Log-rank test, p = 0.364
Unadjusted phtest				
	NA			PH test, p = 0.777

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.14: Time to culture conversion by tertiles of AUC/MIC (BMD, MGIT).

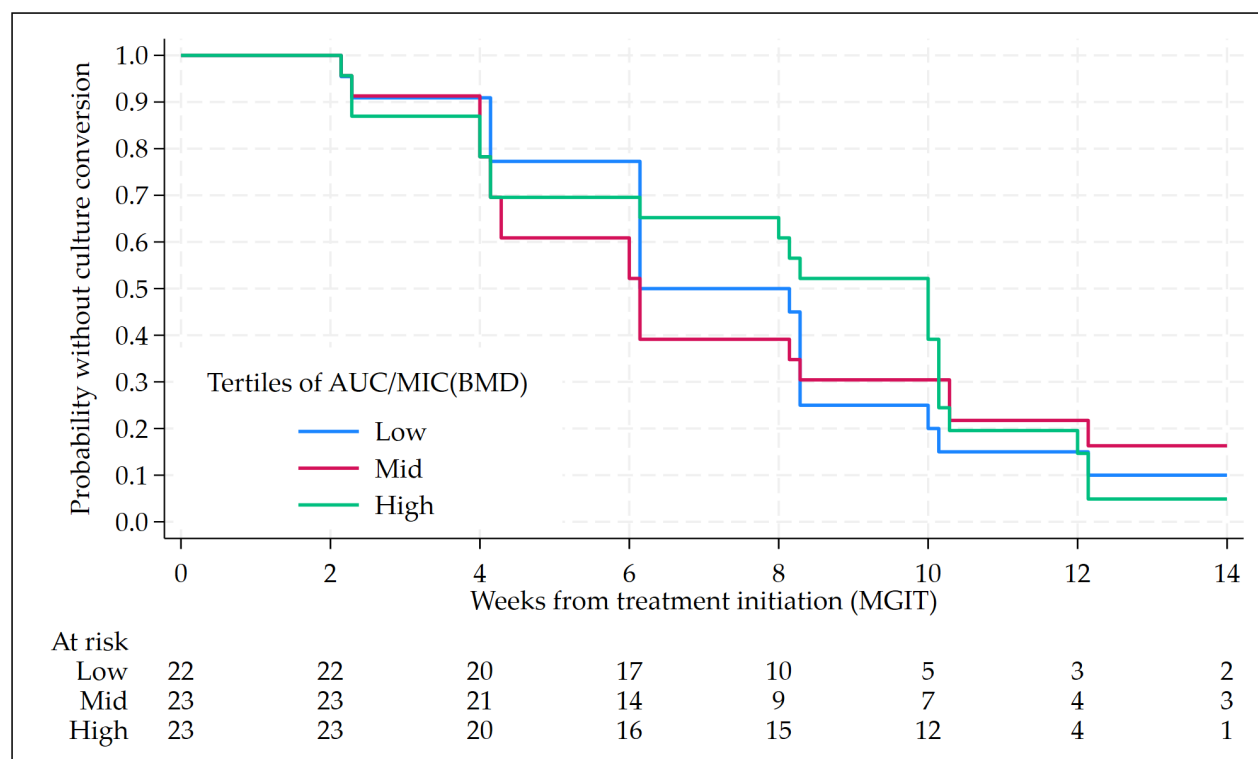


Table S14.14: Time to culture conversion by tertiles of AUC/MIC (BMD, MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
Low	22	6.1	6.1, 10.0	1.00 (1.00, 1.00)
Mid	23	6.1	4.1, 10.3	1.02 (0.54, 1.95)
High	23	10.0	4.1, 10.1	0.72 (0.32, 1.62)
Overall	68			Log-rank test, p = 0.172
Adjusted phtest				
	NA			PH test, p = 0.397
Unadjusted				
Low	22	6.1	6.1, 10.0	1.00 (1.00, 1.00)
Mid	23	6.1	4.1, 10.3	1.07 (0.58, 1.98)
High	23	10.0	4.1, 10.1	0.92 (0.50, 1.71)
Overall	68			Log-rank test, p = 0.595
Unadjusted phtest				
	NA			PH test, p = 0.960

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.15: Time to culture conversion by study site (7H11).

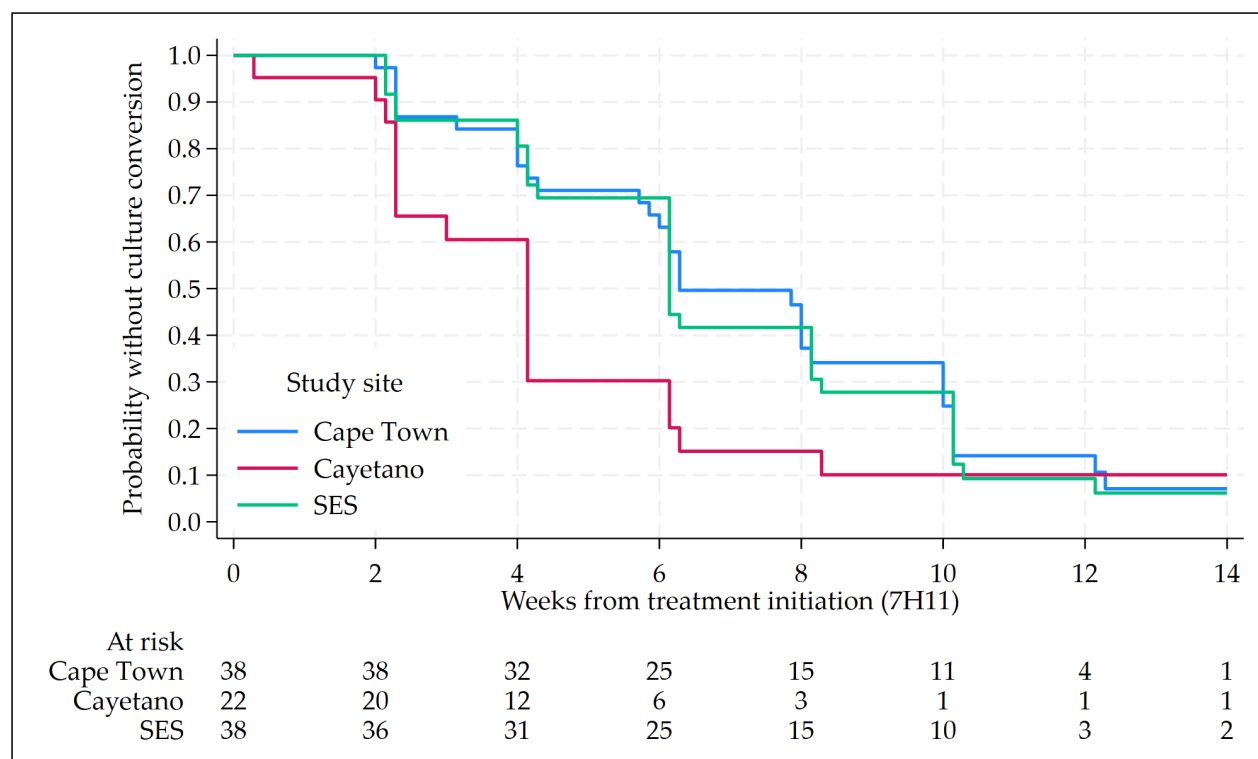


Table S14.15: Time to culture conversion by study site (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
TASK, Cape Town	38	6.3	4.1, 10.0	1.00 (1.00, 1.00)
Cayetano, Lima	22	4.1	2.3, 6.1	2.14 (1.16, 3.93)
Socios en Salud, Lima	38	6.1	4.1, 10.1	1.66 (0.93, 2.96)
Overall	98			Log-rank test, p = 1.000
Adjusted phtest				
	NA			PH test, p = 0.520
Unadjusted				
TASK, Cape Town	38	6.3	4.1, 10.0	1.00 (1.00, 1.00)
Cayetano, Lima	22	4.1	2.3, 6.1	1.99 (1.12, 3.54)
Socios en Salud, Lima	38	6.1	4.1, 10.1	1.05 (0.65, 1.71)
Overall	98			Log-rank test, p = 0.007
Unadjusted phtest				
	NA			PH test, p = 0.481

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.16: Time to culture conversion by study site (MGIT).

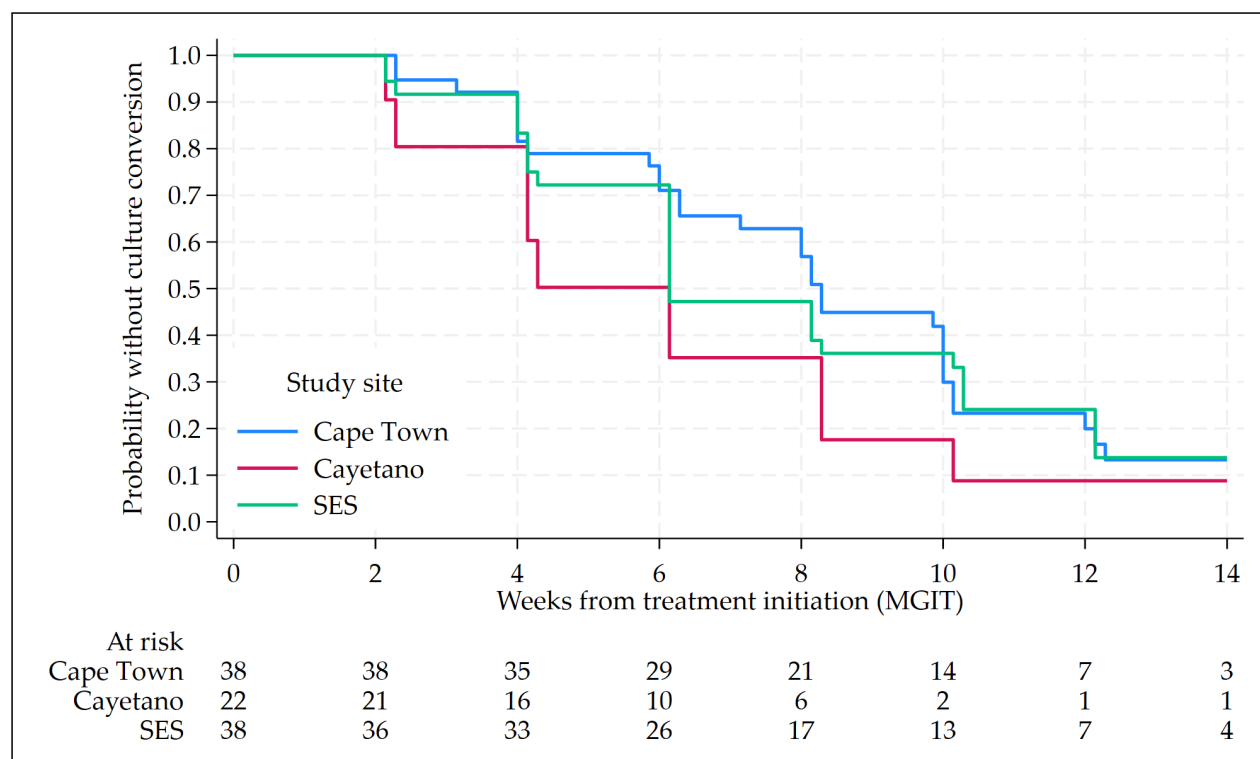


Table S14.16: Time to culture conversion by study site (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
TASK, Cape Town	38	8.3	6.0, 10.1	1.00 (1.00, 1.00)
Cayetano, Lima	22	6.1	4.1, 8.3	1.76 (0.95, 3.27)
Socios en Salud, Lima	38	6.1	4.1, 10.3	1.98 (1.09, 3.60)
Overall	98			Log-rank test, p = 1.000
Adjusted phtest				
	NA			PH test, p = 0.394
Unadjusted				
TASK, Cape Town	38	8.3	6.0, 10.1	1.00 (1.00, 1.00)
Cayetano, Lima	22	6.1	4.1, 8.3	1.75 (0.97, 3.16)
Socios en Salud, Lima	38	6.1	4.1, 10.3	1.08 (0.66, 1.77)
Overall	98			Log-rank test, p = 0.039
Unadjusted phtest				
	NA			PH test, p = 0.892

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.17: Time to culture conversion by pyrazinamide resistance (7H11).

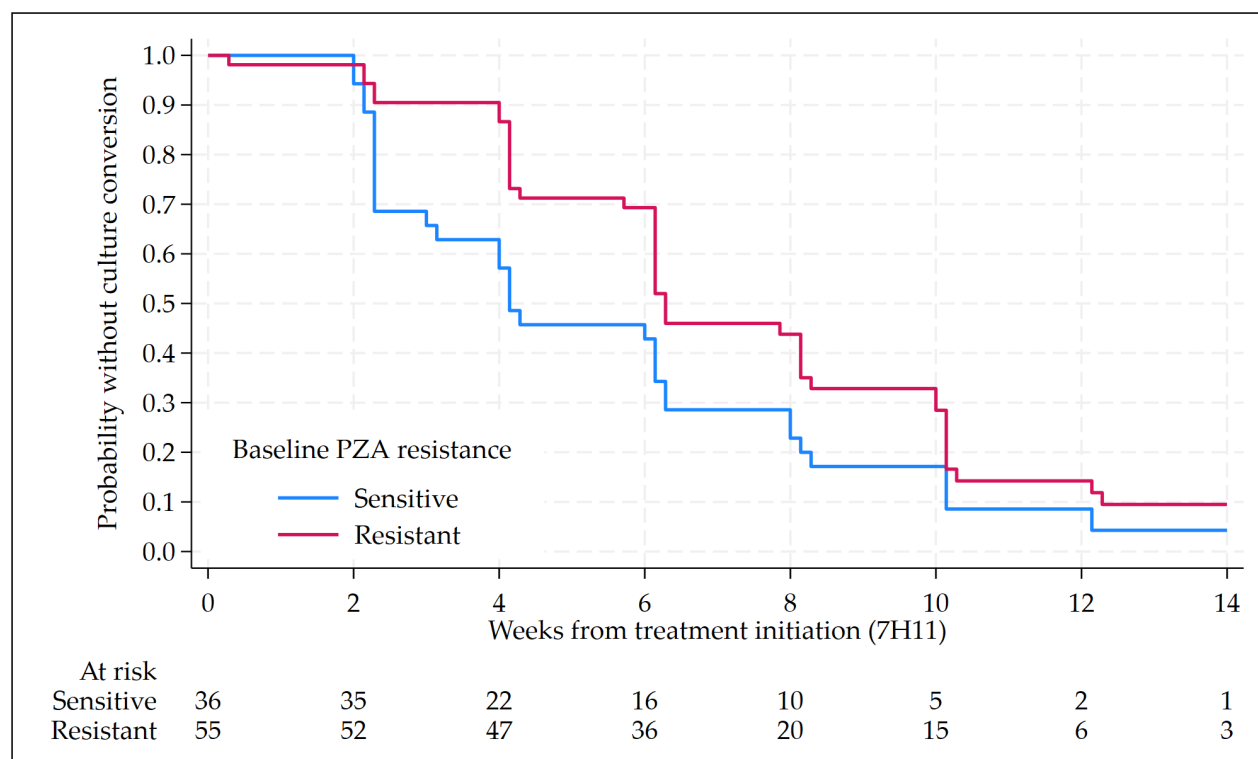


Table S14.17: Time to culture conversion by pyrazinamide resistance (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
Sensitive	36	4.1	2.3, 8.0	1.00 (1.00, 1.00)
Resistant	55	6.3	4.1, 10.1	0.77 (0.46, 1.29)
Overall	91			Log-rank test, p = 1.000
Adjusted phtest				
	NA			PH test, p = 0.520
Unadjusted				
Sensitive	36	4.1	2.3, 8.0	1.00 (1.00, 1.00)
Resistant	55	6.3	4.1, 10.1	0.65 (0.41, 1.02)
Overall	91			Log-rank test, p = 0.045
Unadjusted phtest				
	NA			PH test, p = 0.066

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.18: Time to culture conversion by pyrazinamide resistance (MGIT).

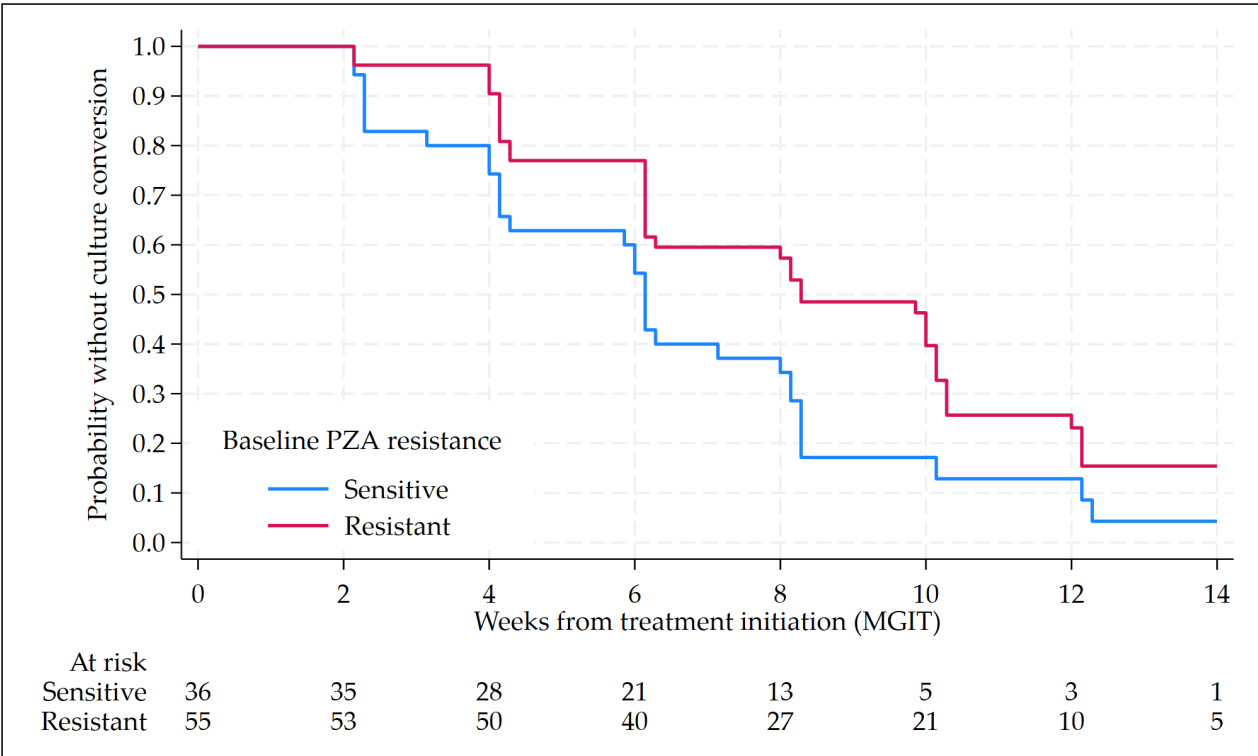


Table S14.18: Time to culture conversion by pyrazinamide resistance (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
Sensitive	36	6.1	4.0, 8.3	1.00 (1.00, 1.00)
Resistant	55	8.3	6.1, 12.0	0.72 (0.43, 1.20)
Overall	91			Log-rank test, p = 1.000
Adjusted phtest				
	NA			PH test, p = 0.394
Unadjusted				
Sensitive	36	6.1	4.0, 8.3	1.00 (1.00, 1.00)
Resistant	55	8.3	6.1, 12.0	0.60 (0.38, 0.96)
Overall	91			Log-rank test, p = 0.022
Unadjusted phtest				
	NA			PH test, p = 0.111

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.19: Time to culture conversion by MGIT days to positivity (7H11).

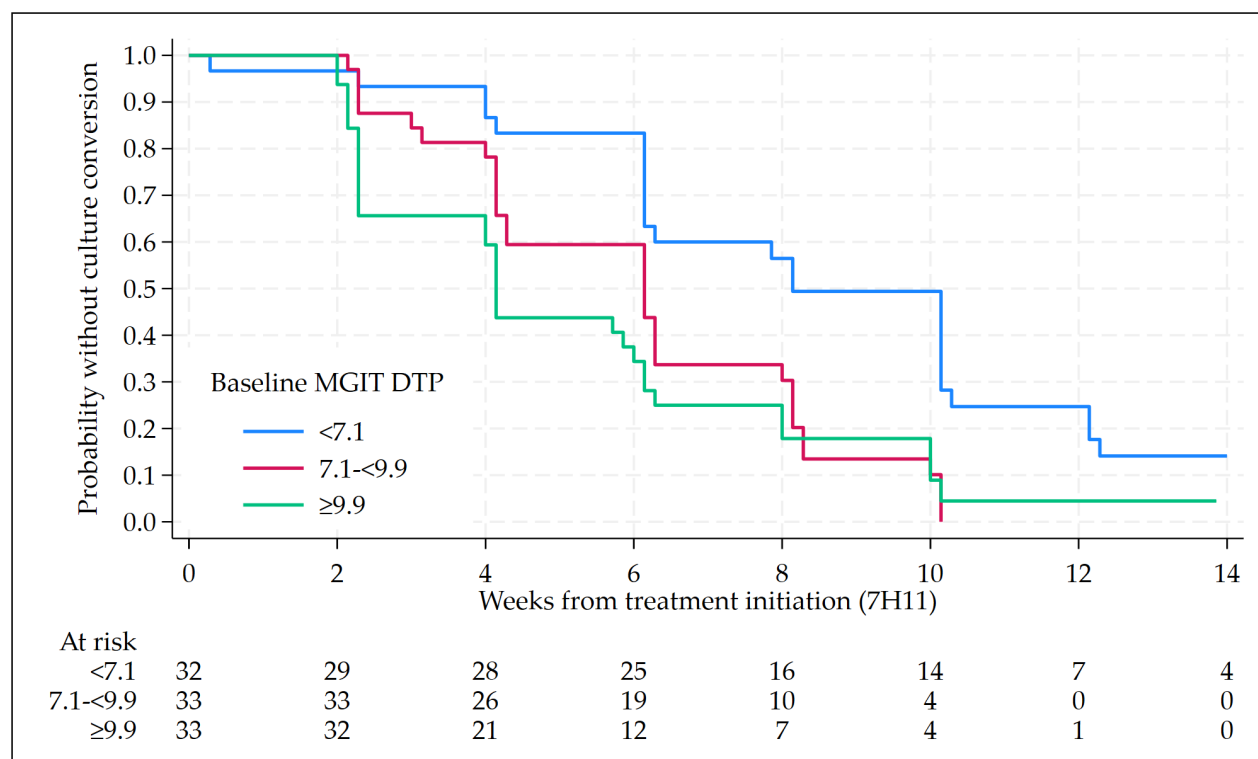


Table S14.19: Time to culture conversion by MGIT days to positivity (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted				
<7.1	32	8.1	6.1, 10.3	1.00 (1.00, 1.00)
7.1-9.9	33	6.1	4.1, 8.1	2.22 (1.17, 4.22)
≥9.9	33	4.1	2.3, 6.3	2.27 (0.93, 5.55)
Overall	98			Log-rank test, p = 1.000
Adjusted ptest				
	NA			PH test, p = 0.459
Unadjusted				
<7.1	32	8.1	6.1, 10.3	1.00 (1.00, 1.00)
7.1-9.9	33	6.1	4.1, 8.1	2.15 (1.21, 3.82)
≥9.9	33	4.1	2.3, 6.3	2.67 (1.53, 4.66)
Overall	98			Log-rank test, p < 0.001
Unadjusted ptest				
	NA			PH test, p = 0.347

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.20: Time to culture conversion by MGIT days to positivity(MGIT).

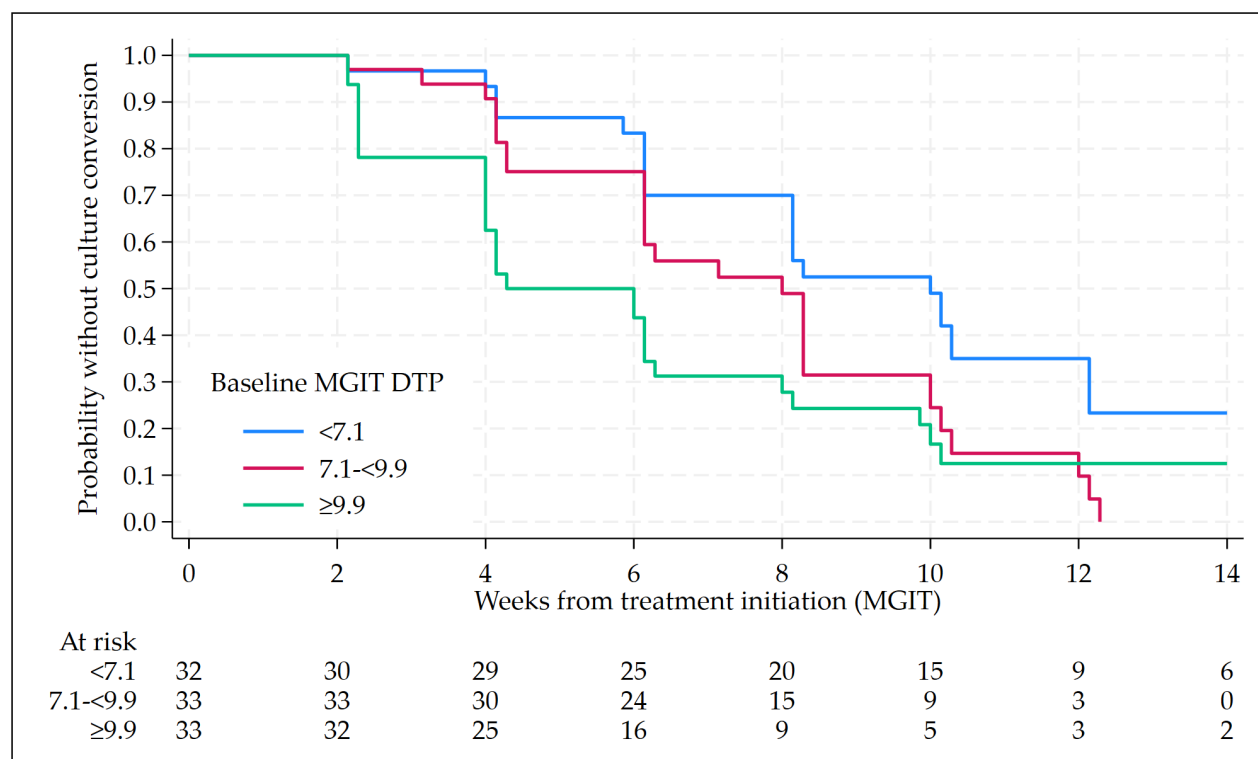


Table S14.20: Time to culture conversion by MGIT days to positivity (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
<7.1	32	10.0	6.1, 12.1	1.00 (1.00, 1.00)
7.1-9.9	33	8.0	6.1, 10.0	1.49 (0.79, 2.82)
≥9.9	33	4.3	4.0, 8.1	1.31 (0.49, 3.49)
Overall	98			Log-rank test, p = 1.000
Adjusted phtest				
	NA			PH test, p = 0.459
Unadjusted				
<7.1	32	10.0	6.1, 12.1	1.00 (1.00, 1.00)
7.1-9.9	33	8.0	6.1, 10.0	1.65 (0.95, 2.87)
≥9.9	33	4.3	4.0, 8.1	2.14 (1.25, 3.69)
Overall	98			Log-rank test, p = 0.003
Unadjusted phtest				
	NA			PH test, p = 0.024

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.21: Time to culture conversion by number of drugs at baseline (7H11).

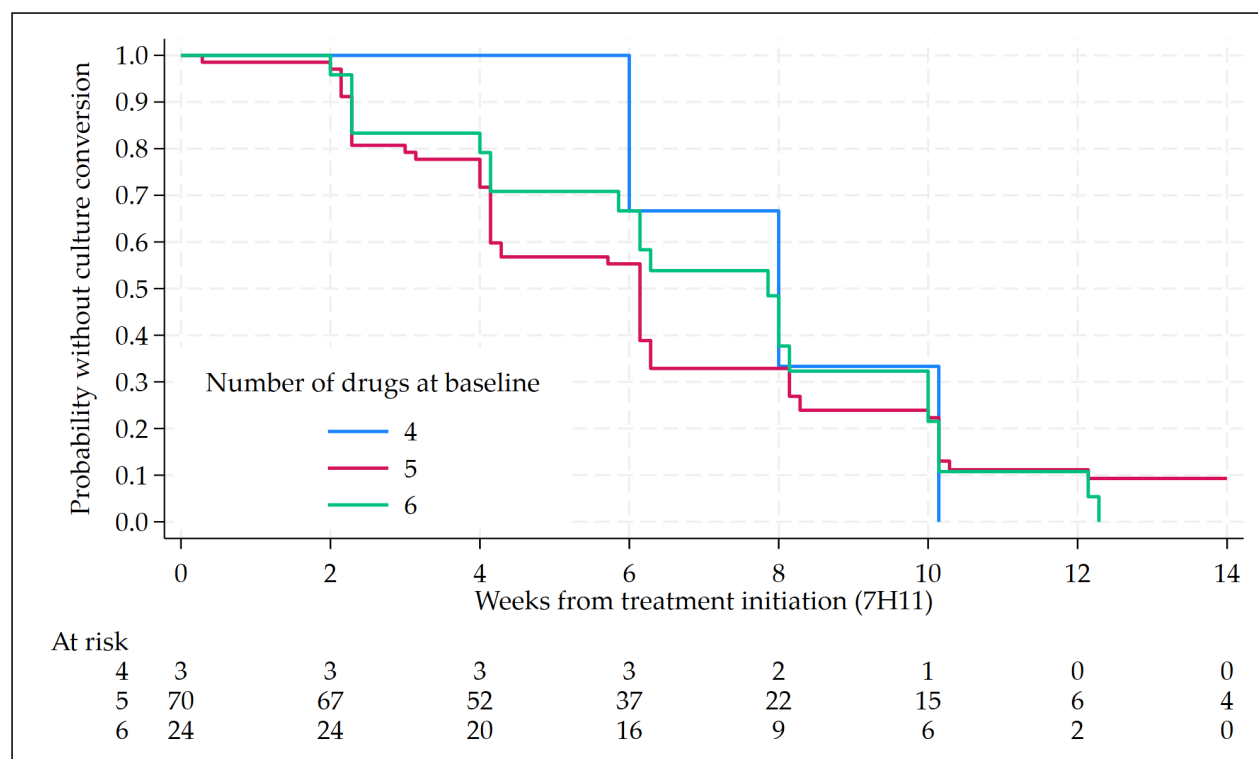


Table S14.21: Time to culture conversion by number of drugs at baseline (7H11).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
4	3	8.0	6.0, 10.1	1.00 (1.00, 1.00)
5	70	6.1	4.0, 8.3	0.96 (0.23, 4.00)
6	24	7.9	4.1, 10.0	1.03 (0.21, 5.00)
Overall	97			Log-rank test, p = 0.736
Adjusted phtest				
	NA			PH test, p = 0.213
Unadjusted				
4	3	8.0	6.0, 10.1	1.00 (1.00, 1.00)
5	70	6.1	4.0, 8.3	1.15 (0.36, 3.66)
6	24	7.9	4.1, 10.0	1.06 (0.32, 3.56)
Overall	97			Log-rank test, p = 0.694
Unadjusted phtest				
	NA			PH test, p = 0.151

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.22: Time to culture conversion by number of drugs at baseline (MGIT).

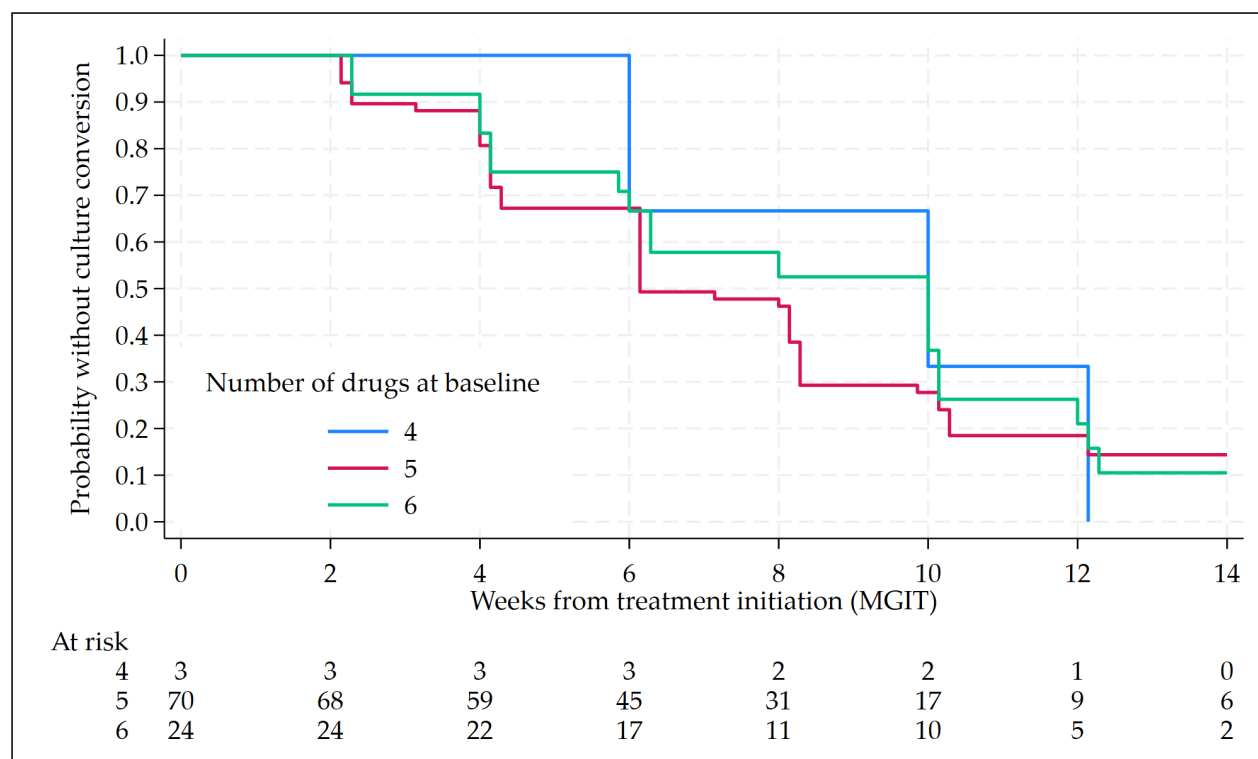


Table S14.22: Time to culture conversion by number of drugs at baseline (MGIT).

Group	Participants	Median (wks)	25th, 75th centile (wks)	Hazard ratio (95% CI)
Adjusted*				
4	3	10.0	6.0, 12.1	1.00 (1.00, 1.00)
5	70	6.1	4.1, 10.1	0.85 (0.20, 3.57)
6	24	10.0	4.1, 12.0	1.46 (0.29, 7.31)
Overall	97			Log-rank test, p = 0.274
Adjusted phtest				
	NA			PH test, p = 0.383
Unadjusted				
4	3	10.0	6.0, 12.1	1.00 (1.00, 1.00)
5	70	6.1	4.1, 10.1	1.16 (0.36, 3.72)
6	24	10.0	4.1, 12.0	1.02 (0.30, 3.43)
Overall	97			Log-rank test, p = 0.564
Unadjusted phtest				
	NA			PH test, p = 0.439

* Adjusted for pyrazinamide resistance, MGIT DTP, and site.

Figure S14.23: Hazard ratio of time to culture conversion by AUC (7H11).

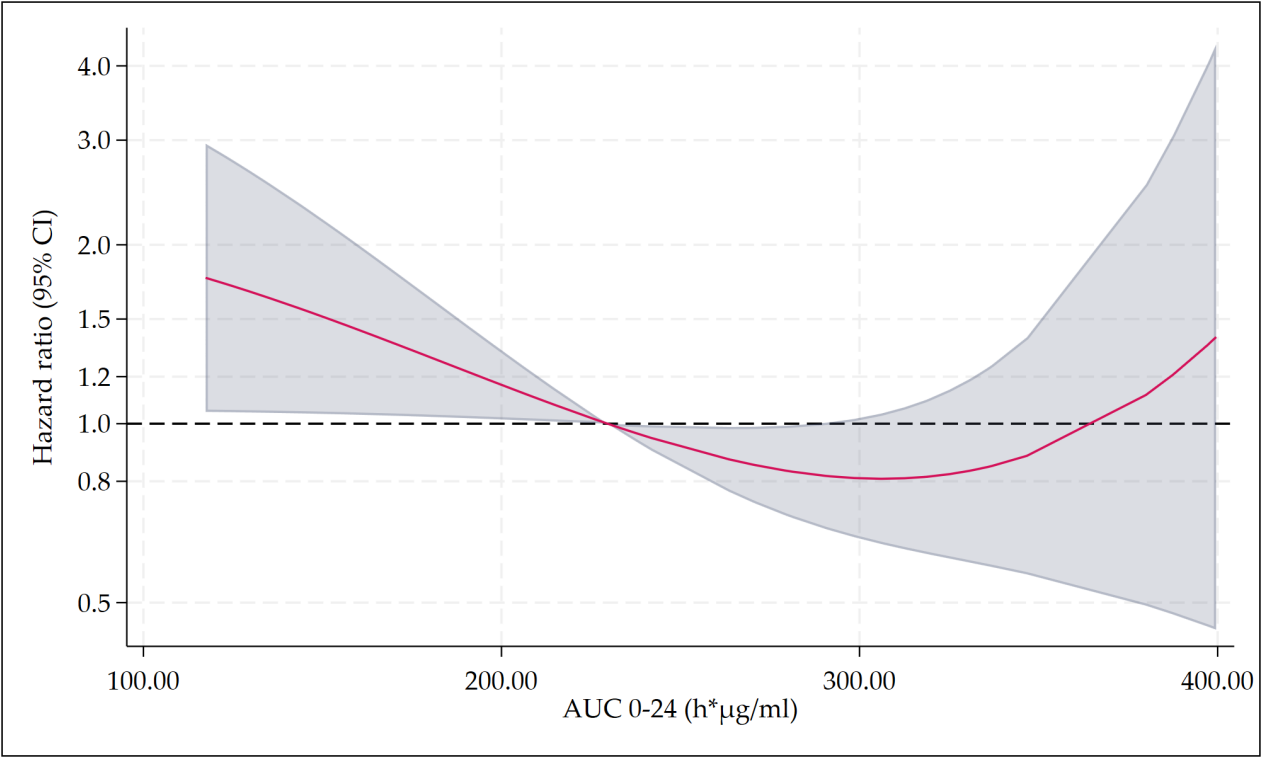


Figure S14.24: Hazard ratio of time to culture conversion by AUC (MGIT).

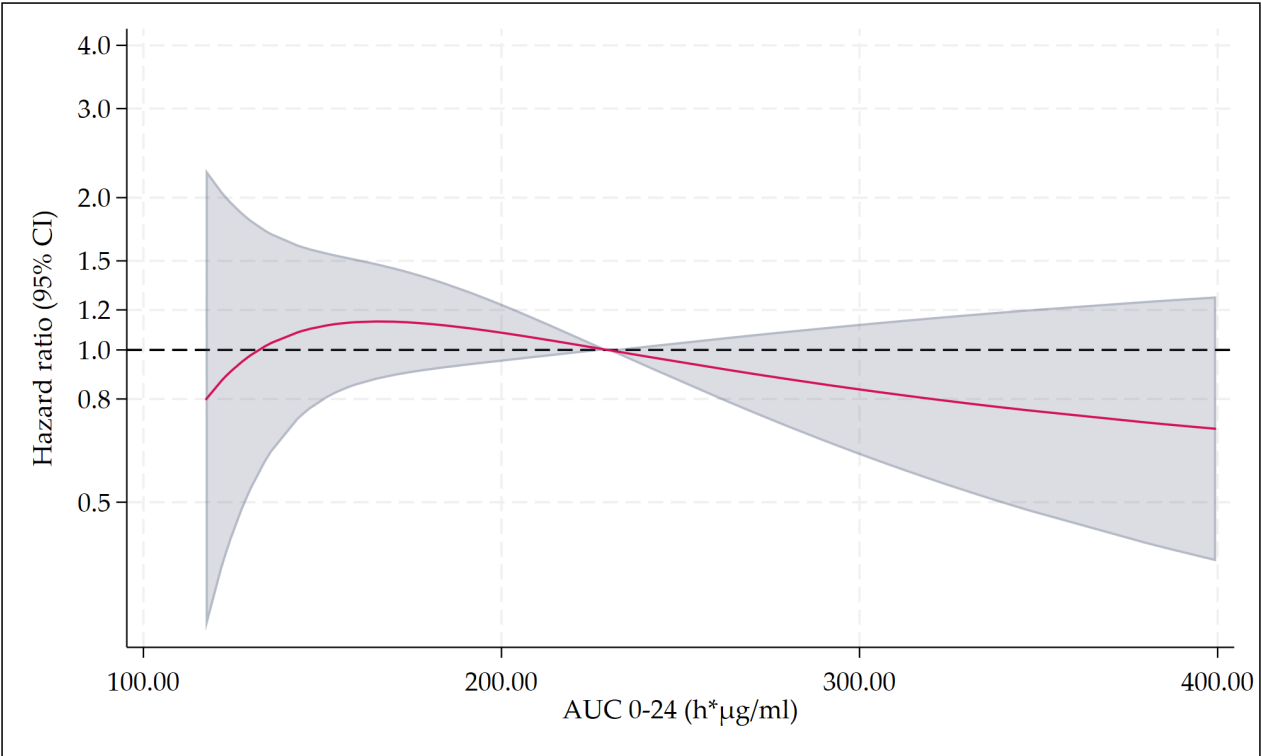


Figure S14.25: Hazard ratio of time to culture conversion by AUC/MIC (AP, 7H11).

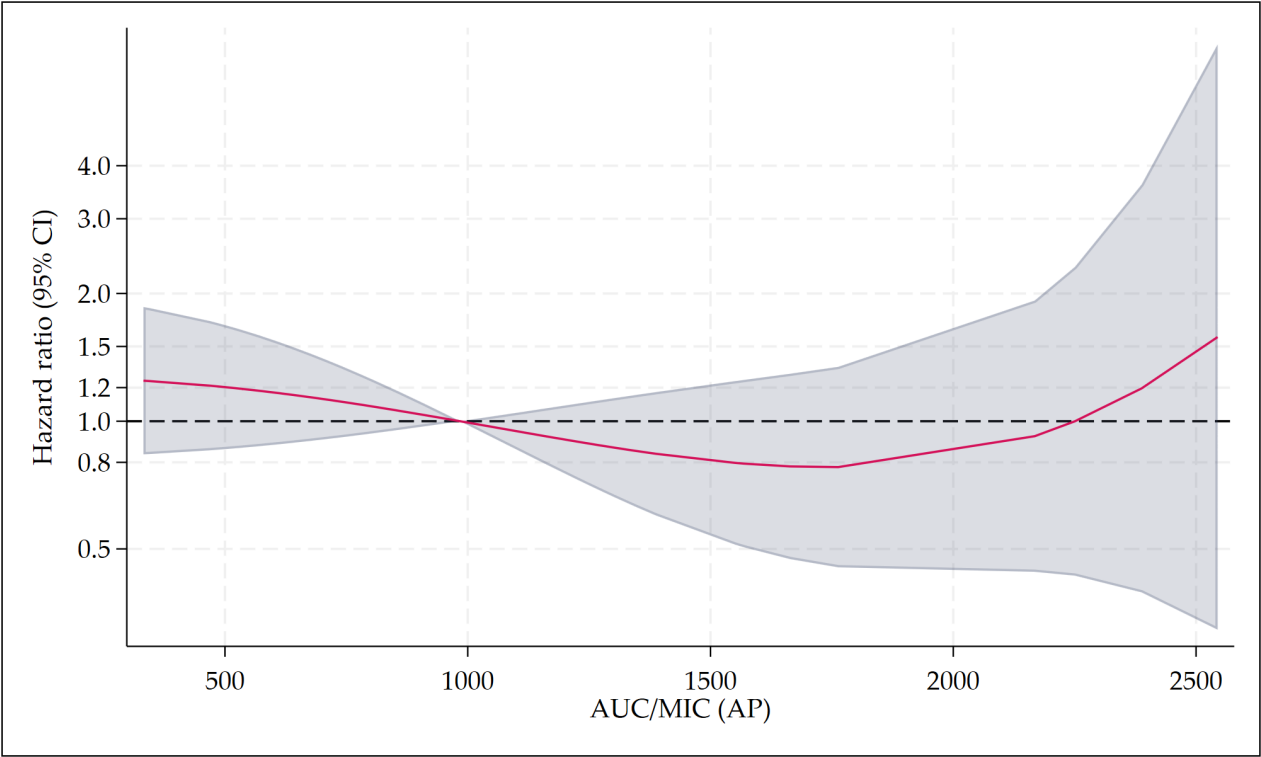


Figure S14.26: Hazard ratio of time to culture conversion by AUC/MIC (AP, MGIT).

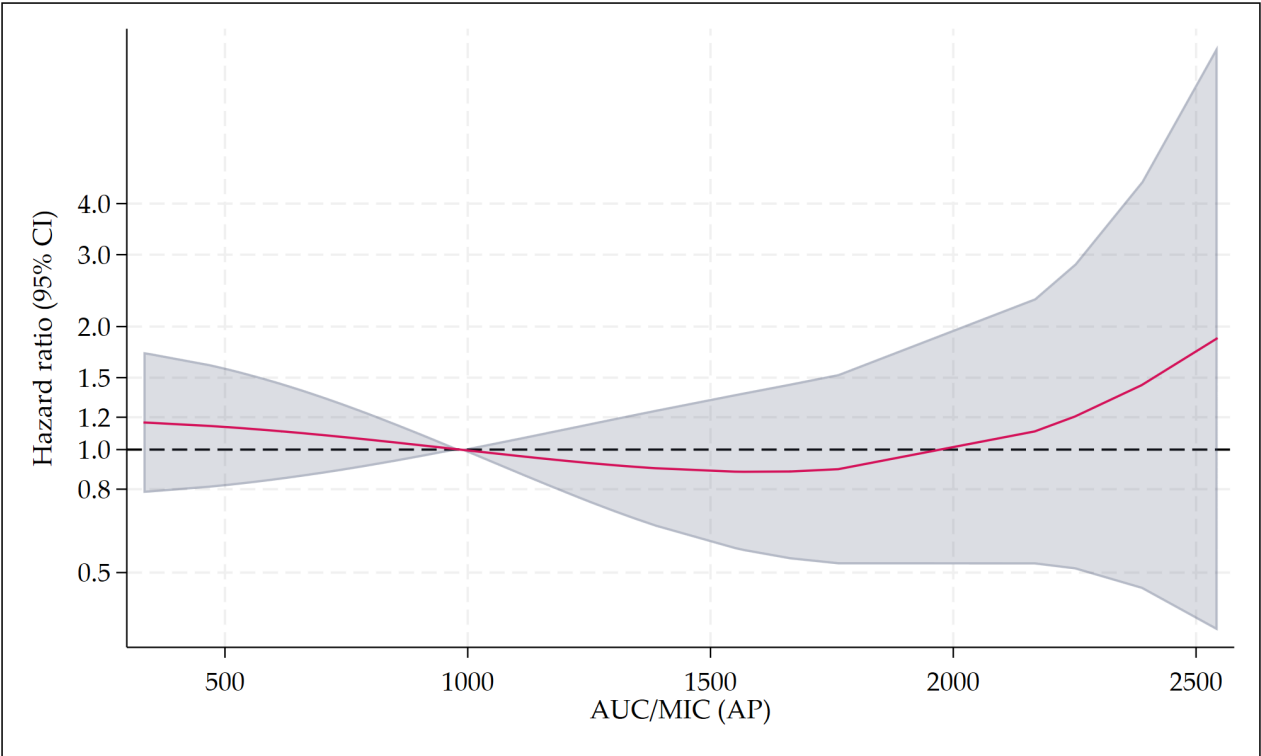


Figure S14.27: Hazard ratio of time to culture conversion by AUC/MIC (BMD, 7H11).

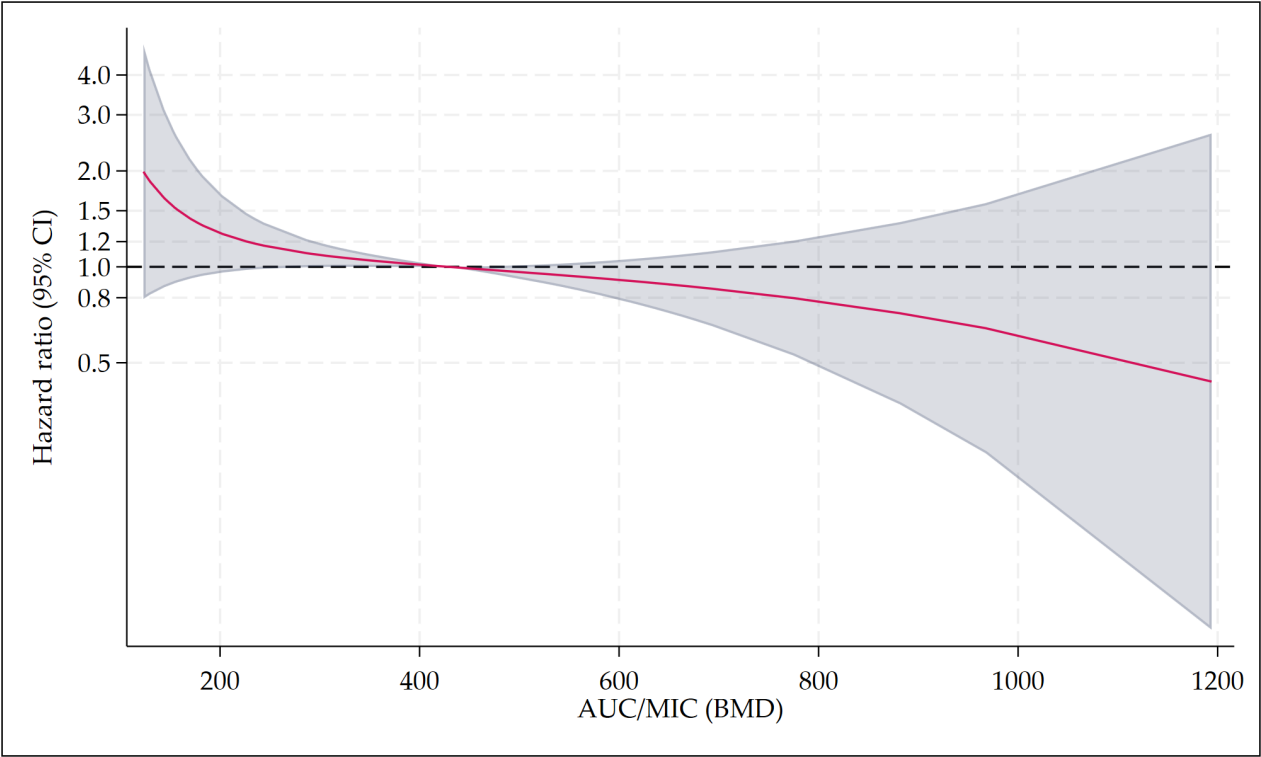


Figure S14.28: Hazard ratio of time to culture conversion by AUC/MIC (BMD, MGIT).

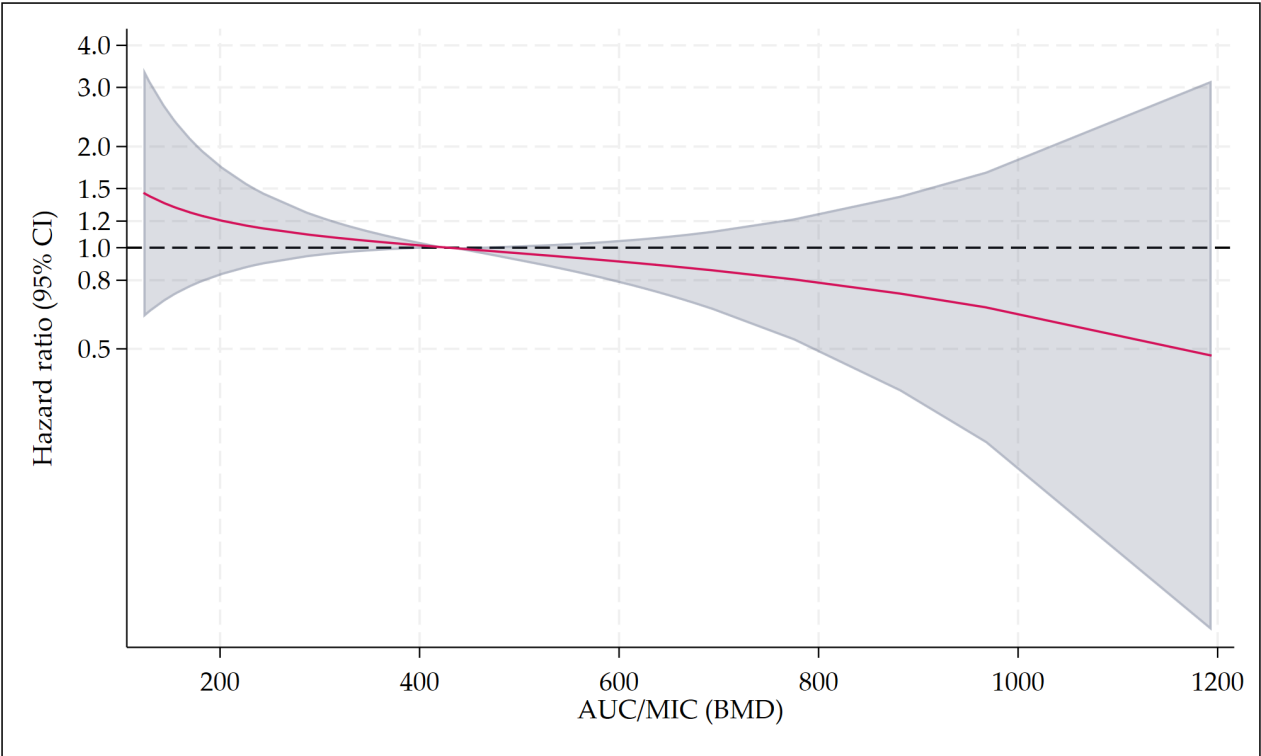


Figure S14.29: Hazard ratio of time to culture conversion by CMax (7H11).

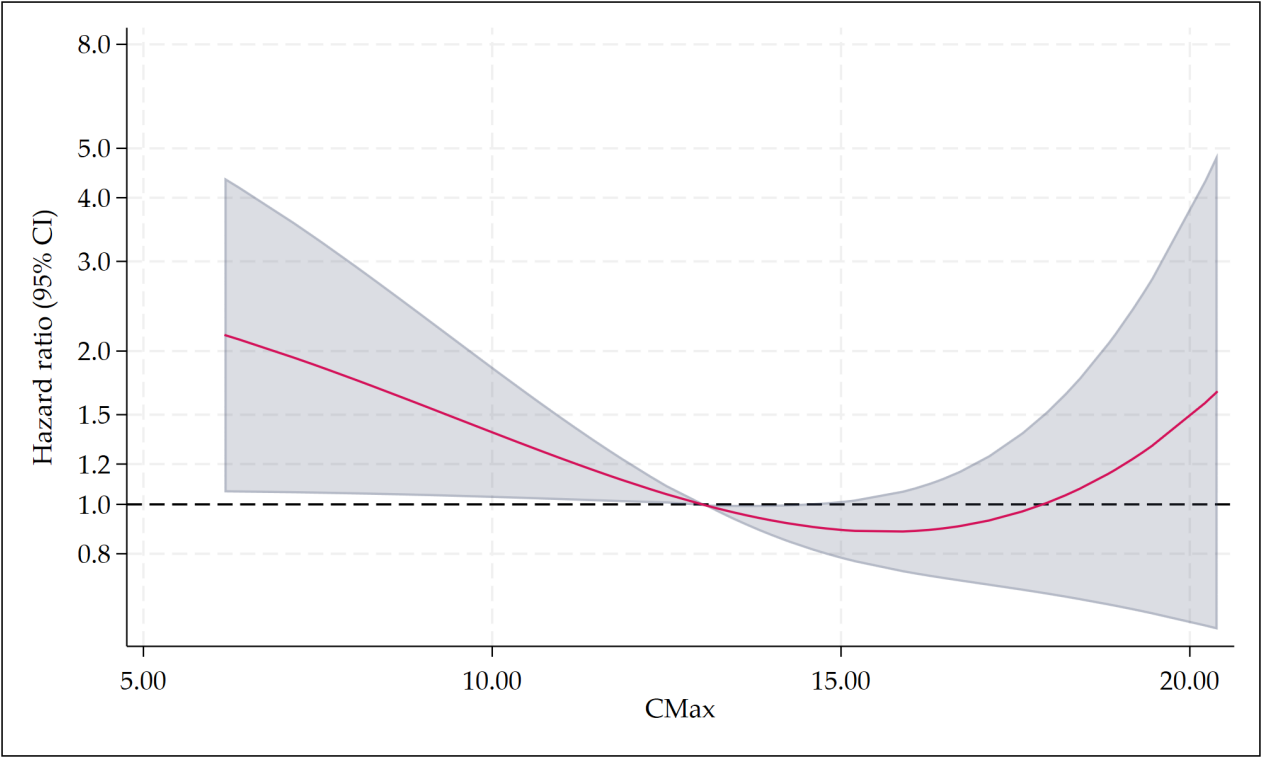


Figure S14.30: Hazard ratio of time to culture conversion by CMax (MGIT).

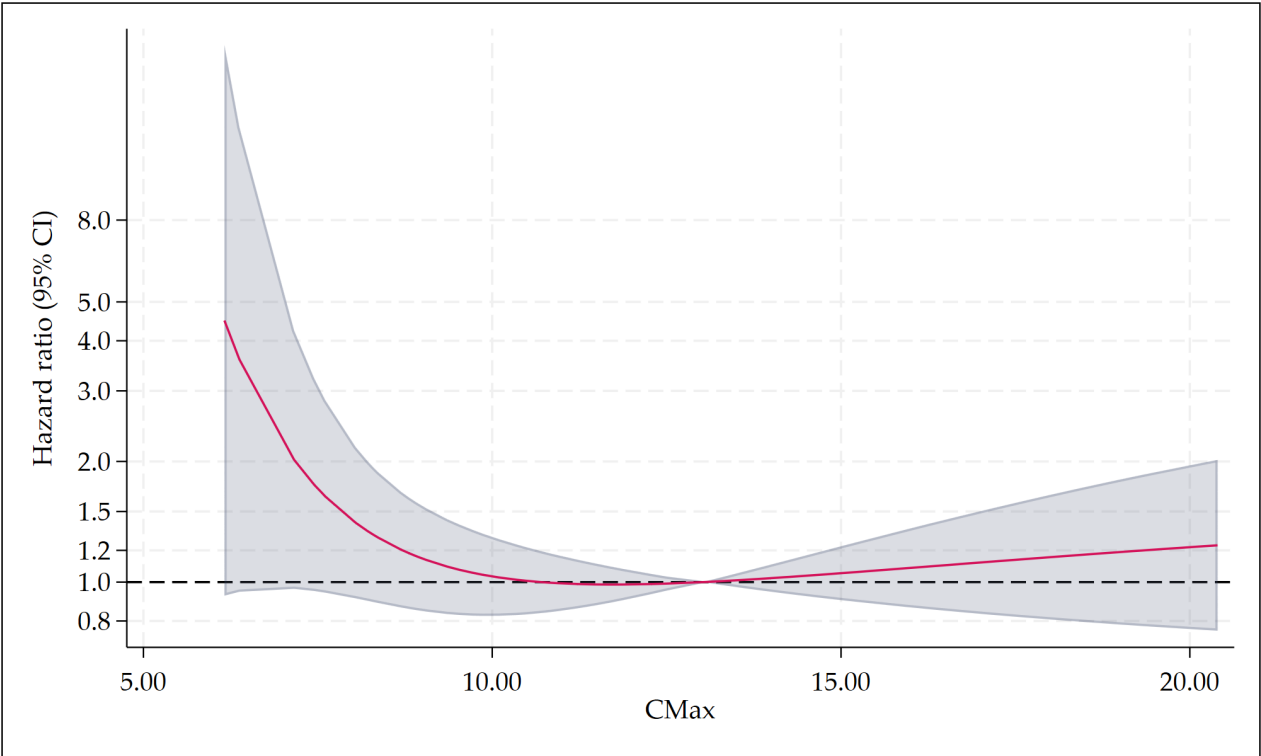


Table S14.23: Proportion of participants achieving culture conversion by treatment arm.

Week	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Solid Culture (7H11)					
7	64.2%	53.8%	60.8%	65.2%	60.7%
9	69.3%	74.8%	70.6%	78.3%	73.4%
11	87.2%	91.6%	85.3%	91.8%	89.2%
13	100.0%	91.6%	85.3%	100.0%	93.3%
MGIT Culture					
7	59.6%	34.6%	47.8%	52.2%	47.9%
9	64.6%	69.5%	52.6%	69.6%	64.1%
11	64.6%	82.6%	76.3%	93.7%	79.2%
13	88.2%	88.4%	76.3%	100.0%	87.5%

Table S14.24: Proportion of participants achieving culture conversion by tertile of AUC/MIC.

Week	Lower tertile	Middle tertile	Upper tertile	Total
Solid Culture (7H11)				
7	61.9%	50.0%	56.5%	60.7%
9	71.4%	72.7%	73.9%	73.4%
11	90.5%	88.6%	87.0%	89.2%
13	95.2%	88.6%	95.7%	93.3%
MGIT Culture				
7	47.6%	50.0%	47.8%	47.9%
9	68.6%	59.1%	60.9%	64.1%
11	73.8%	79.2%	87.0%	79.2%
13	84.3%	86.1%	95.7%	87.5%

Table S14.25: Proportion of participants achieving culture conversion by tertile of AUC.

Week	Lower tertile	Middle tertile	Upper tertile	Total
Solid Culture (7H11)				
7	72.7%	51.9%	58.6%	60.7%
9	81.8%	66.7%	72.4%	73.4%
11	93.9%	88.3%	86.2%	89.2%
13	97.0%	88.3%	93.1%	93.3%
MGIT Culture				
7	57.8%	44.4%	41.4%	47.9%
9	77.3%	59.3%	55.2%	64.1%
11	80.5%	74.5%	82.8%	79.2%
13	88.3%	84.7%	89.7%	87.5%

3.15 Predictors of time to culture conversion

Table S15.1: Univariable predictors of time to culture conversion (7H11). Variable listed if $p < 0.2$ for log-rank or likelihood ratio (LR) test.

Level	Participants	Median (wks)	Hazard ratio (95% CI)	Z-score	log rank test	LR test
7H11 colony count						
<10	1	.	1.00 (1.00, 1.00)		$p < 0.001$	$p < 0.001$
1+ (10-100)	22	4.1	0.36 (0.05, 2.81)	$p = 0.330$	$p < 0.001$	$p < 0.001$
2+ (>100)	22	5.7	0.21 (0.03, 1.62)	$p = 0.133$	$p < 0.001$	$p < 0.001$
3+ (>200)	47	8.1	0.08 (0.01, 0.64)	$p = 0.017$	$p < 0.001$	$p < 0.001$
Mean MGIT DTP (log scale), continuous						
	98	6.1	2.83 (0.37, 21.69)	$p < 0.001$		$p < 0.001$
Smear grading						
Negative	1	.	Ref.		$p < 0.001$	$p < 0.001$
Scanty	2	2.3	0.19 (0.02, 2.30)	$p = 0.191$	$p < 0.001$	$p < 0.001$
1+	25	4.1	0.10 (0.01, 0.81)	$p = 0.031$	$p < 0.001$	$p < 0.001$
2+	16	4.1	0.10 (0.01, 0.87)	$p = 0.037$	$p < 0.001$	$p < 0.001$
3+	54	8.0	0.04 (0.00, 0.31)	$p = 0.002$	$p < 0.001$	$p < 0.001$
Mean MGIT DTP (not log scale), continuous						
	98	6.1	1.08 (0.93, 1.27)	$p < 0.001$		$p < 0.001$
Mean MGIT DTP (not log scale), dichotomized						
Low	49	7.9	Ref.		$p < 0.001$	$p = 0.002$
High	49	4.1	2.06 (1.31, 3.24)	$p = 0.002$	$p < 0.001$	$p = 0.002$
Mean MGIT DTP (), dichotomized						
Low	49	7.9	Ref.		$p < 0.001$	$p = 0.002$
High	49	4.1	2.06 (1.31, 3.24)	$p = 0.002$	$p < 0.001$	$p = 0.002$
Resistant to capreomycin (DST)						
Sensitive	19	4.1	Ref.		$p = 0.008$	$p = 0.002$
Resistant	3	16.1	0.00 (0.00, .)	$p = 1.000$	$p = 0.008$	$p = 0.002$
Resistant to ethambutol (DST)						
Sensitive	45	4.1	Ref.		$p = 0.001$	$p = 0.003$
Resistant	46	8.1	0.50 (0.32, 0.79)	$p = 0.003$	$p = 0.001$	$p = 0.003$
On ethambutol and susceptible at baseline						
Not on drug at baseline, or disease is resistant	49	8.1	Ref.		$p = 0.004$	$p = 0.008$
On drug at baseline, and disease is susceptible	42	4.1	1.86 (1.18, 2.95)	$p = 0.008$	$p = 0.004$	$p = 0.008$
AUC dichotomized2						
Low	44	5.9	Ref.		$p = 0.010$	$p = 0.018$
High	45	7.9	0.59 (0.38, 0.91)	$p = 0.018$	$p = 0.010$	$p = 0.018$
Resistant to kanamycin (DST)						
Sensitive	56	6.1	Ref.		$p = 0.054$	$p = 0.055$
Resistant	8	8.1	0.43 (0.17, 1.12)	$p = 0.084$	$p = 0.054$	$p = 0.055$
Study site						
TASK, Cape Town	38	6.3	1.00 (1.00, 1.00)		$p = 0.026$	$p = 0.061$
Cayetano, Lima	22	4.1	1.99 (1.12, 3.54)	$p = 0.019$	$p = 0.026$	$p = 0.061$
Socios en Salud, Lima	38	6.1	1.05 (0.65, 1.71)	$p = 0.836$	$p = 0.026$	$p = 0.061$
On pyrazinamide and susceptible at baseline						
Not on drug at baseline, or disease is resistant	56	6.3	Ref.		$p = 0.045$	$p = 0.066$
On drug at baseline, and disease is susceptible	35	4.1	1.54 (0.98, 2.43)	$p = 0.062$	$p = 0.045$	$p = 0.066$
Resistant to pyrazinamide (DST)						
Sensitive	36	4.1	Ref.		$p = 0.045$	$p = 0.066$
Resistant	55	6.3	0.65 (0.41, 1.02)	$p = 0.062$	$p = 0.045$	$p = 0.066$
Resistant to kanamycin or Amikacin (DST)						
Sensitive	52	6.1	Ref.		$p = 0.072$	$p = 0.082$
Resistant	9	6.1	0.49 (0.21, 1.17)	$p = 0.110$	$p = 0.072$	$p = 0.082$
Resistant to amikacin (DST)						
Sensitive	89	6.1	Ref.		$p = 0.091$	$p = 0.084$
Resistant	6	6.1	0.45 (0.16, 1.25)	$p = 0.124$	$p = 0.091$	$p = 0.084$
Age (dichotomised)						
Low	45	6.1	Ref.		$p = 0.066$	$p = 0.090$
High	53	6.1	0.68 (0.44, 1.06)	$p = 0.090$	$p = 0.066$	$p = 0.090$

Table S15.1: Univariable predictors of time to culture conversion (7H11). Variable listed if $p < 0.2$ for log-rank or likelihood ratio (LR) test. (continued)

Level	Participants	Median (wks)	Hazard ratio (95% CI)	Z-score	log rank test	LR test
AUC dichotomized						
Low	47	6.1	Ref.		$p = 0.098$	$p = 0.125$
High	42	6.1	0.71 (0.46, 1.10)	$p = 0.126$	$p = 0.098$	$p = 0.125$
AUC (tertiles)						
Low	33	4.1	Ref.		$p = 0.086$	$p = 0.132$
Mid	27	6.3	0.59 (0.34, 1.01)	$p = 0.053$	$p = 0.086$	$p = 0.132$
High	29	6.1	0.69 (0.42, 1.16)	$p = 0.162$	$p = 0.086$	$p = 0.132$
7H11 culture result						
Negative	3	2.3	Ref.		$p = 0.026$	$p = 0.137$
Positive	92	6.1	0.23 (0.07, 0.77)	$p = 0.017$	$p = 0.026$	$p = 0.137$
Contaminated	3	6.3	0.27 (0.05, 1.37)	$p = 0.114$	$p = 0.026$	$p = 0.137$
Cmax (dichotomized)						
Low	46	6.1	Ref.		$p = 0.165$	$p = 0.198$
High	43	6.1	0.75 (0.49, 1.16)	$p = 0.199$	$p = 0.165$	$p = 0.198$
AUC over MIC (BMD, dichotomized)						
Low	34	6.1	Ref.		$p = 0.168$	$p = 0.203$
High	34	8.0	0.73 (0.45, 1.19)	$p = 0.203$	$p = 0.168$	$p = 0.203$
On pyrazinamide at baseline						
Not on drug at baseline	3	4.0	Ref.		$p = 0.125$	$p = 0.221$
On drug at baseline	95	6.1	0.36 (0.09, 1.49)	$p = 0.158$	$p = 0.125$	$p = 0.221$

Table S15.2: Univariable predictors of time to culture conversion (MGIT). Variable listed if $p < 0.2$ for log-rank or likelihood ratio (LR) test.

Level	Participants	Median (wks)	Hazard ratio (95% CI)	Z-score	log rank test	LR test
7H11 colony count						
<10	1	.	1.00 (1.00, 1.00)		$p < 0.001$	$p < 0.001$
1+ (10-100)	22	4.1	0.17 (0.02, 1.43)	$p = 0.103$	$p < 0.001$	$p < 0.001$
2+ (>100)	22	6.3	0.08 (0.01, 0.69)	$p = 0.021$	$p < 0.001$	$p < 0.001$
3+ (>200)	47	10.0	0.05 (0.01, 0.38)	$p = 0.004$	$p < 0.001$	$p < 0.001$
Smear grading						
Negative	1	.	Ref.		$p < 0.001$	$p < 0.001$
Scanty	2	4.1	0.08 (0.00, 1.32)	$p = 0.077$	$p < 0.001$	$p < 0.001$
1+	25	4.1	0.64 (0.08, 4.79)	$p = 0.661$	$p < 0.001$	$p < 0.001$
2+	16	6.1	0.40 (0.05, 3.11)	$p = 0.383$	$p < 0.001$	$p < 0.001$
3+	54	10.0	0.21 (0.03, 1.56)	$p = 0.126$	$p < 0.001$	$p < 0.001$
Resistant to ethambutol (DST)						
Sensitive	45	6.1	Ref.		$p < 0.001$	$p = 0.002$
Resistant	46	9.9	0.46 (0.29, 0.75)	$p = 0.002$	$p < 0.001$	$p = 0.002$
Mean MGIT DTP (log scale), continuous						
	98	8.0	2.24 (0.46, 10.91)	$p = 0.001$		$p = 0.002$
On ethambutol and susceptible at baseline						
Not on drug at baseline, or disease is resistant	49	8.3	Ref.		$p = 0.002$	$p = 0.004$
On drug at baseline, and disease is susceptible	42	6.1	2.03 (1.26, 3.29)	$p = 0.004$	$p = 0.002$	$p = 0.004$
Resistant to capreomycin (DST)						
Sensitive	19	4.3	Ref.		$p = 0.017$	$p = 0.005$
Resistant	3	16.1	0.00 (0.00, .)	$p = 1.000$	$p = 0.017$	$p = 0.005$
Mean MGIT DTP (not log scale), continuous						
	98	8.0	1.07 (0.94, 1.21)	$p = 0.004$		$p = 0.008$
Mean MGIT DTP (not log scale), dichotomized						
Low	49	8.3	Ref.		$p = 0.005$	$p = 0.009$
High	49	6.1	1.81 (1.16, 2.81)	$p = 0.009$	$p = 0.005$	$p = 0.009$
Mean MGIT DTP (), dichotomized						
Low	49	8.3	Ref.		$p = 0.005$	$p = 0.009$
High	49	6.1	1.81 (1.16, 2.81)	$p = 0.009$	$p = 0.005$	$p = 0.009$

Table S15.2: Univariable predictors of time to culture conversion (MGIT). Variable listed if $p < 0.2$ for log-rank or likelihood ratio (LR) test. (continued)

Level	Participants	Median (wks)	Hazard ratio (95% CI)	Z-score	log rank test	LR test
Age (dichotomised)						
Low	45	6.1	Ref.		$p = 0.016$	$p = 0.024$
High	53	8.1	0.59 (0.38, 0.93)	$p = 0.023$	$p = 0.016$	$p = 0.024$
Resistant to pyrazinamide (DST)						
Sensitive	36	6.1	Ref.		$p = 0.022$	$p = 0.034$
Resistant	55	8.3	0.60 (0.38, 0.96)	$p = 0.031$	$p = 0.022$	$p = 0.034$
On pyrazinamide and susceptible at baseline						
Not on drug at baseline, or disease is resistant	56	8.3	Ref.		$p = 0.022$	$p = 0.034$
On drug at baseline, and disease is susceptible	35	6.1	1.66 (1.05, 2.63)	$p = 0.031$	$p = 0.022$	$p = 0.034$
Resistant to amikacin (DST)						
Sensitive	89	8.0	Ref.		$p = 0.077$	$p = 0.065$
Resistant	6	16.1	0.43 (0.15, 1.19)	$p = 0.103$	$p = 0.077$	$p = 0.065$
Resistant to kanamycin or Amikacin (DST)						
Sensitive	52	6.1	Ref.		$p = 0.109$	$p = 0.116$
Resistant	9	8.1	0.52 (0.22, 1.25)	$p = 0.145$	$p = 0.109$	$p = 0.116$
On pyrazinamide at baseline						
Not on drug at baseline	3	4.0	Ref.		$p = 0.037$	$p = 0.118$
On drug at baseline	95	8.0	0.25 (0.06, 1.06)	$p = 0.060$	$p = 0.037$	$p = 0.118$
AUC dichotomized2						
Low	44	6.1	Ref.		$p = 0.103$	$p = 0.124$
High	45	8.3	0.71 (0.45, 1.10)	$p = 0.123$	$p = 0.103$	$p = 0.124$
Actual dose of levofloxacin received (categorical)						
750	39	8.1	1.00 (1.00, 1.00)		$p = 0.116$	$p = 0.171$
1000	33	6.1	1.08 (0.65, 1.81)	$p = 0.761$	$p = 0.116$	$p = 0.171$
1250	20	6.1	1.77 (0.98, 3.20)	$p = 0.056$	$p = 0.116$	$p = 0.171$
1500	6	10.1	0.67 (0.23, 1.90)	$p = 0.450$	$p = 0.116$	$p = 0.171$
Study site						
TASK, Cape Town	38	8.3	1.00 (1.00, 1.00)		$p = 0.118$	$p = 0.176$
Cayetano, Lima	22	6.1	1.75 (0.97, 3.16)	$p = 0.061$	$p = 0.118$	$p = 0.176$
Socios en Salud, Lima	38	6.1	1.08 (0.66, 1.77)	$p = 0.762$	$p = 0.118$	$p = 0.176$
Resistant to kanamycin (DST)						
Sensitive	56	6.1	Ref.		$p = 0.181$	$p = 0.185$
Resistant	8	8.1	0.56 (0.22, 1.42)	$p = 0.219$	$p = 0.181$	$p = 0.185$

Table S15.3: Final multivariable predictors of time to culture conversion (7H11).

Level	Adjusted hazard ratio (95% CI)	Z-score	LR test
Smear grading			
Negative	Reference		$p < 0.001$
Scanty	0.28 (0.02, 3.52)	$p = 0.327$	
1+	0.15 (0.02, 1.36)	$p = 0.092$	
2+	0.17 (0.02, 1.56)	$p = 0.118$	
3+	0.06 (0.01, 0.51)	$p = 0.010$	
Study site			
TASK, Cape Town	Reference		$p = 0.068$
Cayetano, Lima	1.90 (1.06, 3.43)	$p = 0.032$	
Socios en Salud, Lima	0.95 (0.58, 1.55)	$p = 0.837$	

Table S15.4: Final multivariable predictors of time to culture conversion (MGIT).

Level	Adjusted hazard ratio (95% CI)	Z-score	LR test
Age (dichotomised)			
<26	Reference		$p = 0.005$

Table S15.4: Final multivariable predictors of time to culture conversion (MGIT). (*continued*)

Level	Adjusted hazard ratio (95% CI)	Z-score	LR test
≥26	0.52 (0.32, 0.82)	p = 0.005	
MGIT DTP at baseline (log scale)			
Per 1 day (log scale)	2.59 (1.54, 4.34)	p < 0.001	p < 0.001

3.16 Culture results at 6 months

Includes all culture results within week 24 and week 28 analysis windows (i.e., from day 156 or later). Data from participants with no culture results in this window are not included.

Table S16.1: Solid media (7H11) culture results at 6 months after randomization.

Culture result	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Negative	19 (100%)	21 (95%)	21 (88%)	21 (100%)	82 (95%)
Positive	0	0	2 (8%)	0	2 (2%)
Contaminated	0	1 (5%)	1 (4%)	0	2 (2%)
Total	19	22	24	21	86

Table S16.2: MGIT liquid media culture results at 6 months after randomization.

Culture result	11mg/kg	14mg/kg	17mg/kg	20mg/kg	Total
Negative	19 (100%)	21 (95%)	21 (88%)	20 (95%)	81 (94%)
Positive	0	0	3 (12%)	1 (5%)	4 (5%)
Contaminated	0	1 (5%)	0	0	1 (1%)
Total	19	22	24	21	86