THE LANCET

Supplementary appendix

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

Supplement to: Phillips RO, Robert J, Abass KM, et al. Rifampicin and clarithromycin (extended release) versus rifampicin and streptomycin for limited Buruli ulcer lesions: a randomised, open-label, non-inferiority phase 3 trial. *Lancet* 2020; published online March 12. http://dx.doi.org/10.1016/S0140-6736(20)30047-7.

Table S1- CONSORT Checklist:

Title and abstract			
	1a	Identification as a randomised trial in the title	√
	1b	Structured summary of trial design, methods, results, and conclusions	√
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	√
	2b	Specific objectives or hypotheses	√
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	√
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	na
Participants	4a	Eligibility criteria for participants	√
	4b	Settings and locations where the data were collected	√
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	√
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	√
	6b	Any changes to trial outcomes after the trial commenced, with reasons	na

Sample size	7a	How sample size was determined	√
	7b	When applicable, explanation of any interim analyses and stopping guidelines	√
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	√
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	√
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), (no concealment - open label)	√
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	√
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n.a.
	11b	If relevant, description of the similarity of interventions	√
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	√
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n.a.
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	√
	13b	For each group, losses and exclusions after randomisation, together with reasons	√

Recruitment	14a	Dates defining the periods of recruitment and follow-up	√
	14b	Why the trial ended or was stopped	√
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	√
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	√
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	√
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	√
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n.a.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	√
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	√
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	√
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	√

Other information			
Registration	23	Registration number and name of trial registry	√
Protocol	24	Where the full trial protocol can be accessed, if available	√
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	√

Table S2: Dosing schedule, Streptomycin, Rifampicin and Clarithromycin ER

Dose of Streptomycin (S), Rifampicin (R) and Clarithromycin (C) according to patient body weight				
Body weight of patient (kg)	Streptomycin (1 g) once daily Dose (g)	Rifampicin (300mg/tablet) once daily Dose (mg)	No of tablets	Clarithromycin (extended release once daily tablets 500 mg) Dose (mg)
21-39	0.50	300	1.00	500 (1 tablet)
40-54	0.75	450	1.50	500 (1 tablet)
>54	1.00	600	2.00	1,000 (1 tablet)

Table S3 - Paradoxical response (PR) – 4 definitions based on ARANZ measurements

	RS8		RC8		Total		
	n	%	n	%	n	%	p-value
Any increase relative to previous measurement	95	62,9	82	56,2	177	59,6	0,236
Any increase after initial decrease	79	52,3	62	42,5	141	47,5	0,089
Increase of ≥20% after initial decrease	65	43,0	49	33,6	114	38,4	0,093
Two consecutive increases after initial decrease	22	14,6	23	15,8	45	15,2	0,776

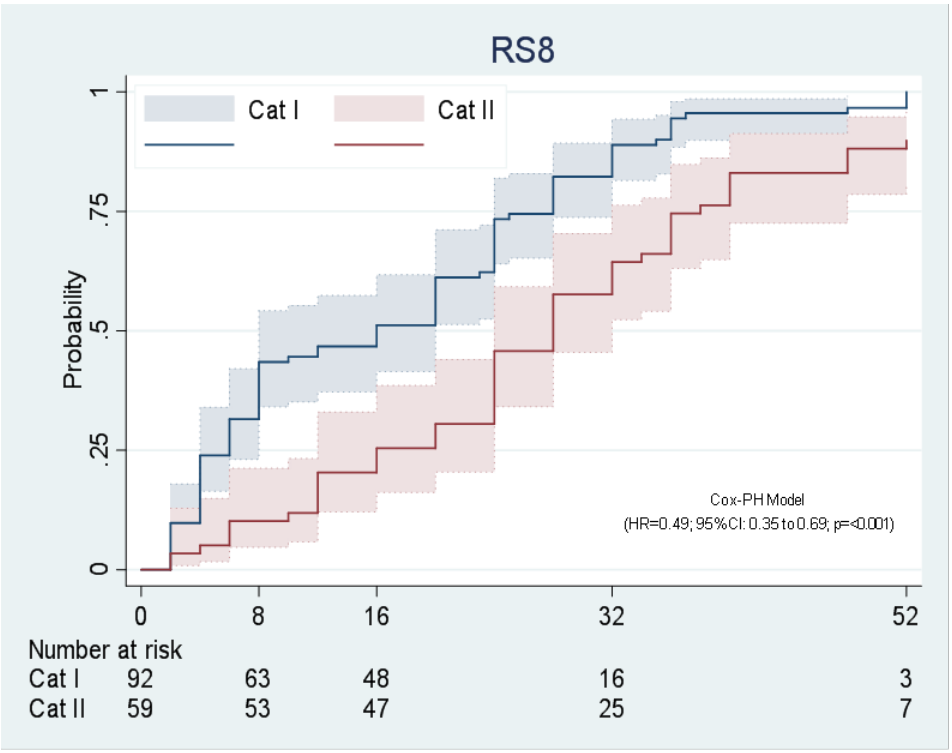
Table S4 - healing time by lesion size - Category I: <5 cm; Category II: 5-10 cm cross sectional diameter

	RS8			RC8		
	Cat I	Cat II	Total	Cat I	Cat II	Total
Number of Subjects	92	59	151	92	54	146
Time at Risk in person weeks	1586	1664	3250	1547	1286	2833
Incidence Rate (per 100 person weeks)	5,7	3,2	4,4	5,7	4,0	4,9
Median (IQR) healing time in weeks	16 (6 -28)	28 (16 -38)	24 (8 - 32)	13 (6 - 24)	20 (12 - 32)	16 (8 - 25)
P-value		<0.001			0,031	

Table S5 - healing time by lesion type: ulcer versus Nodule/Plaque/Oedema (N/P/O)

	RS8			RC8		
	ulcer	N/P/O	Total	ulcer	N/P/O	Total
Number of Subjects	83	68	151	73	73	146
Time at Risk in person weeks	1707	1543	3250	1340	1493	2833
Incidence Rate (per 100 person weeks)	4,7	4,1	4,4	5,2	4,7	4,9
Median (IQR) healing time in weeks	20 (8 -28)	24 (6 - 35)	24 (8 - 32)	12 (8 - 24)	20 (8 - 25)	16 (8 - 25)
P-value		0,310			0,597	

Figure S1: time to healing, for lesion size (category I versus category II) and treatment allocation (RS8 versus RC8)



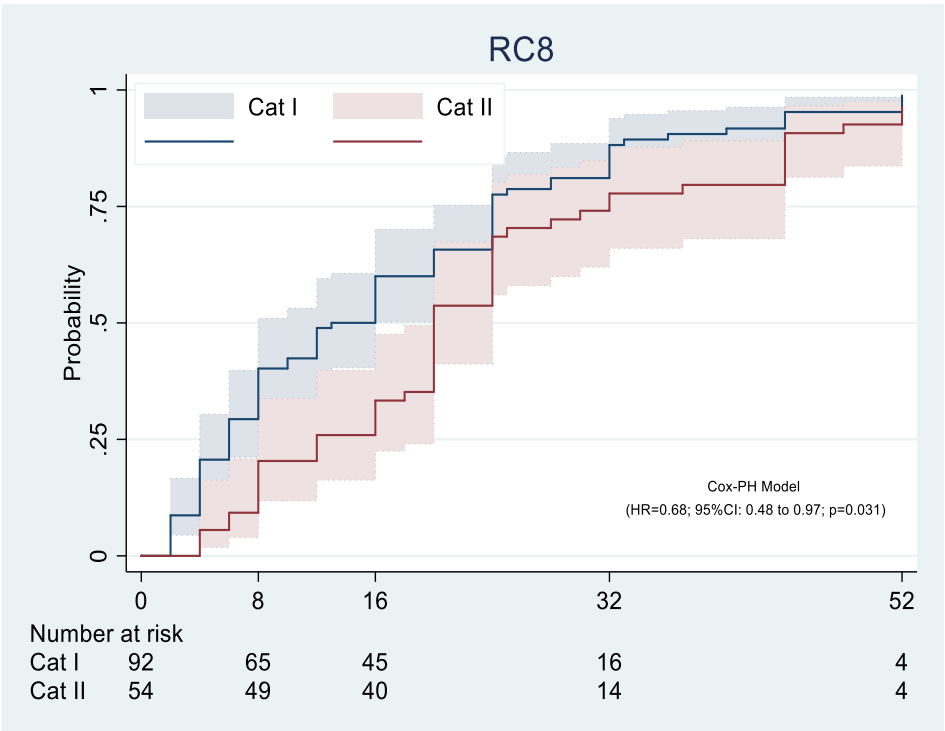
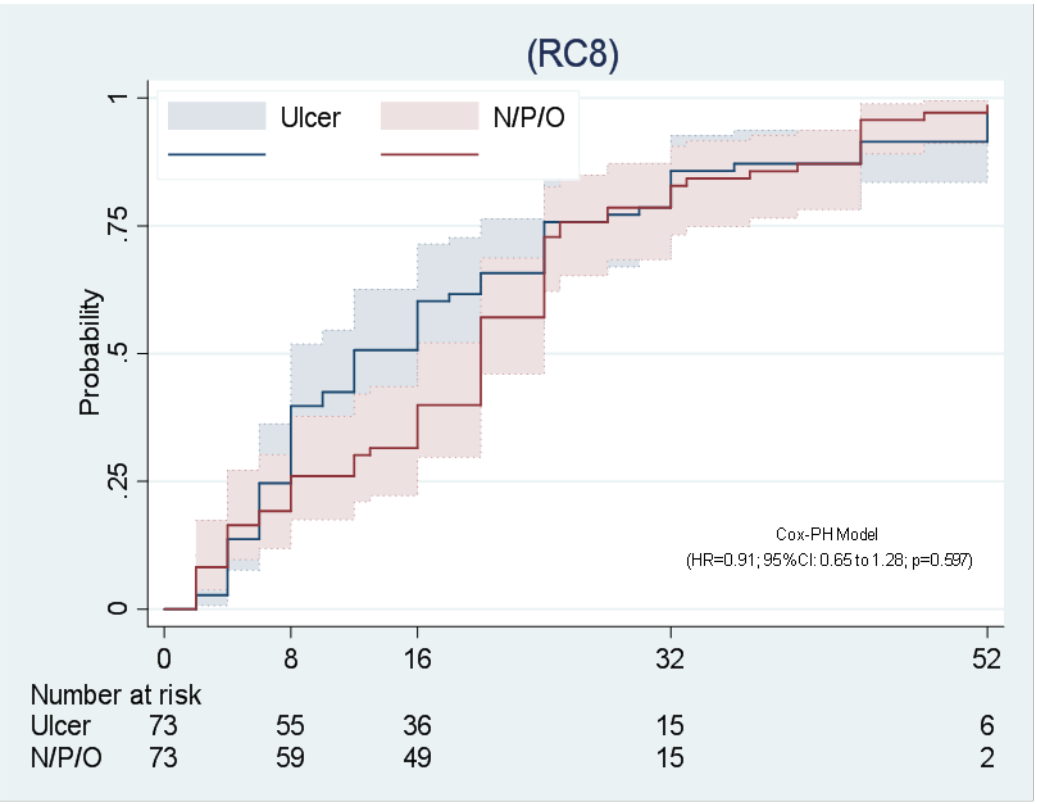


Figure S2: time to healing for ulcerated versus non-ulcerated lesions: Nodule/Plaque/Oedema; in RC8, and in RS8 arms.



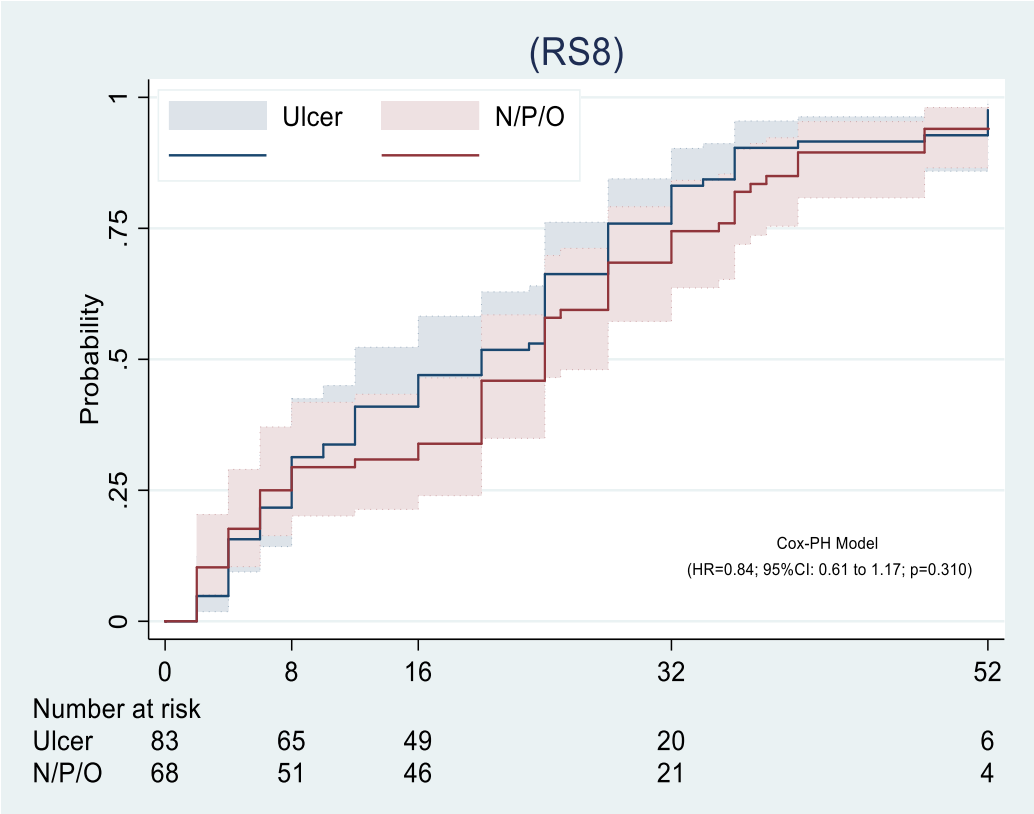


Table S5: details of study participants with unsuccessful outcome

TREATMENT ARM	AGE	SEX	LESION TYPE	LESION CATEGORY	COMMENT
RS8	72	Male	Ulcer	II	Lesion not healed due to trauma which caused enlargement, possibly due to the location of lesion (lateral malleolus)
RC8	26	Female	Ulcer	I	Patient was lost to follow up at week 12 when lesion was unhealed. Could not be traced to establish healing
RS8	9	Female	Ulcer	II	Lesion healed at week 56
RS8	9	Male	Ulcer	II	Lesion healed at week 77
RC8	11	Female	Ulcer	II	Patient was lost to follow up, reported at week 97 but not healed possibly due to improper wound management
RC8	32	Male	Plaque	II	Suspected malignancy. Patient was lost to follow up when referred for further medical checks
RS8	23	Female	Ulcer	II	Patient developed paradoxical reaction, suspected daily trauma due to location of lesion (medial malleolus) and lack of proper wound care
RS8	7	Male	Plaque	I	Patient lost to follow up after week 12. Unable to establish healing at week 52
RC8	7	Female	Oedema	II	Lesion not healed due to unresolved osteomyelitis
RS8	75	Female	Ulcer	II	Patient was lost to follow up, traced after week 52 but not healed
RS8	14	Male	Ulcer	II	Lesion not healed after 52 weeks - participant took to traditional treatment being reluctant to accept per-protocol wound care offered
RC8	84	Female		II	Patient could not be traced after baseline. No documentation to support healing although lesion said to heal at week 20
RC8	45	Female	Ulcer	I	Patient was lost to follow up after week 20. Patient reported lesion not healed when called by phone after week 52 - possibly due to improper wound care

Table S6: accrual of study participants at study sites over time

Year / Site	2013	2014	2015	2016	Total	%
Agogo, Ghana	41	51	33	16	141	45.7
Tepa, Ghana	13	11	21	17	62	20.3
Dunkwa, Ghana	4	11	9	6	30	9.5
Nkawie, Ghana	5	7	5	4	21	6.8
Pobè, Benin	8	22	8	18	56	17.7
Total	**71**	**102**	**76**	**61**	**310**	100