Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

Supplementary material

Table of Contents

The RIFASHORT trial investigators

St. George's, University of London
Institute for Infection and Immunity, Division of Clinical Science, St George's, University of London, Cranmer Terrace, London, SW17 0RE, United Kingdom: Amina Jindani, Thomas Harrison, Philip Butcher, Jasvir Dhillon, Jack Adams, Tulika Munshi, Claire Robb, Nanita Patel, Nandini Shah, Sally Abdelmalik, Sarah Burton, Dr Danni Kirwan.

The London School of Hygiene and Tropical Medicine
Keppel Street, London, WC1E 7HT, United Kingdom: Professor Katherine Fielding, Dr Daniel Grint.

University of Leicester
Department of Infection, Immunity and Inflammation, University of Leicester, Leicester: Professor Michael Barer, Jonathan Decker, Galina Mukamolova.

University of Sussex
Brighton BN1 9PX Medical Research Building, Brighton and Sussex Medical School: Dr Simon Waddell

Botswana CDC
Botswana, University of Botswana, Gaborone, Botswana: Alyssa Finlay Rosanna Boyd, Dr. Tefera Agizew, Dr Jose Gaby Tshikuka, Dr John T Tlhakanelo, Anikie Mathoma, Unami Mathebula, Joyce Basotli, Norah Dudzai Mawoko, Gagoope Mowaneg, Evelyn Dintwa, Maitumelo Masole, Malebogo Masono

Uganda
MSF- Epicentre, PO Box 1956, Mbarara, Uganda: Dr Daniel Atwine, Dr Adolf Byamukama, Ivan Mugisha Taremwa, Patrick Orikiriza, Deborah Nanjebe K.T., Dan Nyehangane, Dr Keneth Kananura, Dr Rachel Kyohairwe, Susan Lagoose Akatuhebwa, Dinnah Kansime Lydia, Amelia Arimpa, Yvonne Sheila Mbabazi, Derek Kamulegeya, Eva Natukunda, Brenda Asiimwe, Emmanuel Mucunguzi, Rinah Arinaitwe, Dianah Birungi, Claire Nimusima, Justus Ashaba

TransVIHMI – University of Montpellier – INSERM
U1175 & Epicentre, Kampala, Uganda
Dr. Maryline Bonnet, Institut de Recherche pour le Développement, UMI 233

Guinea
Service de Pneumo-Phtisiologie, Centre Hospitalier Universitaire Ignace Deen, B.P: 634, Conakry, République De Guinée: Prof Lansana Mady Camara, Prof Oumou Younoussa Bah, Dr Boubacar Bah, Fulgence Nzabintwali, Dr Diallo Alhassane Djeima, Mme Nene Mamata Mme, Sow Maimouna, Mme Aissatou Bah, Moussa Conde, Kindy Sadjo Bah, Falilou Bah, Sylla Karamoko, Abdourahmane Barry, Mme Kadiatou Balde, Abdourahmane Bah Harouna, Barry Mamadou, Saliou Barry, Alpha Saliou Barry

Lima

Hospital Dos de Mayo and Universidad Nacional Mayor de San Marcos (UNMSM), Lima, Peru: Dr. Eduardo Ticona Chávez, Dra. Luz Huaroto, Dr. Victor Manuel Chávez Pérez, Dr. Juan Genaro Sosa Páucar, Dr. César Eduardo Ticona Huaroto Dra. Paola Rondan Raquel Mugruza Pineda, Wendy Shulay Guevara Condorhuamán, Gloria Espinoza Vergaray, Verónica Carmona Flores, Julio Tanta Vergaray, Luis Vizuña Lorenzo, Maria Elena Vilca Valverde, María Isabel López Moreno, Wilfredo Vargas Onofre, Karín Canchari Salazar, Mónica Basauri Infantes, Ynocente Raúl Joaquín Vásquez, Jessica Chávez Echevarría, Rossana Pacheco Aguilar, Gaby Evelyn Alvarez Mantari, Miriam Quispe Quispe, Ismael Armando Collantes Diaz, José Julio Zúñiga Cruz.

University of New Mexico, Albuquerque, USA: Dr. Marcos Burgos

Nepal

GENETUP, PO Box 1494, Kalimati, Kathmandu, Nepal: Dr Bhabana Shrestha, Dr. Neko Mitra Shrestha, Sanu Tandukar, Bhagwan Maharjan, Bijesh Tandukar, Bijendra Bhakta Raya, Matina Maharjan, Samriddhi Karki, Meera Shrestha.

Pakistan

Department of Pathology/Microbiology, Aga Khan University, Karachi. Pakistan: Dr Saeed Hamid, Dr Bushra Jamil, Dilshad Begum, Dr Imran Ahmed, Professor Rumina Hasan, Dr Irfan Muhammad, Ammara Muzammil, Dr Paras Shahzad, Dr Anum Adil, Dr Hira Jawed.

Shaukat Khanum Memorial & Cancer Research Centre, Lahore, Pakistan: Dr. Faisal Sultan, Dr. Mariam Hassan, Dr. Iqra Masood, Dr. Summiya Nizamuddin.

Statistical note on the method of primary analysis

The method of analysis stipulated for the primary outcome in the statistical analysis plan was a generalized linear regression model with gaussian distribution and identity link function. This method is commonly used to estimate the risk difference for binomial data. However, it is open to model convergence issues when the number of events is low in some subgroups of adjusted analysis.

With few participants and unfavorable outcomes in some study sites in RIFASHORT, we encountered issues with the convergence of the generalized linear models. With questionable model convergence attained in many instances.

As such the Cochran-Mantel-Haenszel (CMH) weighting method was used instead to calculate the risk difference adjusted for study site. The CMH method is commonly used in the analysis of non-inferiority trials,[1] while it has been demonstrated to have similar power to the generalized linear regression model approach but without the drawback of problematic model convergence.[2]

[1] Dorman SE, Nahid P, Kurbatova EV, Phillips PP, Bryant K, Dooley KE, Engle M, Goldberg SV, Phan HT, Hakim J, Johnson JL. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. New England Journal of Medicine. 2021 May 6;384(18):1705-18.

[2] Mohamed K, Embleton A, Cuffe RL. Adjusting for covariates in non-inferiority studies with margins defined as risk differences. Pharmaceutical Statistics. 2011 Sep;10(5):461-6.

Administration of treatment and pill burden

All participants were given standard fixed dose combinations (FDC) of isoniazid, pyrazinamide and ethambutol plus 10 mg/kg rifampicin (HRZE) during the intensive phase and isoniazid and rifampicin (HR) during the continuation phase, with those randomised to study regimens 1 and 2 receiving additional supplementary rifampicin, dependent on their weight band (detailed below), making up their total dose to their respective study regimens.

Details of dosing are shown below:

I. **Control regimen (R10)** (2HRZE/4HR)**:**

Intensive Phase: The standard regimen of daily isoniazid, pyrazinamide and ethambutol plus 10 mg/kg rifampicin for the initial 8 weeks,

Continuation Phase: An additional 4 months of daily isoniazid and rifampicin (at the same dose size)

II. **Study regimen 1(SR1)** ($2EHR_{1200}Z/2HR_{1200}$)**:**

Intensive Phase: 2 months of daily isoniazid, pyrazinamide and ethambutol plus 10 mg/kg rifampicin with an additional rifampicin supplement to take the total daily dose of rifampicin to 1200mg**.**

Continuation Phase: 2 months of daily isoniazid and rifampicin (at the same dose).

Specifically the rifampicin supplements will be as follows:

- Rifampicin 900mg (weight bands 35-39kg),
- Rifampicin 750 mg (weight band 40-54kg),
- Rifampicin 600mg (weight band 55-70kg) and
- Rifampicin 450 mg (weight band more than 70 kg)

For further details see **Table 3**

Study regimen 2(SR2) ($2EHR_{1800}Z/2HR_{1800}$)**:**

Intensive Phase: 2 months of daily isoniazid, pyrazinamide and ethambutol plus 10 mg/kg rifampicin with an additional rifampicin supplement to take the total daily dose of rifampicin to 1800mg,

Continuation Phase: 2 months of daily isoniazid and rifampicin (at the same dose).

Specifically the rifampicin supplements will be as follows:

- Rifampicin 1500mg (weight bands 35-39kg),
- Rifampicin 1350mg (weight band 40-54kg),
- Rifampicin 1200mg (weight band 55-70kg) and
- Rifampicin 1050 mg (weight band more than 70 kg)

  For further details see **Table 4**

Details of Drug Dosages:

The doses of drugs to be given to each patient are shown below and are based on the weight of the patient at the time of starting treatment (baseline). Doses should be changed if the patient changes weight during the trial, all patients (control and study regimens) should be weighed monthly at clinic visits 1, 3, 4, 5. Patients in the control group will also be weighed at clinic visit 6 and 7. If the patient crosses the weight band the doses of FDC and additional Rifampicin should be changed according to their new weight band as indicated in Tables 1 and 2. This applies to both the intensive and continuation phases.

Table 1. Intensive phase- All regimens - daily for 2 months.

MEDICATION (4FDC)	**Number of tablets for different weights (kg)**			
	35-39 kg	**40-54 kg**	**55-70 kg**	**>70 kg**
ethambutol(275mg) isoniazid(75mg) rifampicin(150mg) pyrazinamide(400mg)	2	3	4	5

Table 2. Continuation phase- All regimens: rifampicin and isoniazid daily.

MEDICATION (FDC)	**Number of tablets for different weights (kg)**			
	35-39 kg	**40-54 kg**	**55-70 kg**	**>70 kg**
rifampicin (150mg) isoniazid (75mg)	2	3	4	5

The duration of the continuation phase treatment will be 4 months for patients allocated to the Control Regimen and 2 months for patients allocated to the study regimens.

SR1 only:

All patients will receive additional rifampicin to bring the daily dose to 1200mg throughout the 4 months of treatment (Table 3).

Table 3: Amount of rifampicin supplement

MEDICATION	Number of tablets for different weights (kg)			
	35-39 kg	**40-54 kg**	**55-70 kg**	**>70 kg**
Rifampicin supplement	900mg	750mg	600mg	450mg
R300mg tab	3	2	2	1
R150mg tab	0	1	0	1

SR2 only:

All patients will receive additional of rifampicin to bring the daily dose to 1800mg throughout the 4 months of treatment (Table 4).

Table 4: Amount of rifampicin supplement

MEDICATION	Number of tablets for different weights (kg)			
	35-39 kg	**40-54 kg**	**55-70 kg**	**>70 kg**
Rifampicin supplement	1500mg	1350mg	1200mg	1050mg
R300mg tab	5	4	4	3
R150mg tab	0	1	0	1

NOTE: One Rifampicin 300mg tablet can be replaced by 2 Rifampicin 150mg tablets.

All patients will receive pyridoxine supplementation daily throughout the period of treatment in accordance with local availability.

Definition of chest x-ray grading

The term **miliary** disease is reserved for a distinctive pattern of diffuse rounded opacities 1-2mm in diameter involving the majority of the lung fields.

A **cavity** is defined as a visible gas-containing space within the lung parenchyma surrounded by a wall greater than 1mm thick. The wall usually is irregular in contour. This wall thickness criterion distinguished cavities from air cysts and bullae that are thin-walled structures usually due to degenerative, inflammatory, or other non-infectious causes.

Extent of disease
The following grading system has to be used for assessing the extent of radiographic involvement by tuberculosis.

Grade Descriptive Grade Definition
0 Normal. No visible intrathoracic radiographic abnormalities suggestive of TB

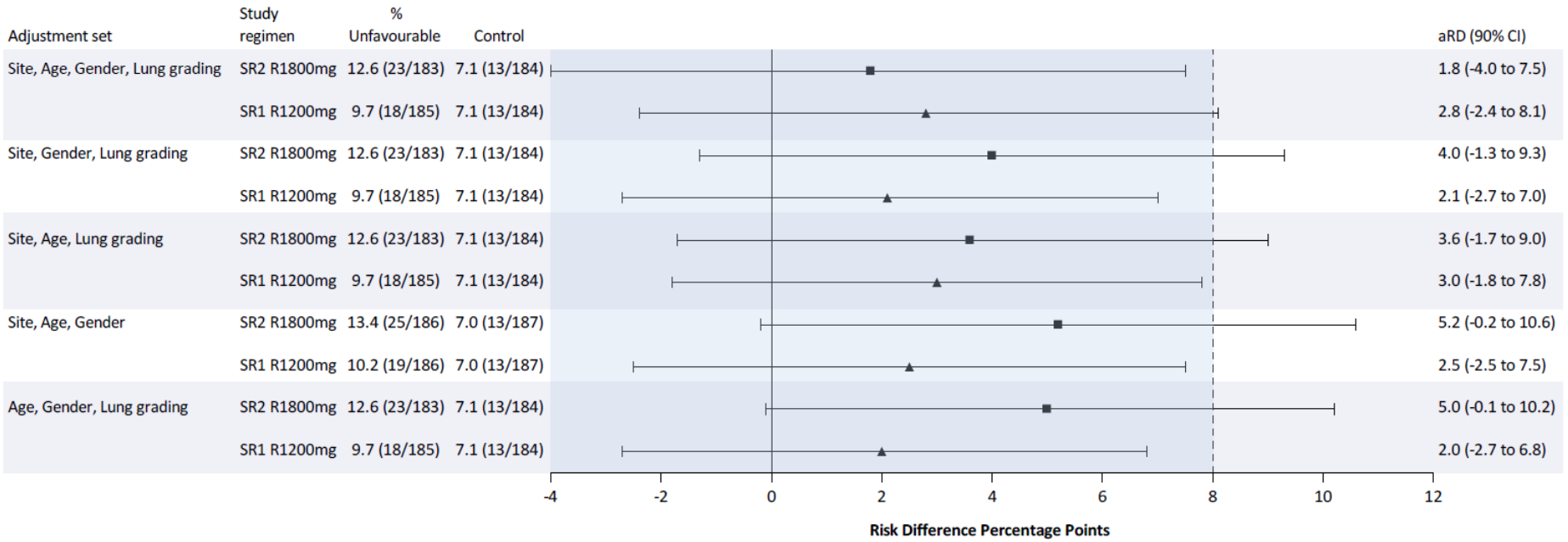
1 Minimal disease. Infiltrates of slight to moderate density. Disease may be present in a small portion of both lungs. The total volume of the infiltrate(s) must be = the volume of one lung present above the second costochondral junction and the spine of the fourth or the body of the fifth thoracic vertebra. No cavitation may be present.

2 Moderately advanced disease. Disease may be present in one or both lungs; the total extent must not be more than the following:
(i) scattered lesions of slight to moderate density may not involve more than the total volume of one lung or the equivalent volume of both lungs
(ii) dense, confluent lesions may not involved more than 1/3 of the volume of one lung.
(iii) The total diameter of cavity(ies) may not be > 4 cm.

3 Far advanced. Lesions more extensive than moderately advanced

Zone score: Number of lung zones involved by disease
The zone score is the number of lung regions (0-6) involved by disease. Each lung is dividing into three zones (upper, middle and lower) by dividing the distance between apex of the lung and the ipsilateral hemidiaphragm by 3. The zone score is the number of lung zones where visible disease is present and recorded as an integer (0-6).

Figure S1 Adjusted analyses of the primary outcome



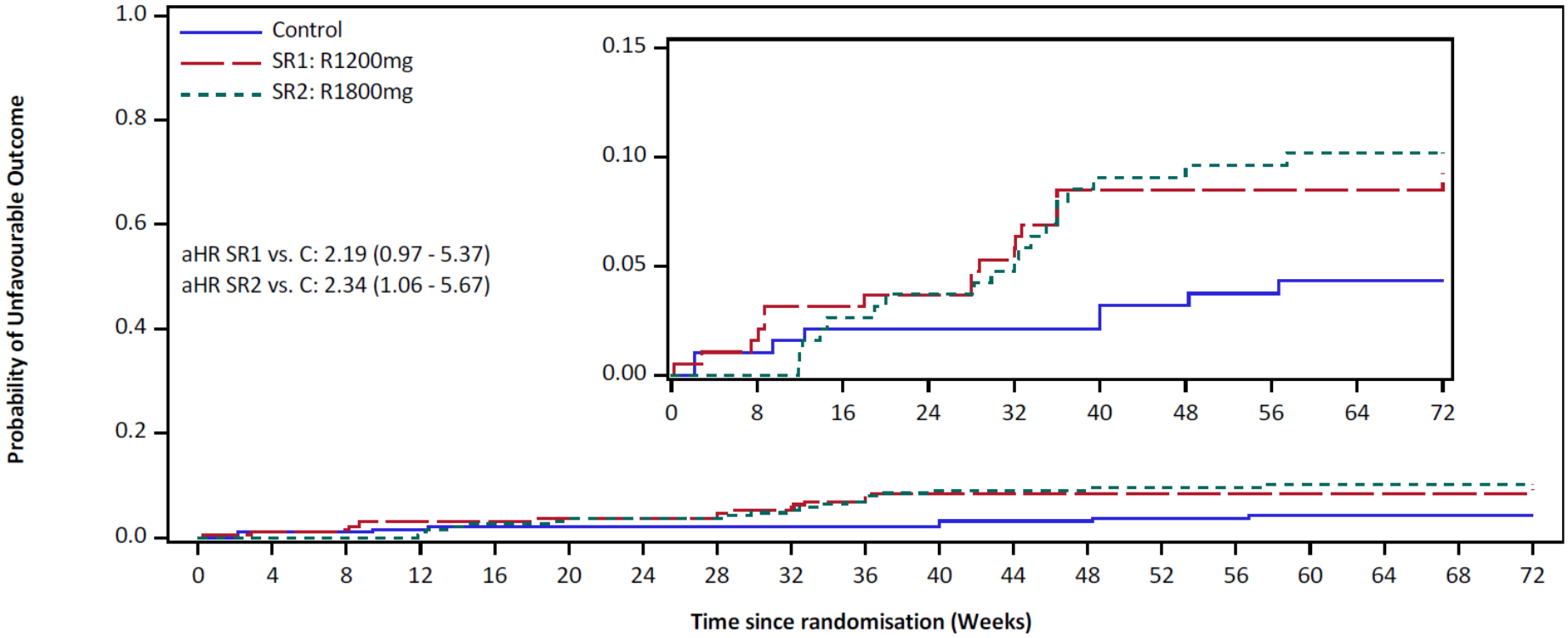
SR1: Study regimen 1 (1200mg Rifampicin); SR2: Study regimen 2 (1800mg Rifampicin); aRD: Adjusted risk difference; CI: Confidence interval.

The primary analysis method used the stratified Cochran Mantel-Haenszel test with adjustment, or more accurately stratification by study site. Additional analyses included further stratification factors where there was some imbalance at baseline between the characteristic of the population in each study arm.

Full adjustment for study site, age, gender, and lung grading at baseline resulted in many small substrata. To combat this, analysis was performed for each triplet of stratification factors in turn.

The results of the full stratification set and each triplet are presented above.

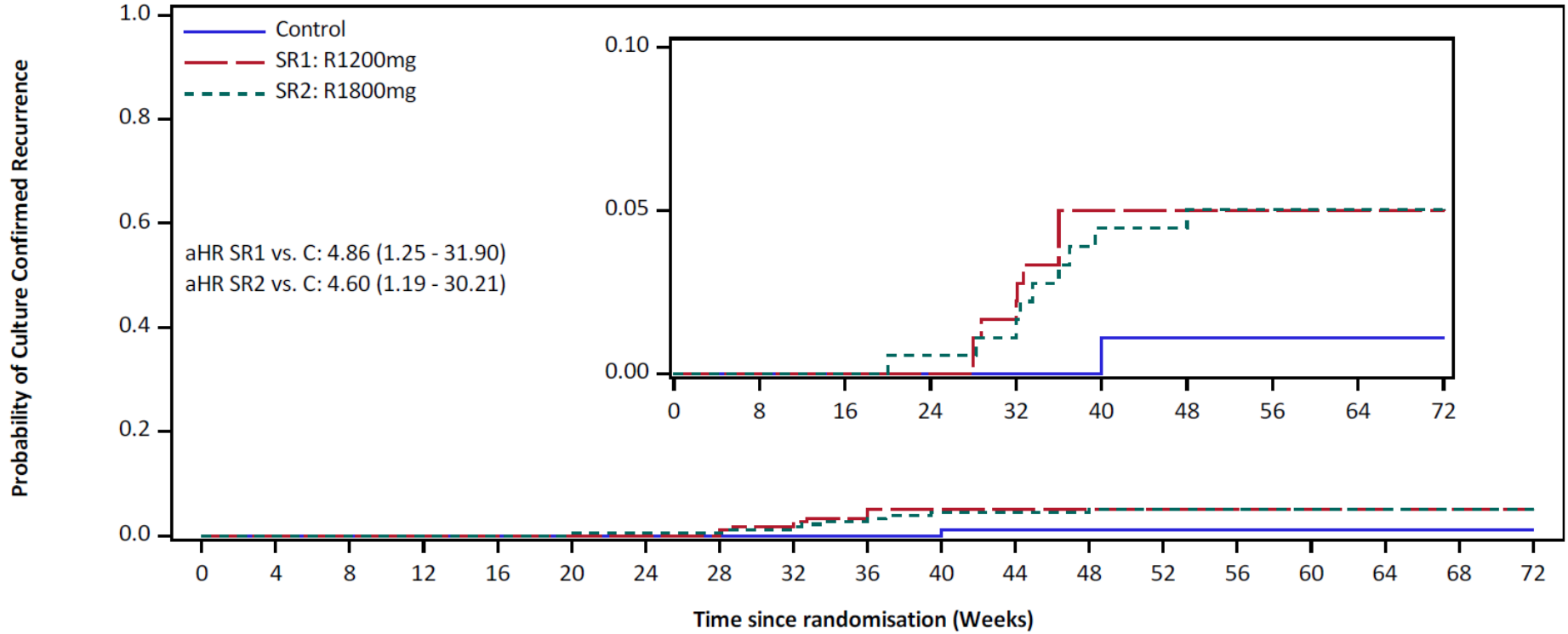
Figure S2 Kaplan-Meier plot of time to unfavorable outcome, PP-M population



N at Risk																			
Control	191	188	186	185	183	182	181	181	181	181	180	177	177	173	168	161	155	146	126
SR1: R1200mg	192	188	187	184	184	182	181	180	176	173	171	170	170	166	161	155	150	142	123
SR2: R1800mg	195	190	190	188	184	182	182	180	177	173	169	168	163	160	157	152	147	140	122

C: Control; SR1: Study Regimen 1 (1200mg Rifampicin); SR2: Study Regimen 2 (1800mg Rifampicin); aHR: Adjusted Hazard Ratio; N at Risk: Number at Risk.

Figure S3 Kaplan-Meier plot of time to culture confirmed recurrence, mITT-M population

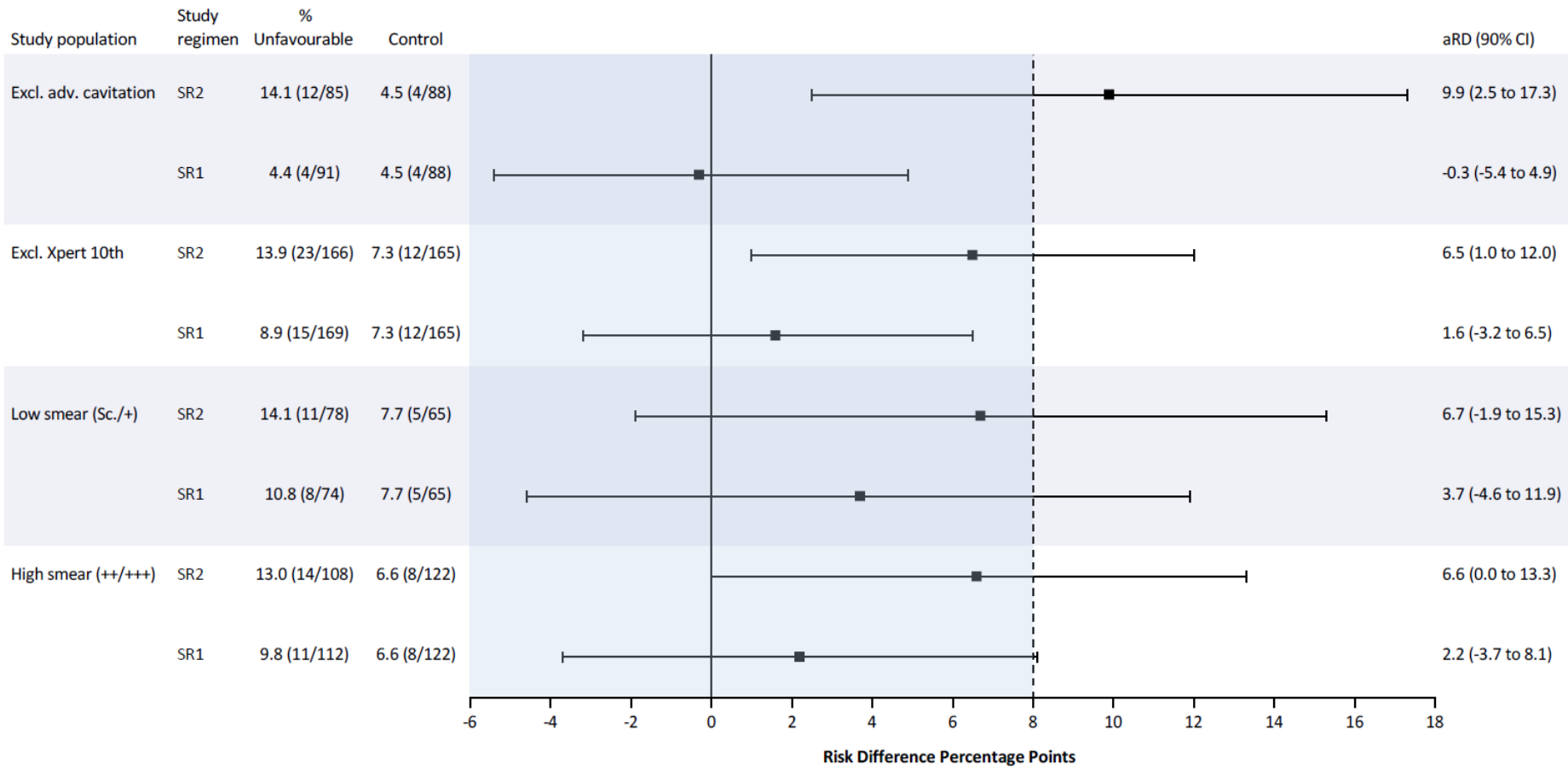


N at Risk

Control	191	188	186	185	183	182	181	181	181	181	180	177	177	173	168	161	155	146	126
SR1: R1200mg	192	188	187	184	184	182	181	180	176	173	171	170	170	166	161	155	150	142	123
SR2: R1800mg	195	190	190	188	184	182	182	180	177	173	169	168	163	160	157	152	147	140	122

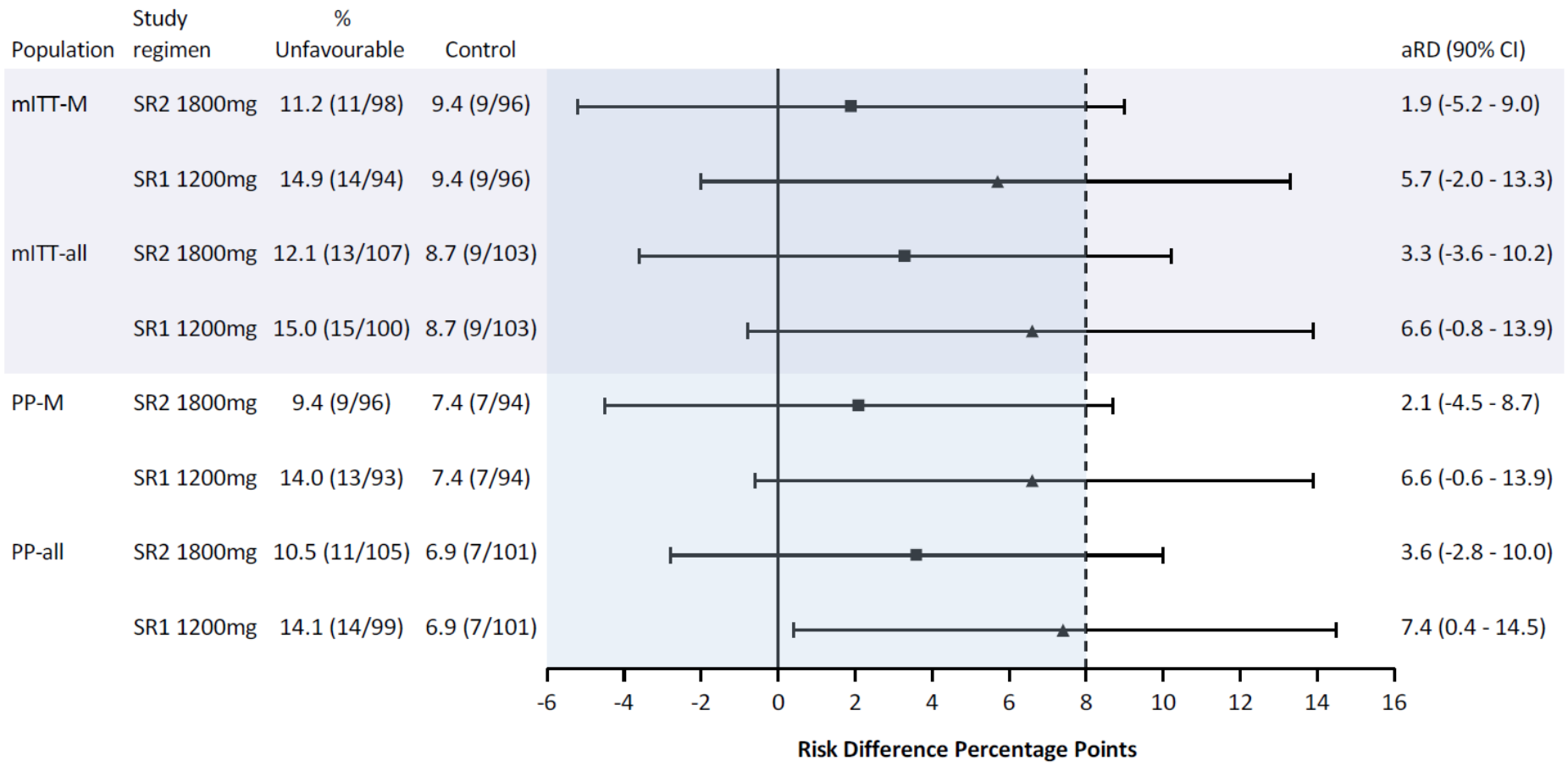
C: control; SR1: Study Regimen 1 (1200mg Rifampicin); SR2: Study Regimen 2 (1800mg Rifampicin); aHR: Adjusted Hazard Ratio; N at Risk: Number at Risk.

Figure S4 Primary outcome analysis among population subgroups, mITT-M population



Excl. adv. cavitation: Population excluding those with advanced cavitation on chest x-ray; Excl. Xpert 10th: Population excluding those with the lowest 10% of Xpert cycle threshold values; Low smear: Population with scanty or + baseline smear microscopy grading; High smear: Population with ++ or +++ baseline smear microscopy grading; SR1: Study regimen 1 (1200mg Rifampicin); SR2: Study regimen 2 (1800mg Rifampicin); aRD: Adjusted risk difference; CI: Confidence interval.

Figure S5 Primary outcome analysis among the population subset with far advanced disease and cavitation on baseline chest x-ray



mITT-M: Modified intention-to-treat microscopy positive population; mITT-all: Modified intention-to-treat inclusive population; PP-M: Per protocol microscopy positive population; PP-all: Per protocol inclusive population; SR1: Study regimen 1 (1200mg Rifampicin); SR2: Study regimen 2 (1800mg Rifampicin); aRD: Adjusted risk difference; CI: Confidence interval.

Table S1 Baseline characteristics of the mITT-M population, extended

Characteristic	Control (N=191)	Study regimen 1 (N=192)	Study regimen 2 (N=195)
Age - n (%)			
Median (IQR)	29.0 (23.0 - 38.0)	29.0 (22.0 - 36.0)	28.0 (23.0 - 43.0)
18-24	57 (29.8)	64 (33.3)	72 (36.9)
25-34	73 (38.2)	69 (35.9)	53 (27.2)
>34	61 (31.9)	59 (30.7)	70 (35.9)
Weight - n (%)			
Median (IQR)	52.2 (47.0 - 57.7)	51.9 (46.8 - 58.1)	52.6 (48.0 - 58.0)
30-39Kg	9 (4.7)	6 (3.1)	3 (1.5)
40-54Kg	111 (58.1)	113 (58.9)	114 (58.5)
55-70Kg	64 (33.5)	63 (32.8)	71 (36.4)
>70Kg	7 (3.7)	10 (5.2)	7 (3.6)
BMI			
Median (IQR)	18.4 (16.9 - 20.2)	18.6 (16.9 - 20.8)	18.8 (17.0 - 21.0)
Sex - n (%)			
Male	137 (71.7)	151 (78.6)	146 (74.9)
Female	54 (28.3)	41 (21.4)	49 (25.1)
Ethnicity - n (%)			
African	136 (71.2)	133 (69.3)	134 (68.7)
Hispanic	1 (0.5)	2 (1.0)	1 (0.5)
Mixed	32 (16.8)	34 (17.7)	36 (18.5)
Indigenous (South American)	1 (0.5)	1 (0.5)	0 (0.0)
Asian	21 (11.0)	22 (11.5)	24 (12.3)
Smoking status - n (%)			
Current	47 (24.6)	33 (17.2)	36 (18.5)
Former	15 (7.9)	15 (7.8)	17 (8.7)
Never	129 (67.5)	144 (75.0)	142 (72.8)
CXR cavitation - n (%)			
Unreadable/unknown	0	1 (0.5)	1 (0.5)
Yes	165 (86.4)	174 (90.6)	174 (89.2)
No	26 (13.6)	17 (8.9)	20 (10.3)
CXR grading - n (%)			

Characteristic	Control (N=191)	Study regimen 1 (N=192)	Study regimen 2 (N=195)
Unreadable/unknown	3 (1.6)	1 (0.5)	3 (1.5)
Normal or minimal disease	3 (1.6)	4 (2.1)	4 (2.1)
Moderately advanced disease	86 (45.0)	88 (45.8)	85 (43.6)
Far advanced disease	99 (51.8)	99 (51.6)	103 (52.8)
Sputum smear grading - n (%)			
+ or scanty	68 (35.6)	77 (40.1)	81 (41.5)
++	52 (27.2)	41 (21.4)	49 (25.1)
+++	71 (37.2)	74 (38.5)	65 (33.3)
Previous TB treatment at randomisation			
Yes - n (%)	111 (58.1)	119 (62.0)	116 (59.5)
Days - median (IQR)	2.0 (0.0 - 4.0)	2.0 (0.0 - 4.0)	2.0 (0.0 - 4.0)

BMI: Body mass index; CXR: Chest X-ray; IQR: Interquartile range.

Table S2 Baseline characteristics of the safety population

Characteristic	Control (N=224)	Study regimen 1 (N=223)	Study regimen 2 (N=225)
Age - n (%)			
Median (IQR)	29.0 (23.5 - 38.5)	29.0 (23.0 - 37.0)	28.0 (22.0 - 43.0)
18-24	66 (29.5)	72 (32.3)	88 (39.1)
25-34	84 (37.5)	78 (35.0)	60 (26.7)
>34	74 (33.0)	73 (32.7)	77 (34.2)
Weight - n (%)			
Median (IQR)	52.0 (47.0 - 57.5)	52.1 (47.0 - 58.4)	52.0 (47.6 - 58.0)
30-39Kg	10 (4.5)	6 (2.7)	3 (1.3)
40-54Kg	134 (59.8)	131 (58.7)	134 (59.6)
55-70Kg	71 (31.7)	75 (33.6)	79 (35.1)
>70Kg	9 (4.0)	11 (4.9)	9 (4.0)
BMI			
Median (IQR)	18.5 (16.9 - 20.5)	18.7 (17.0 - 21.0)	18.8 (16.9 - 21.0)
Sex - n (%)			
Male	157 (70.1)	169 (75.8)	168 (74.7)
Female	67 (29.9)	54 (24.2)	57 (25.3)
Ethnicity - n (%)			
African	151 (67.4)	149 (66.8)	149 (66.2)
Hispanic	1 (0.4)	2 (0.9)	1 (0.4)
Mixed	38 (17.0)	39 (17.5)	40 (17.8)
Indigenous (South American)	1 (0.4)	1 (0.4)	0 (0.0)
Asian	33 (14.7)	32 (14.3)	35 (15.6)
Smoking status - n (%)			
Current	52 (23.2)	38 (17.0)	43 (19.1)
Former	18 (8.0)	16 (7.2)	17 (7.6)
Never	154 (68.8)	169 (75.8)	165 (73.3)
CXR cavitation - n (%)			
Unreadable/unknown	0 (0.0)	3 (1.3)	1 (0.4)
Yes	188 (83.9)	195 (87.4)	200 (88.9)
No	36 (16.1)	25 (11.2)	24 (10.7)
CXR grading - n (%)			

Characteristic	Control (N=224)	Study regimen 1 (N=223)	Study regimen 2 (N=225)
Unreadable/unknown	3 (1.3)	3 (1.3)	4 (1.8)
Normal or minimal disease	9 (4.0)	7 (3.1)	4 (1.8)
Moderately advanced disease	98 (43.8)	103 (46.2)	96 (42.7)
Far advanced disease	114 (50.9)	110 (49.3)	121 (53.8)
Sputum smear grading - n (%)			
No AFB seen	16 (7.1)	14 (6.3)	17 (7.6)
+ or scanty	76 (33.9)	86 (38.6)	89 (39.6)
++	55 (24.6)	45 (20.2)	50 (22.2)
+++	77 (34.4)	78 (35.0)	69 (30.7)
Previous TB treatment at randomisation			
Yes - n (%)	130 (58.0)	137 (61.4)	133 (59.1)
Days - median (IQR)	2.0 (0.0 - 4.0)	2.0 (0.0 - 4.0)	2.0 (0.0 - 4.0)

BMI: Body mass index; CXR: Chest X-ray; AFB: Acid-fast bacillus; IQR: Interquartile range.

Table S3 Primary analysis outcomes in the PP-M population

PP-M primary analysis assessable outcomes	Control (N=182)	Study regimen 1 (N=182)	Study regimen 2 (N=180)
Favorable			
Participants with outcome - n (%)	174 (95.6)	165 (90.7)	161 (89.4)
Unfavorable			
Participants with outcome - n (%)	8 (4.4)	17 (9.3)	19 (10.6)
Adjusted risk difference to control (95% CI)			
Death during the treatment phase	3 (1.6)	4 (2.2)	0
Post-treatment death, TB a plausible cause	0	1 (0.5)	0
Change in treatment due to adverse event[1]	1 (0.5)	2 (1.1)	7 (3.9)
Two consecutive positive cultures after completing treatment	2 (1.1)	9 (4.9)	9 (5.0)
Retreated for TB due to clinical signs and symptoms without two consecutive positive cultures	2 (1.1)	1 (0.5)	3 (1.7)
Unassessable Outcomes	9	10	15
Post-treatment death deemed unrelated to TB or treatment	2	1	2
Treatment phase LTFU	2	0	1
Post-treatment LTFU when culture negative	1	3	5
Evidence of exogenous TB reinfection	0	1	2
Withdrawal during the treatment phase	3	2	5
Withdrawal during the treatment phase when culture negative	1	0	0
Post-treatment withdrawal when culture negative	0	1	0
Switched to control regimen due to pregnancy	0	2	0

PP-M primary analysis assessable outcomes	Control (N=182)	Study regimen 1 (N=182)	Study regimen 2 (N=180)
Secondary analysis outcomes			
Confirmed culture conversion from positive to negative – n/N (%)			
Eight weeks from randomization	157/183 (85.8)	166/179 (92.7)	163/181 (90.1)
Twelve weeks from randomization	181/184 (98.4)	180/184 (97.8)	183/186 (98.4)

LTFU: Loss to follow-up.

[1]All changes in treatment due to AE involved high liver transaminases or jaundice, except for one in SR1 due to depression.

Table S4 Listing of adverse events that led to a change in allocated study treatment

AE #	DAIDS grade	Main diagnosis	Narrative summary	Outcome
Control Regimen				
1	3	DRESS syndrome	After 3 weeks of study treatment, a rash appeared on the thorax and upper limbs. The next day the rash generalized to the back and abdomen with itching. DRESS syndrome was diagnosed following clinical review and the participant was hospitalized with treatment suspended and nil by mouth. Six days later the participant was discharged from hospital reporting no fever or pruritus and able to tolerate oral foods. Due to the potential relationship between first line anti-TB treatment and DRESS syndrome, the participant was withdrawn from the study and referred to the national TB programme where a non-first line regimen was identified for ongoing treatment.	Participant was referred to the national TB program for ongoing treatment with a non-first line anti-TB regimen
Study Regimen 1 (1200mg RIF)				
1	3	Raised ALT; liver toxicity	Full details summarized in Table S5. Study Regimen 1, DILI #1.	Participant stopped trial allocated regimen and moved to national TB program for further treatment
2	3	Depression	10 weeks post-randomisation the participant presented with significant clinical depression such that the participant was unable to continue in the study.	Withdrawn from study treatment due to AE

AE #	DAIDS grade	Main diagnosis	Narrative summary	Outcome
Study Regimen 2 (1800mg RIF)				
1	3	Raised ALT; liver toxicity	Full details summarized in Table S5. Study Regimen 2, DILI #1.	Participant stopped trial allocated regimen and moved to national TB program for further treatment
2	3	DRESS syndrome; liver toxicity	Participant reported fever, nausea, vomiting, malaise, and pruritic rash 1 week after starting treatment, and was diagnosed with DRESS syndrome with suspension of all medication. ALT measured 257 U/L, with no jaundice. The participant was hospitalized 5 days later for close monitoring and corticosteroid treatment when ALT increased to 567 U/L. Following 10 days in hospital the participant was discharged with an ALT of 178 U/L. Five days later ALT had increased again to 335 U/L and corticosteroid treatment was extended for a further 7 days. 2 weeks later symptoms had resolved and ALT normalized. Due to the potential relationship between first line anti-TB treatment and DRESS syndrome, the participant was withdrawn from the study and referred to the national TB programme.	Participant stopped trial allocated regimen and moved to national TB program for further treatment
3	3	Raised ALT; liver toxicity	At week 2, blood tests showed ALT 435 U/L, with normal bilirubin. Participant was called back for repeat blood tests and study medication suspended. The repeat blood test confirmed elevated ALT 450 U/L, and the participant was withdrawn from the study and referred to the national TB programme for re-introduction of standard anti-TB treatment. ALT returned to normal.	Participant stopped trial allocated regimen and moved to national TB program for further treatment

AE #	DAIDS grade	Main diagnosis	Narrative summary	Outcome
4	3	Raised ALT; liver toxicity	Full details summarized in Table S5. Study Regimen 2, DILI #2.	Participant stopped trial allocated regimen and moved to national TB program for further treatment
5	2	Raised ALT	Blood tests at month 1 showed grade 2 elevated ALT 94 U/L which had risen at month 2 (ALT 119 U/L). Site team withdraw participant who was moved to standard treatment through the national TB programme. ALT resolved.	Participant stopped trial allocated regimen and moved to the national TB program for treatment
6	3	Raised bilirubin; jaundice	At week 8, participant developed jaundice and nausea with elevated total bilirubin, 4.1 mg/dL. ALT marginally raised (58). Participant was withdrawn from study medication, and blood tests normalized.	Participant stopped trial allocated regimen and moved to national TB program for further treatment

AE #	DAIDS grade	Main diagnosis	Narrative summary	Outcome
7	4	Raised bilirubin; liver toxicity	Full details summarized in Table S5. Study Regimen 2, DILI #4.	Participant stopped trial allocated regimen and moved to national TB program for further treatment

TB: tuberculosis

Table S5 Drug-induced liver injury events, listing of Hy's law candidates

Hy's law is defined by: ALT >3x ULN and total bilirubin >2x ULN, with no other possible explanation for liver toxicity

DILI #	Peak ALT (U/L)	Peak total bilirubin (mg/dL)	Associated symptoms	Potential additional causes	Summary	Satisfies Hy's law
Study Regimen 1 (1200mg RIF)						
1	350	3.2	Nausea		Participant reported nausea after three weeks of study treatment. ALT and total bilirubin were raised, and participant was withdrawn from study medication. Symptoms and blood test abnormalities resolved.	Yes
Study Regimen 2 (1800mg RIF)						
1	332	9.4	None reported		Liver toxicity detected in blood test results after 18 days of treatment. Study medication was withdrawn and liver toxicity resolved.	Yes
2	416	4.2	Abdominal pain	HBsAg positive	Participant complained of abdominal pain, and lower back pain after 8 weeks of treatment. Participant was jaundiced with raised ALT and bilirubin and participant was withdrawn, with subsequent reduction in ALT and normalization of bilirubin	No

DILI #	Peak ALT (U/L)	Peak total bilirubin (mg/dL)	Associated symptoms	Potential additional causes	Summary	Satisfies Hy's law
3	194	6.6	None reported		At week 2 study treatment was held due to raised total bilirubin. Study medication was reintroduced two weeks later once ALT and total bilirubin had normalized, and treatment completed successfully.	Yes
4	942	29.5	Loss of appetite, joint pains	HBsAg positive	At week 12 visit the participant complained of loss of appetite and joint pain and was jaundiced. Participant was withdrawn from study medication and admitted to hospital but discharged 3 days later in a stable condition with decreasing bilirubin and ALT, which subsequently resolved.	No

ALT: alanine aminotransferase; HBsAg: Hepatitis B surface antigen;

Table S6 Schedule of assessments

Day#	Weeks from enrolment	Consent	Home details	Clinical details	Chest X-ray	Blood and urine tests*	Progress report (including AE review)	Sputum for microscopy & culture (no. of specimens)	Susceptibility test (INH & RIF)
0	**Screening**	√	√	√		FBC, ALT, bilirubin, creatinine, HIV,		**1 and 1 for**	√
						HbA1c		Xpert MTB/RIF	(dst if culture +ve)
						pregnancy			
1	**Enrolment**	√	√	√	√	Hepatitis B and C,	√	**1**	√
									(dst if culture +ve) *if not done at screening
2	**2 weeks**					ALT only	√		
3	**4 weeks**					√ ALT & FBC	√		
3.5	**6 weeks**					√ ALT & FBC	√		
4	**8 weeks**					√ ALT & FBC	√	**2**	√ (dst if culture +ve)
5	**12 weeks**					√ ALT & FBC	√	**2**	√ (dst if culture +ve)
6	**16 weeks**					√ ALT & FBC	√	**2**	√ (dst if culture +ve)
7	**20 weeks**					√ ALT & FBC	√	**2§ /1#**	√ (dst if culture +ve)
8	**24 weeks**					√**§** ALT & FBC	√	**2§ / 1#**	√ (dst if culture +ve)
9	**28 weeks**					√**§** ALT & FBC	√	**1**	√ (dst if culture +ve)
10	**32 weeks**						√	**1**	√ (dst if culture +ve)
11	**36 weeks**						√	**1**	√ (dst if culture +ve)
12	**40 weeks**						√	**1**	√ (dst if culture +ve)
13	**44 weeks**						√	**1**	√ (dst if culture +ve)
14	**48 weeks**						√	**1**	√ (dst if culture +ve)
15	**60 weeks**						√	**2**	√ (dst if culture +ve)
16	**72 weeks**						√	**2**	√ (dst if culture +ve)

Table S7 Representativeness of RIFASHORT study participants

Disease, problem or condition under investigation	Pulmonary tuberculosis (TB), rifampicin-susceptible.
Considerations related to sex or gender	TB disproportionally affects men. In 2021, the World Health Organisation (WHO) reported that 63% of global adult TB cases occurred in men.[3]
Consideration related to age	TB disproportionally affects adults. In 2021, the WHO reported that 89% of global TB cases occurred in adults.[3]
Considerations related to race or ethnic group	There is no biological association between ethnicity/race and pulmonary TB.
Considerations related to geography	In 2021, the WHO regions most affected by TB were South-East Asia, Africa, and the Western Pacific, which accounted for 45%, 23%, and 18% of global TB cases, respectively.[3]
Other considerations	TB is associated with undernutrition, HIV positivity, and diabetes. In 2021, the WHO reported that 6.7% of global incident TB cases were among people living with HIV.[3]
Overall representativeness of the trial	73.5% of the study participants were male. Children under the age of 18 were not enrolled in the study. The median age of study participants was 29 years; 33% were older than 34. Participants were recruited from six sites with high TB prevalence in Africa (Botswana, Guinea, Uganda), South Asia (Nepal, Pakistan), and South America (Peru). People living with HIV or diabetes were not enrolled in the study. The RIFASHORT study participants were broadly representative of the global burden of TB. A slightly higher proportion were male, however, which is a common phenomenon in TB treatment trials. The age distribution was highly representative of the global burden of TB. The participants were primarily recruited from the two WHO regions most affected by TB (South-East Asia and Africa). People living with HIV or diabetes were not recruited, as has been common in TB treatment trials due to concerns about adverse events and drug interactions in these groups. Future trials are planned including these groups.

[3] World Health Organization, 2022. Global tuberculosis report 2022. In *Global tuberculosis report 2022*.

FBC: full blood count; ALT: alanine aminotransferase; HIV: human immunodeficiency virus; HgA1c: hemoglobin A1c; dst: direct susceptibility testing; TB: tuberculosis.