**SUPPLEMENTARY MATERIALS**

**Title:** Levofloxacin preventive treatment in children exposed to MDR-TB: a randomized trial

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**S1 TB-CHAMP TRIAL TEAM**

**Core author trial team**

Anneke C. Hesseling[1]
Susan E. Purchase[1]
Neil A. Martinson[2]
Lee Fairlie[3]
H. Simon Schaaf[1]
Joanna Brigden[4]
Suzanne Staples[5]
Francesca Conradie[6]
Diana M. Gibb[4]
Anthony Garcia-Prats[1,7]
Charlotte McGowan[4]
Charlotte Layton[4]
Elize Batist[1]
Anne-Marie Demers [1,8]
Lisa Frigati[9]
Samukelisiwe Nyamathe[1]
Rebecca M Turner [4]
Trinh Duong[4]
James A. Seddon[1,11]

**Additional authors**

Tumelo Moloantoa[2]
Nadia Sabet[2]
Modiehi Mosala[2]
Faeeza Patel[3]
Janet Grab[3]
Hamisha Soma-Kasiram[3]
Ian R. White[4]
Rob Aarnoutse[11]
Leo Martinez[12]
Louise Choo[4]
Angela Crook[4]
Lindsey Masters[4]
Susan Ford[5]
Shrivani Padayachee[5]
Asanda Poswa[6]

**Affiliations**

[1]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, South Africa

[2]Perinatal HIV Research Unit, University of the Witwatersrand, South Africa and Johns Hopkins Center for TB Research, Baltimore, MD

[3]Wits Research Health Institute, Faculty of Health Sciences, University of the Witwatersrand, South Africa

[4]Medical Research Council Clinical Trials Unit at University College London, United Kingdom

[5]Tuberculosis & HIV Investigative Network, KwaZulu Natal, South Africa

[6]Isango Lethemba TB Research Unit, Port Elizabeth, Wits Health Consortium, South Africa

[7]Department of Pediatrics, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, United States of America

[1,8]Division of Microbiology, Department of Laboratory Medicine, CHU Sainte-Justine, and Department of Microbiology, Immunology and Infectious Diseases, Faculty of Medicine, University of Montreal, Canada and [1]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, South Africa

[9]Department of Paediatrics and Child Health, Stellenbosch University, South Africa
[10]Department of Infectious Disease, Imperial College London, United Kingdom
[11]Department of Pharmacy, Radboud Institute for Medical Innovation, Radboud University Medical Center, Nijmegen, The Netherlands

[12] Boston University, School of Public Health, Department of Epidemiology, Boston, Massachusetts, USA

**Trial Steering Committee (TSC)**

Stephen Graham, Australia

Peter Donald, South Africa

David Moore, United Kingdom

Carl Lombard, South Africa

**End Point Review Committee (ERC)**

Steven Welch, United Kingdom

Eric Wobudeya, Uganda

Ben Marais, Australia

**Independent Data Monitoring Committee (IDMC)**

Tim Peto, United Kingdom

Katherine Fielding, United Kingdom

Alwyn Mwinga, Zambia

Andrew Steenhoff, United States of America

**Study team**

**Desmond Tutu TB Centre, Stellenbosch University, Cape Town**

Anneen van Deventer

Muhammad Osman

Elisa Lopez-Varela

Daphne van Ster

Queen Mda

Elizabeth Viljoen

Klassina Zimri

Grayson Lamore

Tina Sachs

Theo Smith

Rory Dunbar

Jennie Slabber

Gezina De Beer

Simphiwe Simelane

Daphne van Ster
Marilyn Mentor
Andiswa Vazi
Zimela Dyosi
Zingiwe Mramba
Boniswa Mvinjelwa
Queen Mda
Elizabeth Viljoen
Sindiswa Kigenyi
Hazel Davids-Ruiters
Lumka Mafu
Eunice Mtshamba
Deon Meyer
Mzwanele Lawrence
Sabelo Ziqhu
Andile Miti
Lindelani Mavume
Anele Klaas
Waylin Wenn
Yanga Tshukuse
Sandise Tyelentombi
Nangamso Cawe
Lerato Mdaka
Megan Palmer
Heidi van Deventer
Warren Zimri
Shane Maker
Ralton Beukes
Randy Harley
Regina Gioio

**Matlosana, Perinatal Health Research Consortium, Klerksdorp, University of the Witwatersrand**

Nandipha Mmile
Modiehi Mosala
Oteng Letlape

Abdul Hamid Kaka
Zakkiyya Jeeva
Abraham Pattamukkil
Mbusiseni Ngema
Dora Tshabalala
Puleng Machubela
Tshegofatso Sereo
Angelinah Montwedi
Kgaugelo Kgasago
Thabang Mongale
Katlego Mothlaoleng
Molebogeng Plaaitjie
Ebrahim Variava

**Shandukani, Wits Health Research Institute, Johannesburg, University of the Witwatersrand**
Israel Mzizi
Stella Mthombeni
Elizea Horne
Mrinmayee Dhar
Mapule Moloi
Molebogeng Masemola
Saajida Akhalwaya
Gugu Hlongwane

**Tuberculosis & HIV Investigative Network, Durban, KwaZulu Natal**
Ronelle Moodliar
Seshni Moorgas
Siyabonga Myeza
Thabisile Gumede
Lungile Phakathi
Khaya Kunene
Muziwoduma Zuma
Mzi Shosha
Lorraine Mkhize
Neo Mojapela

Mthokozisi Khyzwayo
Suraksha Chirunt
Anita Jacobs

**Isango Lethemba TB Research Unit, Gqeberha Wits Health Consortium**
Judy Sparg
Abelang Mosweou
Ntombizodwa Komeni
Jaylin Faro
Leilani Novem
Xabisa Makeleni
Bernadette Rance
Tamsin Economou
Natalene Gallant.
Zaheer Gaida
Roche Hall
Maxine Leo
Tasneem Noorshib
Kelvin Vaaltyn
Mary Godongwana
Sonya Goliath
Lubabalo Dingana
Zoleka Nini
Ayanda Daniso
Buntu Myemane
Hannelise Feyt
Zuko Mntonintshi
Shaheed Arendse

**Medical Research Council Clinical Trials Unit at University College London, UK**
Christos Maniatis
Cindy Goldstein
Margaret Thomason
Martha Campos
Karen Scott
Ellen Owen-Powell

Keith Fairbrother
Janet Cairn
Kristen Lebeau
Hannah Vaughan
Rachel Bennett
Azizat Oyegoke
Lina Bergstrom
Joshua Gaza
Anna Turkova

**BENEFIT Kids Scientific Advisory Committee**
Norbert Ndjeka, South Africa
Carol Mitnick, USA
Dick Menzies, Canada
Kelly Dooley, USA
Ben Marais, Australia
Paul Domanico, USA

**BENEFIT Kids Community Advisory Board**
Jeffry Acaba, APCASO, Thailand
Blessina Kumar: Global Coalition of TB Advocates, India
Arne von Delft, TB Proof, South Africa

**Contributor Statements**

Study design was led by ACH, JAS, analysis led by TD, data collection led by SP, NM, LF, SS, FC. ACH and TD vouches for data and analysis. ACH, JAS, TD wrote the paper, and ACH, with support of all authors, decided to submit for publication. TD also provided ongoing scientific input and statistical oversight, and oversaw the MRC CTU team. JB and CL carried out the statistical analyses, and JB assisted with preparation of the manuscript. DG provided ongoing scientific and analytical input. CMG managed trial implementation. SEP led implementation at site and also supported other trial sites, and contributed to writing. EB coordinated local trial implementation and provided overall sites support. NM, LF, SS and FC oversaw local trial implementation as site principal investigators. LF oversaw safety of participants on trial. HSS supported trial design, analysis and drafting of the

manuscript. SN supported clinical trial implementation. AMD led trial microbiological oversight and analysis. BT supported statistical analysis. LF was the independent trial physician. All authors reviewed the submitted and final version of the manuscript and approved of it.

There were no agreements concerning data confidentiality between the sponsor (Stellenbosch University) and the authors/institution

## S2 SUPPLEMENTARY METHODS

### S2.1 Trial oversight

Stellenbosch University (trial sponsor), the Medical Research Council Clinical Trials Unit at University College London, the trial steering committee, and the independent data monitoring committee provided trial oversight. The trial protocol, available at NEJM.org, was approved by the South African Health Products Regulatory Authority (SAHPRA) and all relevant local ethics committees. Caregivers provided written informed consent, and children provided assent, as appropriate. The authors vouch for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial to the protocol.

### S2.2 Inclusion/Exclusion criteria

Participants were considered eligible for enrolment in this trial if they fulfilled all the inclusion criteria, and none of the exclusion criteria, as defined below.

Adult index patients inclusion criteria

- Age ≥18 years
- Bacteriologically confirmed pulmonary tuberculosis (TB) diagnosed from a sputum sample, having started treatment for multi-drug resistant TB (MDR-TB) within the preceding 6 months
- Genotypic or phenotypic resistance to isoniazid (INH) and rifampin (RIF). If only tested by Xpert MTB/RIF or MTB/RIF Ultra or other approved molecular tests e.g. line probe assay, the index case can be included if RIF-resistant, without other confirmed DST; i.e. confirmation of both RIF and INH resistance is not required.
- Written informed consent from the index case (or a close relative if the index case is deceased prior to the completion of screening)
- At least 1 household contact below the age of 18 years reported to have been residing in the same household as the adult index case in the previous 6 months

Adult index patient exclusion criteria

- MDR-TB with confirmation of genotypic or phenotypic resistance to fluoroquinolones*

  * From version 3.0 protocol, imlemented 30 Sep 2021

Child/adolescent participant inclusion criteria

- Child or adolescent <18 years who is a household contact of an adult MDR-TB index case (as stated under adult MDR-TB eligibility criteria)*.
- Primary residence in the household of the adult MDR-TB index patient or any contact resulting in significant exposure of the child
- Consent from the parent or legal guardian for the child/adolescent for HIV testing
- Consent obtained from the parent or legal guardian for the child/adolescent to be enrolled
- Assent obtained from any child/adolescent 7 years or older
- If ³5 years and < 18 years of age, the child/adolescent must have a positive interferon-gamma release assays (IGRA; Quantiferon-Gold Plus, Qiagen) test before enrorment unless HIV positive**

  * Up to Version 2.0 protocol, only children aged<5 years were eligible

  ** Children <5 years of age are eligible regardless of IGRA status. All HIV-positive children <18 years of age are eligible regardless of IGRA test status.

Child/adolescent participant exclusion criteria

- TB disease at enrolment
- Currently on INH or a fluoroquinoline (e.g. levofloxacin, moxifloxacin, ofloxacin or ciprofloxacin) for ≥14 days. TB preventive therapy may be interrupted provided that the child/adolescent participant is recruited into the study as soon as possible.
- Treated for TB in the previous 12 months
- Known concurrent exposure to an INH-susceptible (including RIF mono-resistant) index case
- Weight below 3.0 kg
- Positive pregnancy test at enrolment. *Note: in females who become pregnant on study, continuation on study treatment is allowed.*
- 6 months or less post-partum

**S2.3 Background information on the broader population affected by MDR-TB globally**

| | |
|---|---|
| - Disease, problem, or condition under investigation | Multidrug-resistant (MDR) tuberculosis (TB). |
| - Special considerations related to | |
| Sex and gender | No difference in risk of progression to MDR-TB disease following exposure to *M. tuberculosis* by sex or gender. |
| o Age | Risk of progression to TB disease affects young children (<5 years) more than adults (ratio:3:1) following exposure to *M. tuberculosis.* |
| o Race or ethnic group | MDR-TB disproportionately affects black African and mixed-race populations in South Africa. |
| o Geography | MDR-TB is a worldwide problem Globally, MDR-TB caused an estimated 160,000 deaths in 2022. The eight countries ranked in descending order of their total number of MDR/RR-TB incident cases in 2022 were India, the Philippines, the Russian Federation, Indonesia, China, Pakistan, Myanmar and Nigeria. |
| o Other considerations | TB, including MDR-TB, is a disease of poverty globally. This is also the case in South Africa, where the trial was conducted. |
| | The participants in the present trial (~90% were <5 years of age) demonstrated the expected ratio of males to females. Biologic sex was reported by the participants' caregivers as sex assigned at birth. Options were female, male, and not known. Gender was not reported. |
| o Overall representativeness of this trial | The study specifically focused on children below 5 years of age, given their high risk of progression to TB disease following exposure to *M.tb*. Approximately 10% of trial participants were children and adolescents aged 5-17 years, to increase overall representativeness of participants across the pediatric/adolescent population. The overall age distribution of children exposed to MDR-TB in the household is likely to differ between South Africa and some other countries given the broad population pyramid in the study setting (i.e. young age in the study setting). The proportion of Black patients who underwent randomization overall was 81% . All participants were enrolled in Africa. |

**S2.4 Trial procedures**

A chest x-ray (anteroposterior (AP) and lateral images) was completed at baseline and if any evidence of TB on the chest x-ray, or if the child had any symptoms or signs suggestive of TB, children underwent sampling for microbiological confirmation. Interferon-Gamma Release Assay (IGRA: Quantiferon-Gold Plus, Qiagen) and HIV testing (DNA PCR in children < 18 months of age and ELISA in children 18 month and older) was done in all children at baseline, with the result required prior to enrolment of children 5-17 years. A pregnancy test was performed at baseline for any female participants who had begun menstruation. A full blood count, alanine transaminase and bilirubin were also collected at baseline in all children.

Children were followed at 4, 8, 12, 16, 24, 48 and 72 weeks and at additional unscheduled visits as clinically indicated. At each visit, children were assessed clinically for symptoms and signs of TB and for evidence of any adverse events due to the medication. Adherence to medications was quantified with pill returns and counts, treatment diaries and questionnaires. Weight and height were measured at each visit, all concomitant medications documented, and any outpatient or inpatient healthcare visits were recorded. A chest x-ray (AP and lateral) was done at baseline, 12 and 48 weeks, and at any time of clinical concern. Two respiratory samples were collected for microbiological confirmation if the child had any symptoms or signs suggestive of TB, or if they had an abnormal chest x-ray.

Sampling for suspected pulmonary TB consisted of induced sputum or gastric aspiration in children <5 years, with children 5 years and older encouraged to produce an expectorated sputum sample. Samples for suspected extrapulmonary TB were guided by site of disease. All samples underwent concentrated fluorescence smear microscopy, Xpert® MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA), liquid culture (BACTEC™ MGIT™ 960 TB System (Becton Dickinson Microbiology Systems, Sparks, MD) and solid culture on Löwenstein-Jensen. Drug susceptibility testing (DST) for first-and second-line drugs was performed on all positive TB cultures using genotypic (GenoType® MTBDR*plus*; Hain Lifescience, Nehren, Germany) and phenotypic (MGIT DST) methods. All trial laboratory procedures were performed in the same central laboratory (Bio Analytical Research Corporation South Africa or BARC SA). Some children had respiratory samples collected and tested in the nationally accredited TB laboratories (National Health Laboratory Service, NHLS) if investigated in routine care. These results were documented.

## S2.5 Primary and secondary end points

### Primary endpoint

The primary efficacy endpoint was incident TB disease (bacteriologically confirmed or clinically diagnosed, i.e. “confirmed or unconfirmed TB”) or TB death by the 48-weeks study visit following randomization, with a 6-week window allowed i.e. though week 54.

### Secondary endpoint

The prespecified main secondary endpoint for safety was adverse events (AEs) grade ≥3 assessed by the site investigator as at least possibly associated with study treatment.

Other secondary endpoints included:

- TB disease by 72 weeks
- All-cause mortality
- Any AEs grade ≥3 from starting study treatment up to 30 days after last study drug dose
- Serious adverse events (SAEs) up to 30 days after last study drug dose
- Discontinuation of study treatment due to AE(s)
- Selected pre-defined AEs, from starting treatment up to 30 days after last study drug dose unless stated otherwise (arthritis/arthralgia/tendinopathy during overall study follow-up, peripheral neuropathy, central nervous system (CNS) effects, severe rash/cutaneous reaction and drug related fever)
- Treatment adherence

Incident TB and cause of death were adjudicated by an independent Endpoint Review Committee (ERC) unaware of the randomized treatment allocation, based on all available clinical, radiological, microbiological, and molecular data using standard international consensus case definitions. TB was classified as confirmed or unconfirmed.

**Table S2.1 Schedule of evaluations**

| | Screening | Week 0 | Week 4 | 8 | 12 | 16 | 24 | 36 | 48 | 72 | Unscheduled/Early exit/ incident TB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Symptom screening | • | • | • | • | • | • | • | • | • | • | • |
| Medical history | • | • | • | • | • | • | • | • | • | • | • |
| Pregnancy test (if female and started menstruating) | • | | | | | | | | | | |
| Clinical examination | • | • | • | • | • | • | • | • | • | • | • |
| Chest radiograph | • | # | # | # | • | # | # | # | • | # | # |
| Intercurrent TB exposure[a] | | | • | • | • | • | • | • | • | • | • |
| Bacteriological investigation, DST, genotyping (child participants) | # | # | # | # | # | # | # | # | # | # | # |
| EQ-5D-Y | | • | | | • | | • | | | • | |
| Historical TB microbiology data (adult index patient) | • | | | | | | | | | | |
| Anthropometrics (height/length & weight, mid-upper arm circumference) | • | • | • | • | • | • | • | • | • | • | # |
| QuantiFERON Gold Plus | • | | | | | | | | | | |
| HIV status ((all) HIV negative participants to be tested) | • | | | | | | | | • | | |
| WHO staging (HIV-positive children/adolescents only) | | • | | | | | | | • | | |
| CD4 count (HIV-positive children/adolescents only) | • | | | | | | • | | • | • | |
| HIV viral load (HIV-positive children/adolescents only) | • | | | | | | • | | • | • | # |
| Solicited adverse events | | | • | • | • | • | • | • | • | • | • |
| Adherence | | | • | • | • | • | • | | | | # |
| Acceptability and palatability | | • | • | • | | | • | | | | |
| Outcome (incident TB, mortality) | | | • | • | • | • | • | • | • | • | • |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hematology (FBC, differential) | | • | | • | | | | | | | # |
| Liver function tests (ALT, BR) | | • | | • | | | | | | | # |
| Biomarkers | | • | | • | | | | | | | • |

## S3 ADDITIONAL DETAILS FOR STATISTICAL ANALYSIS

### S3.1 Sample size calculations

In the original sample size calculations, we assumed a 50% reduction in TB disease incidence by 48 weeks (i.e. 50% efficacy of levofloxacin), from 7% in the control group to 3.5% in the levofloxacin group. We originally calculated that a planned sample of 1556 participants would provide 80% power for the study at a 5% two-sided significance level, assuming the following: an average of two participants enrolled per household, the household intra-class correlation was 0.10, and 10% loss to follow-up.

In May 2019, following discussion with the Trial Steering Committee and the Independent data Monitoring Committee (IDMC), the target sample size was reduced to 1009, based on an assumed efficacy of 60% for levofloxacin (with other assumptions remaining unchanged). This assumption was considered more in line with results from the recently published meta-analysis by Marks *et al*., showing a 90% reduction in TB incidence associated with MDR-TB preventive treatment (TPT).[1]

The V-QUIN MDR trial (ACTRN12616000215426) had assumed a 70% efficacy for levofloxacin, while the PHOENix trial (NCT03568383) assumes a 50% efficacy for delamanid vs. isoniazid efficacy. At the time, the observed overall 48-week TB incidence (with 95% confidence interval) in TB-CHAMP in the two treatment groups combined was consistent with the assumptions of a 7% event rate in the control group and 60% levofloxacin efficacy. The unblinded trial statistician was not involved in the discussion regarding the change in sample size calculations.

## S3.2 Primary estimand

**Table S3.1. Definition of the estimand for the primary efficacy analysis**

| Attribute | Definition |
|---|---|
| Treatments | The comparison is between 24 weeks daily dosing with levofloxacin vs. no TB prevention treatment |
| Population | Children and adolescents aged <18 years who are household contacts of adult MDR-TB index cases, and fulfilling the inclusion/exclusion criteria for TB-CHAMP as defined in Section 1.5. |
| Endpoint | Incident TB disease (confirmed or unconfirmed TB) including TB-related death, by 48 weeks |
| Intercurrent events | The main intercurrent events and how they will be handled in the estimand are as follows:<br>1. Early treatment discontinuation for any reason - treatment policy strategy<br>2. Missed doses of study treatment - Treatment policy strategy<br>3. Non-TB related death - Hypothetical strategy |
| Population-level summary measure | Marginal hazard ratio with 95% confidence interval |

**S3.3 Analysis populations**

**Table S3.2: Definition of analysis populations**

| **Analysis Population** | **Definition** |
|---|---|
| Intention to treat (ITT) | All randomized participants |
| Modified intention to treat (mITT) | All randomized participants excluding children with TB disease at baseline who were enrolled but in whom TB was subsequently detected |
| Per protocol (PP) | All randomized participants excluding the following<br>- late screening failures (defined in Section 3.3)<br>- participants who received the incorrect treatment to their original allocation (see below)<br>- participants **with a TB endpoint** who took <80% of doses prescribed up to the time of TB diagnosis; for example, a TB case diagnosed at week 16 who took <90 of the 112 doses prescribed to then<br>- participants **without a TB endpoint** who discontinued study follow-up before completing treatment and took <80% of doses prescribed up to the date of last follow-up (see Section 3.8); for example, a participant withdrawing from study follow-up at week 16 who took <90 of the 112 doses prescribed to then<br>- participants **without a TB endpoint** who were followed up to at least the end of 24-28 weeks treatment period (allowing for 4 weeks treatment extension) and took <80% of the overall 168 allocated doses (see Section 3.9)<br>- Participants with missing information on number of doses taken<br>This definition is a modification of those used in previous studies (3-5) and took into account (i) a participant could be taking <80% of doses prescribed up to the time of TB diagnosis and still be on treatment when they were diagnosed with TB (ii) the exact timing of when a participant was first failing to take ≥80% of prescribed doses was difficult to ascertain |

Further details are provided in the full Statistical Analysis Plan available at NEJM.org.

**S3.4 Statistical analysis**

Kaplan-Meier plots of the cumulative incidence of TB disease were generated, with the 95% confidence intervals estimated allowing for household clustering.

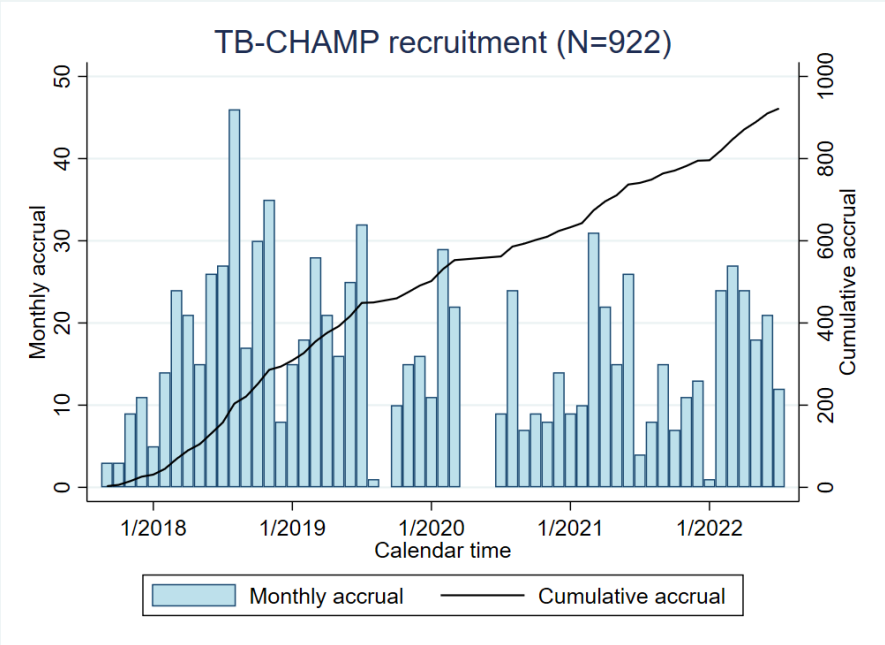
Cox regression was used to estimate the marginal hazard ratio comparing levofloxacin vs placebo, assuming non-informative censoring. Intra-household correlation was accounted for using cluster robust variance. The model was adjusted for site (randomisation stratification factor) and age group (<5 vs. 5-17 years). Owing to the small number of TB endpoints, covariate adjustment was done using Inverse Probability of Treatment Weighting (IPTW), which involves fitting two models.[2] We first used logistic regression to predict the probability of being randomised to the treatment group the participant was in fact randomised to, given site and age group. We then fitted a Cox model comparing the treatment groups, weighted according to the inverse probability of treatment estimated by the first model. Effectively, the participants are weighted such that the two trial groups are balanced in terms of the weight, by site and age group.

We tested the proportional hazards assumption using the Grambsch-Therneau test.

The number-needed-to treat (NNT) to prevent 1 TB case by 54 weeks was derived from the reciprocal of the estimated absolute difference in TB incidence between treatment groups. We fitted flexible parametric survival models to estimate the incidence of TB by 54 weeks.[3,4] If the treatment effect was not statistically significant at 5% level, the 95% confidence interval (CI) for the absolute risk reduction would include zero, and the corresponding CI for the NNT would be presented as recommended by Altman (1998).[5]

## S4 RECRUITMENT

**Figure S4.1 Overall monthly and cumulative accrual over time***




* Recruitment was paused twice: August-September 2019 while pending funding extension decisions (except for 1 participant who had already passed screening in July 2019); and 26 March-28 July 2020 due to COVID-19 interruptions and national restriction on non-COVID-19 clinical research in South Africa

**Table S4.1 Total number of child participants randomized***

| | Date first participant randomized | Date last participant randomized | Levofloxacin | Placebo | Total |
|---|---|---|---|---|---|
| **Overall** | 28sep2017 | 29jul2022 | 453 (100%) | 469 (100%) | 922 (100%) |
| **By site** | | | | | |
| DTTC | 28 Sep 2017 | 29 Jul 2022 | 222 (49%) | 230 (49%) | 452 (49%) |
| Shandukani | 21 Nov 2017 | 29 Jul 2022 | 92 (20%) | 80 (17%) | 172 (19%) |
| Matlosana | 03 Nov 2017 | 17 Aug 2021 | 117 (26%) | 142 (30%) | 259 (28%) |
| ILTBRU | 02 Feb 2022 | 28 Jun 2022 | 3 (1%) | 4 (1%) | 7 (1%) |
| THINK | 15 Dec 2021 | 25 Jul 2022 | 19 (4%) | 13 (3%) | 32 (3%) |

* 922/1009 (91%) of target sample size reached.

DTTC: Desmond Tutu TB Centre; Shandukani: Wits Research Health Institute, Matlosana: Perinatal HIV Research Unit, THINK: Tuberculosis & HIV Investigative Network, ILTBRU: Isango Lethemba TB Research Unit

**Table S4.2 Number of child participants per household overall**

| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| **N households** | 248 | 249 | 497 |
| **N children per household** | | | |
| 1 | 136 (55%) | 134 (54%) | 270 (54%) |
| 2 | 69 (28%) | 60 (24%) | 129 (26%) |
| 3 or 4 | 28 (11%) | 43 (17%) | 71 (14%) |
| >=5 | 15 (6%) | 12 (5%) | 27 (5%) |
| Mean* | 1.8 | 1.9 | 1.9 |
| Range | 1, 9 | 1, 17 | 1, 17 |

* Study power calculations assumed an average of 2 children enrolled per household.

**Table S4.3 Randomized participants re-enrolled into the trial following completion of study follow-up**

| **Initial enrolment** | | | **Re-enrolment** | | |
|---|---|---|---|---|---|
| Study number | Date randomized | Treatment allocation | Study number | Date randomized | Treatment allocation |
| D007410X | 14jun2018 | Placebo | D029103V | 24jun2021 | Levofloxacin |

* Guidance to allow re-enrolment of children who have already participated in the trial and completed follow-up was issued on 9 Oct 2020 and formally incorporated in version 3.0 protocol.

**Table S4.4. Late screening failures**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| **N randomized** | 453 | 469 | 922 |
| **Late screening failures** | 17 (3.8%) | 12 (2.6%) | 29 (3.1%) |
| **By site** | | | |
| DTTC | 4 | 9 | 13 |
| Shandukani | 1 | 1 | 2 |
| Matlosana | 1 | 0 | 1 |
| THINK | 11 | 2 | 13 |
| **Reason** | | | |
| TB at baseline | 2 | 4 | 6 |
| INH-susceptible index patient | 14 | 4 | 18 |
| FQN-resistant index patient | 1 | 3 | 4 |
| Other * | 0 | 1 | 1 |

* Participant did not have adequate exposure to index case.

INH; isoniazid; FQN: fluoroquinolone

## S5 BASELINE CHARACTERISTICS

**Table S5.1 Baseline characteristics of adult index patients contributing randomized child participants**

| | | Levofloxacin | Placebo | Total |
|---|---|---|---|---|
| N index cases | N | 248 (100%) | 249 (100%) | 497 (100%) |
| Sex | Male | 105 (42%) | 107 (43%) | 212 (43%) |
| Age at enrolment (years) | median | 35.8 | 36.3 | 36.0 |
| | IQR | 28.3, 46.3 | 28.9, 44.4 | 28.6, 45.5 |
| | range | 18.3, 76.6 | 18.4, 80.3 | 18.3, 80.3 |
| | <30 | 76 (31%) | 71 (29%) | 147 (30%) |
| | 30 to <50 | 129 (52%) | 144 (58%) | 273 (55%) |
| | >=50 | 43 (17%) | 34 (14%) | 77 (15%) |
| Race | Black South African | 193 (78%) | 199 (80%) | 392 (79%) |
| | Mixed race | 53 (21%) | 47 (19%) | 100 (20%) |
| | Mixed race | 0 (0%) | 1 (0%) | 1 (0%) |
| | Other | 2 (1%) | 2 (1%) | 4 (1%) |
| HIV status | Positive | 162 (66%) | 158 (63%) | 320 (65%) |
| | Negative | 85 (34%) | 91 (37%) | 176 (35%) |
| | N missing | 1 | 0 | 1 |
| On ART if HIV-positive | No | 31 (19%) | 27 (17%) | 58 (18%) |
| Most recent CD4 count | N | 142 | 136 | 278 |
| | median | 163 | 190 | 174 |
| | IQR | 50, 394 | 79, 386 | 62, 387 |
| | N missing | 20 | 22 | 42 |
| Most recent viral load if on ART | N | 88 | 87 | 175 |
| | median log10 copies/ml | 3.1 | 2.9 | 3.0 |
| | IQR | 1.7, 4.9 | 1.9, 4.8 | 1.7, 4.8 |
| | VL<400 | 34 (39%) | 35 (40%) | 69 (39%) |
| | VL>400 | 54 (61%) | 52 (60%) | 106 (61%) |
| | N missing | 43 | 44 | 87 |
| Previously received TB treatment | No | 112 (45%) | 107 (43%) | 219 (44%) |

| | | | | |
|---|---|---|---|---|
| Treatment received if previously treated | DR | 18 (16%) | 11 (10%) | 29 (13%) |
| | DS | 98 (84%) | 104 (90%) | 202 (87%) |
| | N missing | 20 | 27 | 47 |
| Started TB treatment for current episode | No | 11 (4%) | 7 (3%) | 18 (4%) |
| Weeks from TB treatment started to first HHCC enrolled* | Median | 4.9 | 4.0 | 4.3 |
| | IQR | 2.3, 10.3 | 2.0, 8.0 | 2.1, 9.3 |
| | range | 0.3 , 25.1 | -0.1 , 25.9 | -0.1 , 25.9 |
| | <=12 weeks | 190 (80%) | 208 (86%) | 398 (83%) |
| | >12 weeks | 47 (20%) | 34 (14%) | 81 (17%) |

* Includes 1 child enrolled 1 day before index patient started MDR-TB treatment.

**Table S5.2. Tuberculosis exposure history in randomized child participants at enrolment**

| | | Levofloxacin | Placebo | Total |
|---|---|---|---|---|
| N children randomized | N | 453 (100%) | 469 (100%) | 922 (100%) |
| Whether the MDR-TB index is child's primary caregiver | Primary carer | 101 (22%) | 100 (21%) | 201 (22%) |
| | Not primary carer but regularly cares for child | 191 (42%) | 221 (47%) | 412 (45%) |
| | Neither | 160 (35%) | 147 (31%) | 307 (33%) |
| | N missing | 1 | 1 | 2 |
| Relationship of index to child participant | Mother | 78 (17%) | 81 (17%) | 159 (17%) |
| | Father | 49 (11%) | 43 (9%) | 92 (10%) |
| | Other family member | 278 (61%) | 292 (62%) | 570 (62%) |
| | Non-family | 48 (11%) | 53 (11%) | 101 (11%) |
| Daily contact between the child and index on most days in past 6 months | No | 20 (4%) | 15 (3%) | 35 (4%) |
| | Yes | 433 (96%) | 454 (97%) | 887 (96%) |
| Slept in the same room as index on most nights over past 6 months | No | 263 (58%) | 308 (66%) | 571 (62%) |
| | Yes | 190 (42%) | 161 (34%) | 351 (38%) |
| Average number hours per day child spent with index past 6 months | 0-4 hours | 72 (16%) | 77 (16%) | 149 (16%) |

| | | | | |
|---|---|---|---|---|
| | 5-8 hours | 117 (26%) | 122 (26%) | 239 (26%) |
| | 9-12 hours | 79 (17%) | 85 (18%) | 164 (18%) |
| | More than 12 hours | 185 (41%) | 185 (39%) | 370 (40%) |
| Exposed to any additional TB other than the index in the past 6 months | No | 442 (98%) | 456 (97%) | 898 (98%) |
| | Yes | 8 (2%) | 12 (3%) | 20 (2%) |
| | N missing | 3 | 1 | 4 |

**Table S5.3 Baseline IGRA status of randomized child participants, overall and by age**

| | | Levofloxacin | Placebo | Total |
|---|---|---|---|---|
| **Overall** | | | | |
| N participants randomized | | 453 | 469 | 922 |
| IGRA test result | Negative | 297 (67%) | 335 (74%) | 632 (70%) |
| | Positive | 134 (30%) | 108 (24%) | 242 (27%) |
| | Indeterminate | 12 (3%) | 12 (3%) | 24 (3%) |
| | N missing + | 10 | 14 | 24 |
| **Age <5 years*** | | | | |
| N participants randomized | | 405 | 434 | 839 |
| IGRA test result | Negative | 294 (74%) | 334 (80%) | 628 (77%) |
| | Positive | 89 (23%) | 74 (18%) | 163 (20%) |
| | Indeterminate | 12 (3%) | 12 (3%) | 24 (3%) |
| | N missing + | 10 | 14 | 24 |
| **Age ³ 5 years^** | | | | |
| N participants randomized | N | 48 | 35 | 83 |
| IGRA test result | Negative | 3 (6%) | 1 (3%) | 4 (5%) |
| | Positive | 45 (94%) | 34 (97%) | 79 (95%) |

IGRA: Interferon-Gamma Release Assay (QuantiFERON Gold Plus; Qiagen)

* For a small number of children aged <5 years without a test result at screening, test results up to week 4 post-randomization was used.

+ Missing data most often due to difficult blood draw or clotted at baseline.

^ Children aged 5-17 years were required to be IGRA-positive or living with HIV to be eligible for study enrolment.

**Table S5.4 Baseline IGRA status of randomized child participants by site and age**

| | | DTTC | Shandukani | Matlosana | ILTBRU | THINK | Total |
|---|---|---|---|---|---|---|---|
| **Overall** | | | | | | | |
| N participants randomized | | 452 | 172 | 259 | 7 | 32 | 922 |
| IGRA test result | Negative | 282 (64%) | 135 (80%) | 202 (81%) | 1 (14%) | 12 (38%) | 632 (70%) |
| | Positive | 152 (35%) | 33 (20%) | 31 (12%) | 6 (86%) | 20 (63%) | 242 (27%) |
| | Indeterminate | 6 (1%) | 1 (1%) | 17 (7%) | 0 (0%) | 0 (0%) | 24 (3%) |
| | N missing + | 12 | 3 | 9 | 0 | 0 | 24 |
| **Age <5 years*** | | | | | | | |
| N participants randomized | | 400 | 167 | 259 | 0 | 13 | 839 |
| IGRA test result | Negative | 281 (72%) | 134 (82%) | 202 (81%) | 0 | 11 (85%) | 628 (77%) |
| | Positive | 101 (26%) | 29 (18%) | 31 (12%) | 0 | 2 (15%) | 163 (20%) |
| | Indeterminate | 6 (2%) | 1 (1%) | 17 (7%) | 0 | 0 (0%) | 24 (3%) |
| | N missing + | 12 | 3 | 9 | 0 | 0 | 24 |
| **Age ³ 5 years^** | | | | | | | |
| N participants randomized | | 52 | 5 | 0 | 7 | 19 | 83 |
| IGRA test result | Negative | 1 (2%) | 1 (20%) | 0 | 1 (14%) | 1 (5%) | 4 (5%) |
| | Positive | 51 (98%) | 4 (80%) | 0 | 6 (86%) | 18 (95%) | 79 (95%) |

* For a small number of children aged<5 years without a test result at screening, test result up to week 4 post-randomization was used.

+ Missing data often due to difficult blood draw or clotted at baseline.

^ Children aged 5-17 years needed to be IGRA-positive or living with HIV to be eligible for study enrolment.

THINK: Tuberculosis and HIV Investigative Network

## S6 FOLLOW-UP

**Table S6.1. Last study visit attended by child participants**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| **N randomized participants** | 453 | 469 | 922 |
| **Seen after randomization** | 444 (98%) | 462 (99%) | 906 (98%) |
| **Last study visit attended*** | | | |
| 0 (Randomization visit only) | 9 (2%) | 7 (1%) | 16 (2%) |
| Before Week 4 | 0 (0%) | 2 (0%) | 2 (0%) |
| Week 4 | 9 (2%) | 7 (1%) | 16 (2%) |
| Week 8 | 4 (1%) | 5 (1%) | 9 (1%) |
| Week 12 | 7 (2%) | 6 (1%) | 13 (1%) |
| Week 16 | 2 (0%) | 8 (2%) | 10 (1%) |
| Week 24 | 27 (6%) | 16 (3%) | 43 (5%) |
| Week 36 | 29 (6%) | 35 (7%) | 64 (7%) |
| Week 48 | 40 (9%) | 38 (8%) | 78 (8%) |
| Week 72 or after | 326 (72%) | 345 (74%) | 671 (73%) |
| **Number of weeks from randomization to last study visit** | | | |
| Median | 72 | 72 | 72 |
| IQR | 48, 73 | 49, 73 | 48, 73 |
| Range+ | 0 , 125 | 0 , 113 | 0 , 125 |
| **Total person years of follow-up** | 551 | 577 | 1128 |

* 86 (46 Levofloxacin, 40 Placebo) children attended their last scheduled study follow-up visit, but would not have hypothetically reached the 48 weeks window by the trial censoring date (20 Jan 2023) due to their date of randomization.

+ Study follow-up was to week 96 under version 1.0, and participants could attend an unscheduled visit thereafter.

**Table S6.2 Number of children attending scheduled visits**

| Visit | Levofloxacin | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | Visits / Expected visits* | % of expected | Visits / Expected visits* | % of expected | Visits / Expected visits* | % of expected |
| Week 4 | 432/453 | 95% | 448/469 | 96% | 880/922 | 95% |
| Week 8 | 416/453 | 92% | 439/469 | 94% | 855/922 | 93% |
| Week 12 | 406/453 | 90% | 427/469 | 91% | 833/922 | 90% |
| Week 16 | 405/453 | 89% | 431/469 | 92% | 836/922 | 91% |
| Week 24 | 414/453 | 91% | 424/469 | 90% | 838/922 | 91% |
| Week 36 | 368/432 | 85% | 399/457 | 87% | 767/889 | 86% |
| Week 48 | 356/401 | 89% | 374/423 | 88% | 730/824 | 89% |
| Week 72 or after | 326/368 | 89% | 345/396 | 87% | 671/764 | 88% |

*Excludes children who would not have reached the relevant timepoint by the trial censoring date, based on their date of randomization.

**Table S6.3. Retention in study follow-up**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| **N randomized participants** | 453 | 469 | 922 |
| **Left study before week 72*** | 46 (10%) | 57 (12%) | 103 (11%) |
| **Reason for drop-out** | | | |
| Death | 1 (2%) | 1 (2%) | 2 (2%) |
| Withdrew consent | 24 (52%) | 22 (39%) | 46 (45%) |
| Withdrew assent | 0 (0%) | 1 (2%) | 1 (1%) |
| Moved away | 9 (20%) | 16 (28%) | 25 (24%) |
| Lost to follow-up | 11 (24%) | 14 (25%) | 25 (24%) |
| Other + | 1 (2%) | 3 (5%) | 4 (4%) |

* Participants randomized after 17 September 2021 would not have hypothetically reached the week 72 timepoint by trial censoring date. Therefore, those randomized after this date who dropped out of study follow-up before their last scheduled visit are included here, but not those who attended their last scheduled visit. Please refer to Appendix A.1 for summary of follow-up dropout according to whether participant was randomized up to or after 17 Sep 2021.

+ Levofloxacin group: DS-TB contact identified in the household at Week 4, site team withdrew participant from study follow-up for Isoniazid prophylaxis at routine care clinic (1)

+ Placebo group: Late screening failure (LSF) before study guidance clarified follow-up for LSFs (2) and COVID restrictions (1)

**Table S6.4 Baseline characteristics of participants who reached the 48-week visit versus those who did not**

| | | Reached at least 48 weeks of follow-up | Did not reach 48 weeks of follow-up | Total |
|---|---|---|---|---|
| Sex | Male | 368 (49%) | 86 (50%) | 454 (49%) |
| | Female | 381 (51%) | 87 (50%) | 468 (51%) |
| Age (years) | median | 2.8 | 3.4 | 2.8 |
| | IQR | 1.3,4.0 | 1.4,5.4 | 1.3,4.2 |
| | <1yrs | 136 (18%) | 32 (18%) | 168 (18%) |
| | 1 to 2.9 | 272 (36%) | 43 (25%) | 315 (34%) |
| | 3 to 4.9 | 305 (41%) | 51 (29%) | 356 (39%) |
| | 5 to 9.9 | 15 (2%) | 20 (12%) | 35 (4%) |
| | 10 to 14.9 | 16 (2%) | 17 (10%) | 33 (4%) |
| | 15 to 17.9 | 5 (1%) | 10 (6%) | 15 (2%) |
| Race | Black South African | 608 (81%) | 135 (78%) | 743 (81%) |
| | mixed | 125 (17%) | 34 (20%) | 159 (17%) |
| | Mixed race | 14 (2%) | 2 (1%) | 16 (2%) |
| | Other | 2 (0%) | 2 (1%) | 4 (0%) |
| IGRA status: Age <5 years | Negative | 543 (78%) | 85 (71%) | 628 (77%) |
| | Positive | 129 (19%) | 34 (28%) | 163 (20%) |
| | Indeterminate | 23 (3%) | 1 (1%) | 24 (3%) |
| | N missing | 18 | 6 | 24 |
| IGRA status: Age ≥5 years | Negative | 3 (8%) | 1 (2%) | 4 (5%) |
| | Positive | 33 (92%) | 46 (98%) | 79 (95%) |
| HIV status | Positive | 14 (2%) | 5 (3%) | 19 (2%) |
| | HIV-exposed uninfected | 257 (34%) | 56 (33%) | 313 (34%) |
| | HIV-unexposed | 476 (64%) | 110 (64%) | 586 (64%) |
| | N missing | 2 | 2 | 4 |
| BCG vaccination | No | 45 (6%) | 8 (5%) | 53 (6%) |
| | Yes | 701 (94%) | 164 (95%) | 865 (94%) |
| | N missing | 3 | 1 | 4 |

| | | | | |
|---|---|---|---|---|
| Previously received TB treatment* | No | 735 (98%) | 169 (98%) | 904 (98%) |
| | Yes | 14 (2%) | 4 (2%) | 18 (2%) |
| Currently on TB preventative therapy | No | 734 (98%) | 173 (100%) | 907 (98%) |
| | Yes | 15 (2%) | 0 (0%) | 15 (2%) |
| Weight-for-age Z score^ | median | -0.5 | -0.2 | -0.4 |
| | IQR | -1.2,0.3 | -1.0,0.4 | -1.2,0.3 |
| | <-3 | 13 (2%) | 5 (3%) | 18 (2%) |
| | -3 to <-2 | 63 (8%) | 15 (9%) | 78 (8%) |
| | -2 to <-1 | 153 (20%) | 27 (16%) | 180 (20%) |
| | -1 to <0 | 269 (36%) | 53 (31%) | 322 (35%) |
| | 0 to <1 | 171 (23%) | 46 (27%) | 217 (24%) |
| | 1 to <2 | 65 (9%) | 19 (11%) | 84 (9%) |
| | 2 to <3 | 12 (2%) | 7 (4%) | 19 (2%) |
| | >=3 | 3 (0%) | 1 (0%) | 4 (0%) |
| Height-for-age Z score^ | median | -1.0 | -0.7 | -0.9 |
| | IQR | -1.8,-0.2 | -1.6,0.0 | -1.7,-0.2 |
| | <-3 | 47 (6%) | 10 (6%) | 57 (6%) |
| | -3 to <-2 | 108 (14%) | 18 (10%) | 126 (14%) |
| | -2 to <-1 | 207 (28%) | 43 (25%) | 250 (27%) |
| | -1 to <0 | 235 (31%) | 59 (34%) | 294 (32%) |
| | 0 to <1 | 115 (15%) | 31 (18%) | 146 (16%) |
| | 1 to <2 | 31 (4%) | 11 (6%) | 42 (5%) |
| | 2 to <3 | 3 (0%) | 1 (0%) | 4 (0%) |
| | >=3 | 3 (0%) | 0 (0%) | 3 (0%) |
| Site | DTTC | 351 (47%) | 101 (58%) | 452 (49%) |
| | Shandukani | 141 (19%) | 31 (18%) | 172 (19%) |
| | Matlosana | 246 (33%) | 13 (8%) | 259 (28%) |
| | ILTBRU | 1 (0%) | 6 (3%) | 7 (1%) |
| | THINK | 10 (1%) | 22 (13%) | 32 (3%) |

**Table S6.5 New exposure to an additional documented TB index patient in the household during follow-up**

| | | Levofloxacin | Placebo | Total |
|---|---|---|---|---|
| **N randomized participants** | | 453 (100%) | 469 (100%) | 922 (100%) |
| **Reported exposure to an additional adult with TB in the household during follow-up** | | 46 (10%) | 48 (10%) | 94 (10%) |
| **First study visit with reported exposure to additional TB case** | Week 4 | 3 | 4 | 7 |
| | Week 8 | 6 | 8 | 14 |
| | Week 12 | 7 | 5 | 12 |
| | Week 16 | 3 | 1 | 4 |
| | Week 24 | 6 | 6 | 12 |
| | Week 36 | 6 | 8 | 14 |
| | Week 48 | 9 | 6 | 15 |
| | Week 72 or after | 6 | 10 | 16 |

## S7 TREATMENT ADHERENCE

**Table S7.1 Participants prescribed incorrect study drug to original treatment allocation**

| Study number | Original treatment allocation | Study drug prescribed | Number of weeks on treatment |
|---|---|---|---|
| M014906Z | Levofloxacin | Placebo | 24 |

**Table S7.2 Permanent discontinuation of study treatment early before the end of the treatment phase**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| N randomized participants | 453 (100%) | 469 (100%) | 922 (100%) |
| Received at least one dose of study drug | 453 (100.0%) | 468 (99.8%) | 921 (99.9%) |
| Permanently discontinuing study treatment early | 75 (17%) | 80 (17%) | 155 (17%) |
| Reason for discontinuing treatment* | | | |
| Late screening failure | 17 (23%) | 12 (15%) | 29 (19%) |
| Died | 0 (0%) | 1 (1%) | 1 (1%) |
| Suspected incident TB disease | 1 (1%) | 11 (14%) | 12 (8%) |
| Adverse event+ | 6 (8%) | 1 (1%) | 7 (5%) |
| New drug-susceptible TB contact | 7 (9%) | 13 (16%) | 20 (13%) |
| Moved away | 10 (13%) | 13 (16%) | 23 (15%) |
| Withdrew consent | 18 (24%) | 16 (20%) | 34 (22%) |
| Lost to follow-up | 4 (5%) | 5 (6%) | 9 (6%) |
| Not adherent | 10 (13%) | 7 (9%) | 17 (11%) |
| Other | 2 (3%) | 1 (1%) | 3 (2%) |

* Main reason for discontinuing study treatment assigned in the following hierarchical order if more than one reason reported.

+ Further details provided in Table S9.8.

Other: reasons given: travel (2 Levofloxacin); and exposure to MDR-TB cases with *INH* A gene mutation (1 Placebo)

**Table S7.3 Proportion of total study drug doses taken**

| | | Levofloxacin | Placebo | Total |
|---|---|---|---|---|
| N children randomized | | 453 | 469 | 922 |
| N children with relevant adherence data | | 437 | 450 | 887 |
| Proportion of doses taken* | Median | 96% | 96% | 96% |
| | IQR | 88%, 98% | 90%, 99% | 90%, 99% |
| | <80% | 61 (14%) | 63 (14%) | 124 (14%) |
| | 80-89% | 59 (14%) | 38 (8%) | 97 (11%) |
| | >=90% | 317 (73%) | 349 (78%) | 666 (75%) |
| Odds ratio (95% CI), Levofloxacin vs placebo+ | | 0.80 (0.54-1.17) | | |

* The protocol definition of adequate treatment was taking ≥80% of allocated doses, allowing for any treatment extension due to missed doses. Analysis based on participants with treatment adherence information available.

+ Derived from ordinal logistic regression, accounting for household clustering.

## S8 EFFICACY

### S8.1 Primary efficacy analysis

**Table S8.1 Primary efficacy analysis- modified intention-to-treat (mITT) population**

| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| All participants | 451 | 465 | 916 |
| Participants with TB endpoint during overall study follow-up* | 7 (1.6%) | 14 (3.0%) | 21 |
| Confirmed TB | 4 | 7 | 11 |
| Unconfirmed TB | 3 | 7 | 10 |
| **Primary efficacy analysis** | | | |
| **Participants with TB endpoint by 48 weeks +** | **5 (1.1%)** | **12 (2.6%)** | **17** |
| Confirmed TB | 4 | 7 | 11 |
| Unconfirmed TB | 1 | 5 | 6 |
| Person years | 406 | 418 | 825 |
| Rate per 100 person years (95% CI) | 1.2 (0.5-2.9) | 2.9 (1.6-5.2) | |
| **Hazard ratio (95% CI), levofloxacin vs. placebo ^** | **0.44 (0.15-1.25)** | | |
| **P-value** | **0.121** | | |
| Absolute difference in cumulative incidence by 48 weeks+ (95% CI)[$], levofloxacin vs. placebo | **-1.7% (-3.6% to 0.3%)** | | |

* Based on ERC adjudication.

+ Allowing pre-defined 6 weeks window for scheduled visits in the statistical analysis plan, therefore, follow-up time in analysis of primary endpoint was censored at 48+6=54 weeks.

^ Adjusted for site and age group using Inverse Probability of Treatment Weighting (IPTW) model and accounting for household clustering. Test for assessing non-proportional hazards p-value = 0.106.

[$] Estimated using parametric survival models.

**S8.2. Sensitivity and supplementary analyses for the primary endpoint**

Please note that for these analyses, the estimated confidence interval of the hazard ratio was not adjusted for multiplicity.

**Table S8.2 TB events as reported by the sites* - mITT population (sensitivity analysis)**

| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| All participants (mITT population) | 451 | 465 | 916 |
| Participants with TB endpoint by 48 weeks | 4 (0.9%) | 13 (2.8%) | 17 |
| Person years | 406 | 417 | 823 |
| Rate per 100 person years (95% CI) | 1.0 (0.4-2.6) | 3.1 (1.8-5.5) | |
| Hazard ratio (95% CI), levofloxacin vs placebo | 0.33 (0.11-1.02) | | |

* Based on site assessment rather than endpoint review committee adjudication.

mITT : modified intention to treat

**Table S8.3 Primary efficacy endpoint- per protocol population (supplementary analysis)**

| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| All participants (PP population) | 378 | 407 | 785 |
| Participants with TB endpoint by 48 weeks | 5 (1.3%) | 11 (2.7%) | 16 |
| Person years | 357 | 380 | 737 |
| Rate per 100 person years (95% CI) | 1.4 (0.6-3.3) | 2.9 (1.5-5.4) | |
| Hazard ratio (95% CI), levofloxacin vs placebo | 0.50 (0.17-1.46) | | |

**Table S8.4 Primary efficacy endpoint including only children aged<5 years (supplementary analysis)**

| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| All participants (mITT population) | 403 | 430 | 833 |
| Participants with TB endpoint by 48 weeks | 5 (1.2%) | 10 (2.3%) | 15 |
| Person years | 373 | 393 | 766 |
| Rate per 100 person years (95% CI) | 1.3 (0.6-3.2) | 2.5 (1.3-5.0) | |
| Hazard ratio (95% CI), levofloxacin vs placebo | 0.54 (0.18-1.60) | | |

**S8.3 Subgroup analyses for primary efficacy endpoint**

The following are exploratory subgroup analyses pre-specified in the statistical analysis plan

**Table S8.5 Subgroup analyses for primary efficacy end point – mITT population**

| | **Levofloxacin** | | **Placebo** | | |
|---|---|---|---|---|---|
| | Participants with primary endpoint / Total (%) | Rate per 100 PY (95% CI) | Participants with primary endpoint / Total (%) | Rate per 100 PY (95% CI) | Hazard ratio (95% CI) |
| Site | | | | | |
| DTTC | 4/221 (1.81%) | 2.1 (0.8-5.5) | 7/226 (3.10%) | 3.5 (1.7-7.2) | 0.57 (0.17-1.92) |
| Shandukani | 0/92 (0.00%) | 0.0 (0.0-4.4) | 1/80 (1.25%) | 1.4 (0.2-10.4) | 0.86 (0.00-33.71) |
| Matlosana | 1/116 (0.86%) | 0.9 (0.1-5.9) | 4/142 (2.82%) | 2.9 (0.9-9.6) | 0.29 (0.03-2.75) |
| ILTBRU | 0/3 (0.00%) | 0.0 (0.0-199.4) | 0/4 (0.00%) | 0.0 (0.0-137.6) | - |
| THINK | 0/19 (0.00%) | 0.0 (0.0-30.1) | 0/13 (0.00%) | 0.0 (0.0-42.6) | - |
| Sex | | | | | |
| Male | 3/211 (1.42%) | 1.6 (0.5-4.9) | 7/239 (2.93%) | 3.2 (1.6-6.6) | 0.51 (0.13-1.97) |
| Female | 2/240 (0.83%) | 0.9 (0.2-3.7) | 5/226 (2.21%) | 2.5 (0.9-7.0) | 0.37 (0.07-2.00) |
| Index patient being the primary caregiver * | | | | | |
| No | 3/350 (0.86%) | 0.9 (0.3-2.9) | 9/363 (2.48%) | 2.8 (1.4-5.2) | 0.34 (0.09-1.24) |
| Yes | 2/101 (1.98%) | 2.4 (0.6-9.8) | 3/99 (3.03%) | 3.4 (0.8-14.5) | 0.73 (0.10-5.33) |
| Duration of index patient's treatment for the current MDR-TB episode before household contact enrolment + | | | | | |
| <=12 weeks | 5/364 (1.37%) | 1.5 (0.6-3.6) | 10/412 (2.43%) | 2.7 (1.4-4.9) | 0.56 (0.19-1.62) |
| >12 weeks | 0/87 (0.00%) | 0.0 (0.0-4.8) | 2/53 (3.77%) | 4.6 (0.7-30.5) | 0.24 (0.00-3.04) |

| | | | | | |
|---|---|---|---|---|---|
| Whether participant slept in same room as the index patient | | | | | |
| No | 3/262 (1.15%) | 1.3 (0.4-3.9) | 6/308 (1.95%) | 2.2 (1.0-4.8) | 0.62 (0.16-2.45) |
| Yes | 2/189 (1.06%) | 1.2 (0.3-4.7) | 6/157 (3.82%) | 4.2 (1.7-10.4) | 0.27 (0.05-1.40) |
| Average number of hours per day spent with the index patient | | | | | |
| <=8hrs | 1/188 (0.53%) | 0.6 (0.1-4.1) | 5/199 (2.51%) | 2.8 (1.2-6.5) | 0.21 (0.02-1.82) |
| >8hrs | 4/263 (1.52%) | 1.7 (0.7-4.6) | 7/266 (2.63%) | 2.9 (1.3-6.8) | 0.58 (0.16-2.07) |
| TB infection status (restricted to participants aged<5 years) ^ | | | | | |
| Negative | 3/293 (1.02%) | 1.1 (0.4-3.3) | 6/332 (1.81%) | 2.0 (0.8-4.9) | 0.58 (0.14-2.45) |
| Positive | 2/88 (2.27%) | 2.6 (0.7-10.5) | 2/72 (2.78%) | 3.0 (0.7-12.2) | 0.85 (0.12-6.21) |
| HIV exposure status ** | | | | | |
| Not Exposed | 2/287 (0.70%) | 0.8 (0.2-3.0) | 8/296 (2.70%) | 3.1 (1.5-6.1) | 0.24 (0.05-1.14) |
| Exposed | 3/162 (1.85%) | 2.1 (0.7-6.4) | 4/167 (2.40%) | 2.5 (1.0-6.6) | 0.87 (0.20-3.83) |
| Age | | | | | |
| Under 5 years | 5/403 (1.24%) | 1.3 (0.6-3.2) | 10/430 (2.33%) | 2.5 (1.3-5.0) | 0.54 (0.18-1.61) |
| Over 5 years | 0/48 (0.00%) | 0.0 (0.0-11.3) | 2/35 (5.71%) | 7.8 (2.0-31.0) | 0.32 (0.00-4.17) |
| Weight-for-age z-score | | | | | |
| < -1 | 2/131 (1.53%) | 1.7 (0.4-6.4) | 8/141 (5.67%) | 6.4 (3.0-13.7) | 0.26 (0.06-1.23) |
| >=-1 | 3/320 (0.94%) | 1.1 (0.3-3.3) | 4/324 (1.23%) | 1.4 (0.5-3.6) | 0.78 (0.17-3.48) |

* Excludes 3 participants where it is unknown if the index case is the primary caregiver or not.

+ Includes 39 participants in <=12 weeks category where the index case did not start any treatment for the current MDR-TB episode before HHC enrolment.

^ Excludes 48 participants where TB infection status is unknown or indeterminate.

** Excludes 4 participants where HIV exposure status is unknown.

++ Where a subgroup had no events within a treatment group: exact Poisson method was used to estimate the rate with 95% CI for the relevant cell, as well as the rate ratio with 95% for the subgroup (if at least one of the treatment groups had non-zero events within the subgroup); Cox model was used for test for interaction, excluding any subgroup(s) with no events in either treatment group.

### S8.4 Secondary efficacy endpoints

Please note for these analyses, the estimated confidence interval of the hazard ratio was not adjusted for multiplicity.

**Table S8.6 Secondary efficacy endpoints – modified Intention-to treat (mITT) population**

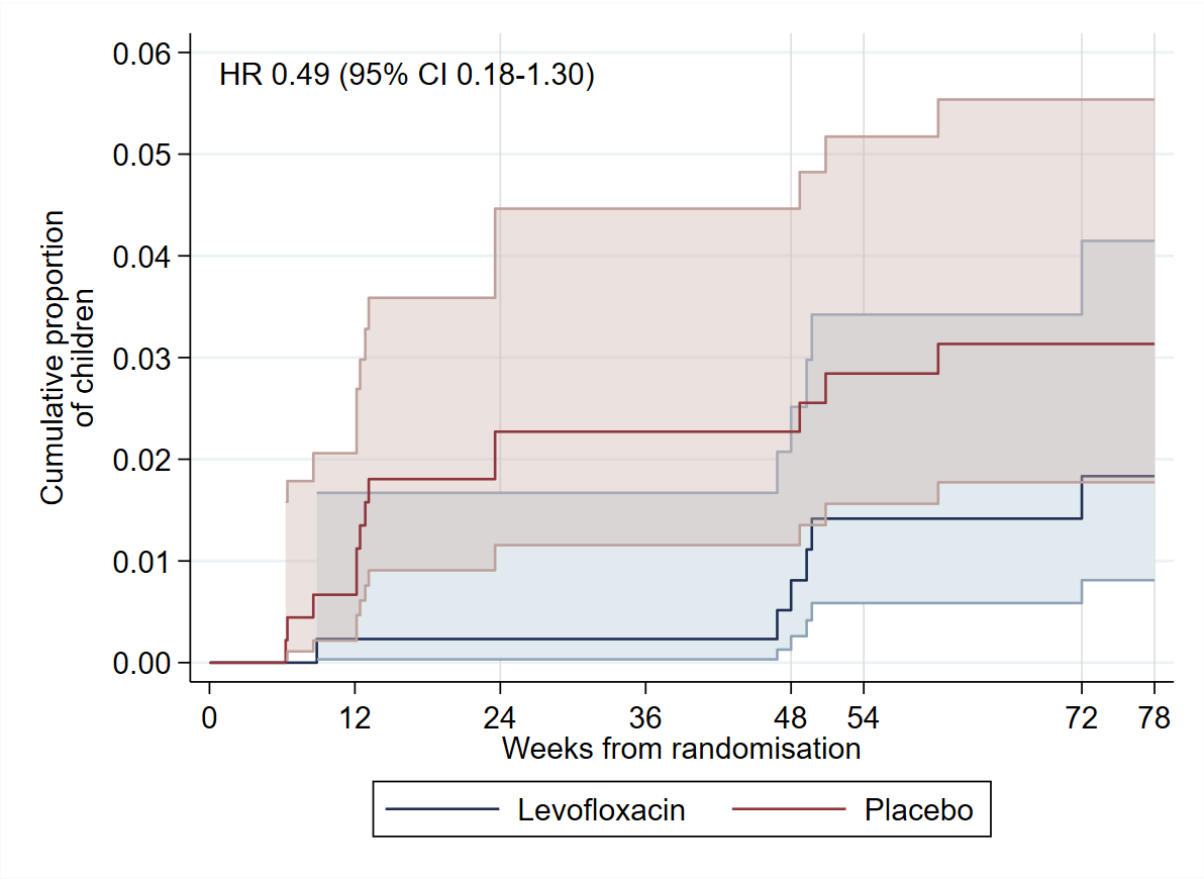
| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| All participants | 451 | 465 | 916 |
| **TB endpoint by 72 weeks*** | | | |
| Participants with event + | 6 (1.3%) | 13 (2.8%) | 19 |
| Rate per 100 person years (95% CI) | 1.1 (0.5-2.5) | 2.4 (1.4-4.3) | |
| Hazard ratio (95% CI^), levofloxacin vs. placebo | 0.49 (0.18-1.30) | | |
| **All-cause mortality by 48 weeks*** | | | |
| Participants died | 1 (0.2%) | 1 (0.2%) | 2 |
| Rate per 100 person years (95% CI) | 0.2 (0.0-1.8) | 0.2 (0.0-1.7) | |
| **All-cause mortality by 72 weeks*** | | | |
| Participants died | 1 (0.2%) | 1 (0.2%) | 2 |
| Rate per 100 person years (95% CI) | 0.2 (0.0-1.4) | 0.2 (0.0-1.3) | |

* Allowing pre-defined 6 weeks window for scheduled visits in statistical analysis plan.

+ Excludes 2 children with TB endpoints after 72+6 weeks window (1 levofloxacin, 1 placebo); see Table 8.1. (NB. Study follow-up was reduced from 96 weeks to week 72 in protocol version 2.0, and the time-frame for these secondary outcomes changed accordingly).

^ The confidence interval was not adjusted for multiplicity.

**Figure S8.1 Time to TB endpoint by 72-week visit* (mITT population)**




* Censoring at 78 weeks (pre-defined 72+6 weeks window).

**S8.5 Sensitivity and supplementary analyses of secondary efficacy endpoints**

Please note for these analyses, the estimated confidence interval of the hazard ratio was not adjusted for multiplicity.

**Table S8.7 TB event by 72 weeks as reported by sites* – sensitivity analysis**

| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| All participants (mITT population) | 451 | 465 | 916 |
| Participants with event | 5 (1.1%) | 14 (3.0%) | 19 |
| Rate per 100 person years (95% CI) | 1.0 (0.4-2.3) | 2.6 (1.5-4.5) | |
| Hazard ratio (95% CI), levofloxacin vs placebo | 0.39 (0.14-1.08) | | |

* Based on site assessment rather than ERC adjudication.

**Table S8.8 TB endpoint by 72 weeks - supplementary analyses**

| | **Levofloxacin** | **Placebo** | **Total** |
|---|---|---|---|
| **Per protocol population** | | | |
| All participants | 378 | 407 | 785 |
| Participants with event | 6 (1.6%) | 12 (2.9%) | 18 |
| Rate per 100 person years (95% CI) | 1.3 (0.6-2.8) | 2.4 (1.3-4.4) | |
| Hazard ratio (95% CI), levofloxacin vs. placebo | 0.55 (0.20-1.48) | | |
| **Including only children aged<5 years (mITT population)** | | | |
| All participants | 403 | 430 | 833 |
| Participants with event | 6 (1.5%) | 11 (2.6%) | 17 |
| Rate per 100 person years (95% CI) | 1.2 (0.6-2.7) | 2.1 (1.1-4.0) | |
| Hazard ratio (95% CI), levofloxacin vs placebo | 0.60 (0.22-1.63) | | |

**Table S8.9 All-cause mortality by 48 and 72 weeks- supplementary analyses**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| **ITT population** | | | |
| All participants | 453 | 469 | 922 |
| **All-cause mortality by 48 weeks** | | | |
| Participants died | 1 (0.2%) | 1 (0.2%) | 2 |
| Rate per 100 person years (95% CI) | 0.2 (0.0-1.7) | 0.2 (0.0-1.7) | |
| **All-cause mortality by 72 weeks** | | | |
| Participants died | 1 (0.2%) | 1 (0.2%) | 2 |
| Rate per 100 person years (95% CI) | 0.2 (0.0-1.3) | 0.2 (0.0-1.3) | |
| **Per protocol population** | | | |
| All participants | 378 | 407 | 785 |
| **All-cause mortality by 48 weeks** | | | |
| Participants died | 1 (0.3%) | 1 (0.2%) | 2 |
| Rate per 100 person years (95% CI) | 0.3 (0.0-2.0) | 0.3 (0.0-1.8) | |
| **All-cause mortality by 72 weeks** | | | |
| Participants died | 1 (0.3%) | 1 (0.2%) | 2 |
| Rate per 100 person years (95% CI) | 0.2 (0.0-1.5) | 0.2 (0.0-1.4) | |

## S8.6 Additional information of child participants with TB endpoints

**Table S8.10 Characteristics of children with TB endpoint during overall study follow-up***

| | | Levofloxacin | Placebo | Total |
|---|---|---|---|---|
| **Participants with TB endpoint** | | **7** | **14** | **21** |
| Age randomized (years) | <1 | 3 (43%) | 5 (36%) | 8 (38%) |
| | 1 to <3 | 3 (43%) | 4 (29%) | 7 (33%) |
| | 3 to <5 | 1 (14%) | 3 (21%) | 4 (19%) |
| | >=5 | 0 (0%) | 2 (14%) | 2 (10%) |
| Time from index patient starting TB treatment to child enrolment | <=12 weeks | 7 (100%) | 12 (86%) | 19 (90%) |
| | >12 weeks | 0 (0%) | 2 (14%) | 2 (10%) |
| HIV status | Negative | 7 (100%) | 13 (93%) | 20 (95%) |
| | Positive | 0 (0%) | 1 (7%) | 1 (5%) |
| Baseline IGRA status | Negative | 3 (43%) | 7 (50%) | 10 (48%) |
| | Positive | 3 (43%) | 5 (36%) | 8 (38%) |
| | Unknown | 1 (14%) | 2 (14%) | 3 (14%) |
| Weight-for-age z-score | < -1 | 2 (29%) | 10 (71%) | 12 (57%) |
| | >=-1 | 5 (71%) | 4 (29%) | 9 (43%) |
| Classification of TB | PTB | 6 (86%) | 11 (79%) | 17 (81%) |
| | PTB+EPTB | 0 (0%) | 2 (14%) | 2 (10%) |
| | Unknown | 1 (14%) | 1 (7%) | 2 (10%) |
| TB treatment received | DS-TB treatment | 0 (0%) | 1 (7%) | 1 (5%) |
| | DR-TB treatment | 6 (86%) | 12 (86%) | 18 (86%) |
| | Not treated + | 1 (14%) | 1 (7%) | 2 (10%) |
| Confirmed / unconfirmed TB | Confirmed TB | 4 (57%) | 7 (50%) | 11 (52%) |
| | Unconfirmed TB | 3 (43%) | 7 (50%) | 10 (48%) |

* As adjudicated by ERC.

+ Considered by ERC as TB endpoint but not by site; see Table 8.1 for further details.

**Table S8.11 Line listing of all TB end points based on end point review committee adjudication**

| | Weeks to TB diagnosis from randomization | Age (years) randomized | Baseline IGRA status | Confirmed/ Unconfirmed TB | TB treatment started |
|---|---|---|---|---|---|
| **Levofloxacin** | | | | | |
| 1 | 8.9 | 0.9 | Negative | Unconfirmed TB | DR-TB treatment |
| 2 | 46.9 | 1.2 | Negative | Unconfirmed TB | DR-TB treatment |
| 3 | 48.0 | 3.2 | Positive | Confirmed TB | DR-TB treatment |
| 4 | 49.3 | 2.9 | Positive | Confirmed TB | Not treated |
| 5 | 49.7 | 0.8 | Negative | Confirmed TB | DR-TB treatment |
| 6 | 72.0 | 0.1 | Unknown | Unconfirmed TB | DR-TB treatment |
| 7 | 79.0 | 1.9 | Positive | Unconfirmed TB | DR-TB treatment |
| **Placebo** | | | | | |
| 1 | 6.3 | 1.7 | Positive | Confirmed TB | DR-TB treatment |
| 2 | 6.4 | 4.4 | Unknown | Confirmed TB | DR-TB treatment |
| 3 | 8.6 | 1.5 | Positive | Unconfirmed TB | DR-TB treatment |
| 4 | 12.1 | 0.1 | Unknown | Confirmed TB | DR-TB treatment |
| 5 | 12.1 | 14.6 | Positive | Unconfirmed TB | DR-TB treatment |
| 6 | 12.4 | 0.5 | Negative | Unconfirmed TB | DR-TB treatment |
| 7 | 12.9 | 1.2 | Negative | Confirmed TB | DS-TB treatment |
| 8 | 13.1 | 3.5 | Negative | Confirmed TB | DR-TB treatment |
| 9 | 23.6 | 0.4 | Negative | Unconfirmed TB | DR-TB treatment |
| 10 | 23.6 | 0.4 | Negative | Unconfirmed TB | DR-TB treatment |
| 11 | 48.7 | 11.5 | Positive | Confirmed TB | Not treated |
| 12 | 50.9 | 3.5 | Negative | Confirmed TB | DR-TB treatment |

| | | | | | |
|---|---|---|---|---|---|
| 13 | 60.1 | 2.6 | Positive | Unconfirmed TB | DR-TB treatment |
| 14 | 100.3 | 1.0 | Negative | Unconfirmed TB | DR-TB treatment |

* The primary endpoints are shown in blue.

+ Considered by independent end point review committee as TB endpoint but not by site; see Table S8.13 for further details.

**Table S8.12 Microbiological characteristics of all child participants with TB endpoints in relation to adult index patients**

| | | | Microbiological characteristics of adult index case | | Microbiological characteristics of child participants with TB endpoint | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Study arm** | **Weeks to TB diagnosis of child** | **MDR** | **FQ and Injectables** | **TB Classification** | **Smear** | **TB detection** | **MDR** | **FQ and Injectables** |
| 1 | LVX | 48 | MDR | FQ S Inj S | Confirmed | Negative | X+(trace) C- | Xpert RIF Indet | |
| 2 | LVX | 49.3 | MDR | FQ S Inj S | Confirmed | Negative | X+(trace) C- | Xpert RIF Indet | |
| 3 | LVX | 49.7 | MDR | FQ S Inj S | Confirmed | Negative | X- C+ | MDR | FQ S Inj R |
| 4 | Placebo | 6.3 | MDR | FQ S Inj S | Confirmed | Negative | X+ C+ | MDR | FQ S Inj S |
| 5 | Placebo | 6.4 | RR-TB | | Confirmed | Negative | X+(trace) C+ | DS-TB | |
| 6 | Placebo | 12.1 | RR-TB | | Confirmed | Negative | X+(very low) C+ | Mono R to RIF | FQ S Inj S |
| 7 | Placebo | 12.9 | MDR | FQ S Inj S | Confirmed | Negative | X+(very low) C+ | DS-TB | |
| 8 | Placebo | 13.1 | MDR | FQ S Inj S | Confirmed | Negative | X+(very low) C- | Xpert RIF R | |
| 9 | Placebo | 48.7 | RR-TB | | Confirmed | Negative | X+(trace) C- | Xpert RIF Indet | |
| 10 | Placebo | 50.9 | MDR | FQ S Inj S | Confirmed | Negative | X+(trace) C- | Xpert RIF Indet | |
| 11 | LVX | 8.9 | MDR | FQ S Inj S | Unconfirmed | Negative | X- C- | | |
| 12 | LVX | 46.9 | MDR | FQ S Inj S | Unconfirmed | Negative | C- | | |
| 13 | LVX | 72 | RR-TB | | Unconfirmed | Negative | X- C- | | |
| 14 | LVX | 79 | RR-TB | FQ S Inj S | Unconfirmed | Negative | C- | | |
| 15 | Placebo | 8.6 | MDR | FQ R Inj S | Unconfirmed | Negative | X- C- | | |
| 16 | Placebo | 12.1 | MDR | FQ S Inj S | Unconfirmed | Negative | X- C- | | |
| 17 | Placebo | 12.4 | MDR | FQ S Inj S | Unconfirmed | Negative | X- C- | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 18 | Placebo | 23.6 | MDR | FQ S Inj S | Unconfirmed | Negative | C- | | |
| 19 | Placebo | 23.6 | MDR | FQ S Inj S | Unconfirmed | Negative | X- C- | | |
| 20 | Placebo | 60.1 | RR-TB | FQ S Inj S | Unconfirmed | Negative | X- C- | | |
| 21 | Placebo | 100.3 | MDR | FQ S Inj S | Unconfirmed | Negative | X- C- | | |

X= Xpert Ultra; C=Culture (MGIT and Löwenstein–Jensen); + = positive or detected; - =negative or not detected; R = resistant; S = susceptible; Indet = indeterminate

DS-TB = drug-susceptible; TB (susceptible to INH and RIF); MDR = multidrug-resistant TB (resistant to INH and RIF); RR-TB = TB resistant to RIF

FQ = fluoroquinolone; Inj = injectable drug

If a cell is empty, no testing done or testing not possible if culture negative for example. Participants are listed by TB diagnostic classification and treatment group and ordered by time to TB diagnosis from randomization

**Table S8.13 Line listing of all TB endpoints considered by the ERC as TB endpoint but not by the site**

| | Treatment group | Number of weeks from randomization to TB diagnosis | Comments from ERC |
|---|---|---|---|
| 1 | Placebo | 48.7 | This case generated debate amongst ERC as they understand clinical decision in referral to disregard trace positive Xpert MTB/RIF in the face of reported normal CXR, no symptoms and no good clinical progression without further treatment. However, the panel noted that in a child who is Xpert MTB/RIF trace positive from a respiratory sample does meet case definition by WHO for confirmed pulmonary TB, and have classified the outcome accordingly. |
| 2 | Levofloxacin | 49.3 | Confirmed TB but indeterminate RIF result means sensitivity cannot be determined. This raises systemic issues of a children with positive microbiology and abnormal CXR consistent with primary infection (albeit long after exposure in this case) and whether all have TB disease that requires treatment, or whether children can be observed without treatment as TB infection only. |

**Table S8.14 Line listing of deaths**

| | Age (years) randomized | Number of weeks to death | Age (years) died | Cause of death* | Attributable to TB | Related to study drug |
|---|---|---|---|---|---|---|
| **Levofloxacin** | | | | | | |
| 1 | 0.3 | 38.9 | 1.0 | Cardiac arrest; congenital cardiac anomaly | Unrelated/Unlikely | Unrelated |
| **Placebo** | | | | | | |
| 1 | 0.8 | 11.3 | 1.0 | Pneumonia; viral | Unrelated/Unlikely | Unlikely |

* As adjudicated by the ERC.

**Table S8.15 Number needed to treat (NNT)**

- The estimated absolute reduction in cumulative incidence of TB by 48-weeks with levofloxacin is 1.7% (95% CI -0.3 to 3.6%); Table S8.1. Since the treatment effect did not reach the 5% significance level in the primary analysis, the confidence interval for the absolute reduction spans zero.
- The estimated NNT to prevent 1 TB case is 60.
- Taking the reciprocal of the values defining the CI for the absolute risk reduction, and reversing the order, would however incorrectly give a CI for the NNT of -337 to 28, i.e. NNT for 1 child/adolescent be harmed (NNTH) of 337 to NNT for 1 child/adolescent to benefit (NNTB) of 28.
- As noted above, the 95% CI for the absolute risk reduction from -0.3% to 3.6% includes zero. Since the NNT is ∞ when the absolute risk reduction is zero, the CI for the NNT should therefore include ∞.
- While two separate intervals for the NNT can be quoted (namely NNTH 337 to ∞ and NNTB 28 to ∞), we follow the recommendation by Alman (1998)[5] and present the NNTB as 60 (95% CI NNTH 337 to ∞ to NTTB 28) to emphasize the continuity.

**Table S8.16 Household intraclass correlation (ICC) coefficient for the primary TB endpoint**

| | |
|---|---|
| ICC assumed in study power calculations | 0.1 |
| ICC estimated within TB-CHAMP | 0.28 (95% CI 0.03 to 0.83) |

## S9 SAFETY

### S9.1 Primary safety endpoint

**Table S9.1 Primary safety endpoint**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| All participants receiving at least one dose of study treatment* | 452 | 469 | 921 |
| **Grade 3 or higher adverse events at least possibly associated with study drug** | | | |
| Number of events | 5 | 8 | 13 |
| Participants with >= 1 event(s) | 4 (0.9%) | 8 (1.7%) | 12 |
| Rate per 100 person years+ (95% CI) | 1.8 (0.7-4.8) | 3.5 (1.8-6.9) | |
| P-value comparing proportion of participants with event | 0.386 | | |
| Hazard ratio (95% CI), levofloxacin vs. placebo+ | 0.52 (0.16-1.71) | | |
| P-value | 0.285 | | |

* Excludes 1 participant (placebo group) who did not start study treatment. Includes 1 participant prescribed the incorrect study treatment to original allocation, who was analyzed according to the drug received (originally allocated levofloxacin but received placebo; see Table S7.1).

+ Analyses based on time to first event. The hazard ratio was estimated adjusting for site, age group and allowing for household clustering.

**Table S9.2. Line listing of grade 3 or higher adverse events which was at least possibly associated with study drug**

| | Weeks from randomization to onset of event(s) | Adverse event | Highest grade | Causal relationship | Action taken regarding study treatment | Date of onset | Date resolved |
|---|---|---|---|---|---|---|---|
| **Levofloxacin** | | | | | | | |
| 1* | .4 | Skin - Rash, urticaria | 3 | Probably | Interrupted | 12jun2022 | 01sep2022 |
| 2* | .7 | Skin – Itching, pruritis, excoriation, scratching | 3 | Probably | Interrupted | 14jun2022 | 01sep2022 |
| 3 | 7.6 | Diarrheal – Gastroenteritis | 3 | Possibly | None | 24may2022 | 15jun2022 |
| 4 | 8 | Hematological – Anemia with no clinical symptoms | 3 | Possibly | None | 23apr2020 | 15jul2021 |
| 5 | 16.3 | Biochemical – Raised ALT | 4 | Possibly | Stopped | 28mar2019 | 24apr2019 |
| **Placebo** | | | | | | | |
| 1 | 7.9 | Hematological – Anemia with no clinical symptoms | 3 | Possibly | None | 23jul2018 | 01feb2019 |
| 2 | 15.9 | Hematological – Thrombocytopenia | 3 | Possibly | None | 20jun2019 | 01aug2019 |
| 3 | 15.9 | Biochemical – Raised ALT | 3 | Possibly | Interrupted | 14mar2018 | 16apr2018 |
| 4 | 16 | Systemic – Wasting syndrome uninvestigated | 3 | Possibly | None | 30jun2022 | 14nov2022 |
| 5 | 16 | Biochemical – Raised liver enzymes | 3 | Possibly | Interrupted | 13dec2018 | 19dec2018 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6 | 16 | Wasting syndrome – Severe weight loss (>10%) | 3 | Possibly | None | 17feb2022 | Ongoing |
| 7 | 16.3 | Hematological – Anemia with no clinical symptoms | 3 | Possibly | None | 13sep2018 | 27sep2018 |
| 8 | 20.6 | CNS – Intracranial pressure | 3 | Possibly | Stopped | 12sep2022 | 20dec2022 |

* Same participant with 2 events.

**The following are exploratory subgroup analyses pre-specified in the statistical analysis plan.**

**Table S9.3 Subgroup analyses for primary safety endpoint**

| | **Levofloxacin** | | **Placebo** | | | |
|---|---|---|---|---|---|---|
| | Participants with event / Total (%) | Rate per 100 PY (95% CI) | Participants with event / Total (%) | Rate per 100 PY (95% CI) | Hazard ratio (95% CI) | P-value interaction |
| Sex | | | | | | |
| Male | 1/212 (0.47%) | 1.0 (0.1-6.9) | 1/242 (0.41%) | 0.8 (0.1-6.1) | 1.19 (0.07-19.09) | 0.496 |
| Female | 3/240 (1.25%) | 2.5 (0.8-7.8) | 7/227 (3.08%) | 6.3 (3.0-13.1) | 0.41 (0.11-1.54) | |
| Age | | | | | | |
| Under 5 years | 4/404 (0.99%) | 2.0 (0.8-5.3) | 7/434 (1.61%) | 3.3 (1.6-6.9) | 0.61 (0.18-2.07) | - |
| Over 5 years* | 0/48 (0.00%) | 0.0 (0.0-17.2) | 1/35 (2.86%) | 5.9 (0.9-38.9) | 0.79 (0.00-30.60) | |
| Weight-for-age z-score | | | | | | |
| < -1 | 2/132 (1.52%) | 3.1 (0.8-11.8) | 1/144 (0.69%) | 1.5 (0.2-10.3) | 2.39 (0.23-25.43) | 0.143 |
| >= -1 | 2/320 (0.63%) | 1.3 (0.3-5.1) | 7/325 (2.15%) | 4.4 (2.1-9.1) | 0.29 (0.06-1.37) | |

* Where a subgroup had no events within a treatment group: exact Poisson method was used to estimate the rate with 95% CI for the relevant cell, as well as the rate ratio with 95% for the subgroup (if at least one of the treatment groups had non-zero events within the subgroup); the test for interaction was not done.

**S9.2 Secondary safety endpoints**

**Table S9.4 Secondary safety endpoints**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| All participants receiving at least one dose of study treatment | 452 | 469 | 921 |
| **Grade 3 or higher adverse events up to 30 days after last study drug dose (excluding ERC adjudicated TB endpoints*)** | | | |
| Number of events | 21 | 30 | 51 |
| Participants with >= 1 event(s) | 14 (3.1%) | 24 (5.1%) | 38 |
| Rate per 100 person years+ (95% CI) | 6.4 (3.9-10.7) | 10.7 (6.6-17.1) | |
| P-value comparing proportion of participants with event | 0.123 | | |
| Hazard ratio (95% CI), levofloxacin vs placebo+ | 0.64 (0.32-1.28) | | |
| P-value | 0.211 | | |
| **Serious adverse events up to 30 days after last study drug dose (excluding ERC adjudicated TB endpoints*)** | | | |
| Number of events | 10 | 10 | 20 |
| Participants with >= 1 event(s) | 9 (2.0%) | 8 (1.7%) | 17 |
| Rate per 100 person years+ (95% CI) | 4.1 (2.1-7.9) | 3.5 (1.6-7.6) | |
| P-value comparing proportion of participants with event | 0.810 | | |
| Hazard ratio (95% CI), levofloxacin vs placebo+ | 1.22 (0.45-3.34) | | |
| P-value | 0.692 | | |
| **Permanent discontinuation of study treatment due to adverse event(s) of any grade^** | | | |
| Participants discontinuing study treatment due to AE(s) | 6 (1.3%) | 1 (0.2%) | 7 |
| Rate per 100 person years+ (95% CI) | 3.2 (1.4-7.0) | 0.5 (0.1-3.6) | |

| | | |
|---|---|---|
| P-value comparing proportion of participants** | 0.065 | |
| Hazard ratio (95% CI), levofloxacin vs placebo+<br>P-value | 5.00 (0.61-41.32)<br>0.135 | |

* Includes 2 participants (both placebo group) who had lower respiratory tract infection diagnosed by site as TB but not by ERC. Please see Table S9.13 for summary of all SAE's up to 30 days of last study drug including for TB events.

+ Analyses based on time to first event.

^ See Table S9.8 for line listing of participants discontinuing study treatment permanently early due to adverse event(s).

** Based on Fisher's exact test.

**Table S9.5 Secondary safety end points (continued): pre-specified adverse events**

| | Levofloxacin | Placebo | Total |
|---|---|---|---|
| All participants receiving at least one dose of study treatment | 452 | 469 | 921 |
| **Arthritis/arthralgia/tendinopathy (any grade)** | | | |
| Number of events | 7 | 4 | 11 |
| Participants with >= 1 event(s) | 6 (1.3%) | 4 (0.9%) | 10 |
| Rate per 100 person years+ (95% CI) | 2.7 (1.1-6.8) | 1.7 (0.7-4.6) | |
| P-value comparing proportion of participants with event | 0.540 | | |
| Hazard ratio (95% CI), levofloxacin vs placebo+ P-value | 1.32 (0.35-4.98) 0.686 | | |
| **CNS effects (any grade)^** | | | |
| Number of events | 11 | 17 | 28 |
| Participants with >= 1 event(s) | 7 (1.5%) | 11 (2.3%) | 18 |
| Rate per 100 person years+ (95% CI) | 3.2 (1.5-6.7) | 4.8 (2.4-9.7) | |
| P-value comparing proportion of participants with event | 0.478 | | |
| Hazard ratio (95% CI), levofloxacin vs placebo+ P-value | 0.59 (0.21-1.62) 0.304 | | |
| **Severe rash/cutaneous reaction (grade>=3)^** | | | |
| Number of events | 1 | 0 | 1 |
| Participants with >= 1 event(s) | 1 (0.2%) | 0 (0.0%) | 1 |

*Please see Tables S9.9-S9.11 for line-listing of relevant adverse events. Note that drug-related fever and peripheral neuropathy were also pre-specified adverse events but there were no events in either treatment group.

+ Analyses based on time to first event Includes events with date of onset up to 30 days after last study drug dose only.

^ Includes events with date of onset up to 30 days after last study drug dose only.

**S9.3 Additional information for the secondary safety endpoints**

**Table S9.6 Grade 3 or higher clinical and laboratory adverse events up to 30 days after last study drug dose, by body system classification**

| | **Levofloxacin** | **Placebo** | **total** |
|---|---|---|---|
| All participants receiving at least one dose of study treatment | 452 | 469 | 921 |
| **Total number of events [Number participants with >= 1 event(s)]** | **21 [14]** | **30 [24]** | **51 [38]** |
| Biochemical | 3 [1] | 2 [2] | 5 [3] |
| CNS | 0 [0] | 1 [1] | 1 [1] |
| Gastrointestinal | 3 [2] | 2 [2] | 5 [4] |
| Hematological | 7 [5] | 9 [8] | 16 [13] |
| Lower respiratory | 4 [4] | 5 [3] | 9 [7] |
| Oral | 0 [0] | 2 [1] | 2 [1] |
| Skin | 2 [1] | 0 [0] | 2 [1] |
| Specific infections | 0 [0] | 4 [3] | 4 [3] |
| Systemic | 2 [1] | 3 [2] | 5 [3] |
| Upper respiratory | 0 [0] | 1 [1] | 1 [1] |
| Wasting syndrome | 0 [0] | 1 [1] | 1 [1] |

**Table S9.7 Serious adverse events up to 30 days after last study drug dose, by body system classification**

| | **Levofloxacin** | **Placebo** | **total** |
|---|---|---|---|
| All participants receiving at least one dose of study treatment | 452 | 469 | 921 |
| **Total number of events [Number participants with >= 1 event(s)]** | **10 [9]** | **10 [8]** | **20 [17]** |
| Biochemical | 1 [1] | 0 [0] | 1 [1] |
| CNS | 0 [0] | 2 [1] | 2 [1] |
| Gastrointestinal | 2 [2] | 2 [2] | 4 [4] |
| Lower respiratory | 4 [4] | 3 [2] | 7 [6] |
| Other | 1 [1] | 0 [0] | 1 [1] |
| Specific infections | 0 [0] | 3 [3] | 3 [3] |
| Systemic | 2 [1] | 0 [0] | 2 [1] |

**Table S9.8. Line listing of participants discontinuing study treatment permanently early due to adverse event(s)**

| | Age (years) randomized | Date stopped treatment | Number of weeks from randomization to stopping treatment | Adverse event(s) (grade) leading to permanent discontinuation of study treatment |
|---|---|---|---|---|
| **Levofloxacin** | | | | |
| 1 | 2.0 | 14jun2022 | 0.7 | rash(3), vomiting(1) |
| 2 | 15.5 | 12dec2021 | 1.4 | acute diarrhea(1), abdominal pain(1), urticaria(1), oedema(1) |
| 3 | 10.5 | 26jan2022 | 10.0 | arthralgia(2), TBC by site - tendonitis(2) |
| 4 | 0.4 | 20apr2021 | 11.6 | vomiting(2), anorexia(1), insomnia(2) |
| 5 | 1.8 | 21jun2021 | 15.4 | anemia- no clinical symptoms(4)* |
| 6 | 4.4 | 01apr2019 | 16.9 | raised ALT(4)** |
| **Placebo** | | | | |
| 1 | 8.9 | 11sep2022 | 20.4 | headache(1), intra-cranial pressure(3) |

* Reported as unlikely to be related to study drug.

** Reported as possibly related to study drug.

**Table S9.9 Line listing of adverse events reported as arthritis / arthralgia / tendinitis of any grade during overall follow-up**

| | Age (years) | Number weeks from randomization to onset | Adverse event description | Relation to study drug | Grade | Number of weeks from randomization to last study treatment dose | Number of weeks from onset of event to resolution |
|---|---|---|---|---|---|---|---|
| **Levofloxacin** | | | | | | | |
| 1 | 3.8 | 0.3 | Musculoskeletal - Myalgia, pain in muscles | unrelated | 1 | 23.9 | 0.3 |
| 2 | 15.2 | 3.0 | Musculoskeletal - Arthralgia, arthritis, pain in joints, arthropathies | possibly | 1 | 23.9 | 5 |
| 3 | 4.9 | 5.0 | Musculoskeletal - Arthralgia, arthritis, pain in joints, arthropathies | possibly | 1 | 23.9 | 1 |
| 4* | 10.5 | 5.1 | Musculoskeletal - Arthralgia, arthritis, pain in joints, arthropathies | probably | 2 | 10 | 6.3 |
| 5* | 10.5 | 5.1 | Tendinitis | probably | 2 | 10 | 7.9 |
| 6 | 4.2 | 7.0 | Musculoskeletal - Myalgia, pain in muscles | unrelated | 1 | 22.9 | 5 |
| 7 | 13.7 | 7.1 | Musculoskeletal - Arthralgia, arthritis, pain in joints, arthropathies | unrelated | 1 | 24 | 2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Placebo** | | | | | | | |
| 1 | 1.0 | 0.1 | Musculoskeletal - Arthralgia, arthritis, pain in joints, arthropathies | unlikely | 1 | 24 | 0.9 |
| 2 | 9.9 | 2.0 | Musculoskeletal - Arthralgia, arthritis, pain in joints, arthropathies | possibly | 1 | 24 | 0.4 |
| 3 | 2.3 | 12.9 | Musculoskeletal - Myalgia, pain in muscles | possibly | 1 | 24.7 | 3.9 |
| 4 | 8.9 | 22.4 | Musculoskeletal - Arthralgia, arthritis, pain in joints, arthropathies | unrelated | 2 | 20.4 | 0.6 |

* Same participant with 2 events.

**Table S9.10 Line listing of adverse events reported as CNS effects of any grade up to 30 days after last study drug dose**

NB. 3 participants in the levofloxacin group and 5 in placebo group had >1 events.

| | Age (years) | Number of weeks from randomization to onset | Adverse event description | Relation to study drug | Grade | Number of weeks from randomization to last study treatment dose | Number of weeks from onset of event to resolution |
|---|---|---|---|---|---|---|---|
| **Levofloxacin** | | | | | | | |
| 1 | 4.8 | 0.7 | CNS - Headache | possibly | 1 | 24.3 | 4.3 |
| 2 | 3.6 | 2.0 | CNS - Headache | possibly | 1 | 24.7 | 0.0 |
| 3 | 15.2 | 3.0 | CNS - Insomnia | possibly | 1 | 23.9 | 5.0 |
| 4 | 6.4 | 3.1 | CNS - Headache | possibly | 2 | 24.0 | 1.4 |
| 5 | 4.0 | 4.0 | Hallucinations | possibly | 1 | 23.6 | 21.7 |
| 6 | 5.0 | 4.3 | CNS - Headache | possibly | 2 | 20.4 | 5.7 |
| 7 | 4.0 | 5.0 | CNS - Dreams, nightmares | possibly | 1 | 23.6 | 3.1 |
| 8 | 0.4 | 9.7 | CNS - Insomnia | possibly | 1 | 11.6 | |
| 9 | 6.4 | 10.0 | CNS - Headache | possibly | 2 | 24.0 | 0.1 |
| 10 | 4.8 | 11.7 | CNS - Headache | possibly | 1 | 24.3 | 0.9 |
| 11 | 4.0 | 12.9 | CNS - Dreams, nightmares | possibly | 1 | 23.6 | 12.9 |
| **Placebo** | | | | | | | |
| 1 | 9.9 | 2.0 | CNS - Headache | possibly | 1 | 24.0 | 0.4 |
| 2 | 14.6 | 2.0 | CNS - Headache | possibly | 1 | 11.6 | 0.6 |
| 3 | 16.9 | 3.7 | CNS - Insomnia | unrelated | 1 | 23.7 | 4.1 |
| 4 | 16.9 | 3.7 | CNS - Headache | unrelated | 1 | 23.7 | 4.1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 | 1.7 | 3.7 | CNS - Epilepsy, fits, convulsions | unrelated | 2 | 6.0 | 0.0 |
| 6 | 4.5 | 3.9 | CNS - Headache | unrelated | 1 | 23.9 | 0.1 |
| 7 | 5.1 | 3.9 | CNS - Headache | possibly | 1 | 23.9 | 0.1 |
| 8 | 3.0 | 4.3 | CNS - Insomnia | unrelated | 1 | 23.9 | 3.9 |
| 9 | 1.7 | 6.0 | CNS - Epilepsy, fits, convulsions | unrelated | 2 | 6.0 | 0.0 |
| 10 | 0.7 | 7.1 | CNS - Insomnia | unrelated | 1 | 23.9 | 0.9 |
| 11 | 5.1 | 7.1 | CNS - Headache | possibly | 1 | 23.9 | 0.1 |
| 12 | 4.4 | 7.3 | CNS - Dreams, nightmares | possibly | 1 | 24.0 | |
| 13 | 9.9 | 7.6 | CNS - Headache | possibly | 1 | 24.0 | 5.1 |
| 14 | 3.7 | 12.0 | CNS - Headache | unrelated | 1 | 19.4 | 0.6 |
| 15 | 8.9 | 14.6 | CNS - Headache | unrelated | 1 | 20.4 | 7.7 |
| 16 | 8.9 | 20.6 | CNS - Intracranial pressure | possibly | 3 | 20.4 | 2.6 |
| 17 | 16.9 | 23.9 | CNS - Headache | unrelated | 1 | 23.7 | 12.1 |

CNS: central nervous system

**Table S9.11 Line listing of adverse events reported as severe rash or cutaneous reactions up to 30 days after last study drug dose**

| | Age (years) | Number of weeks from randomization to onset | Adverse event description | Related to study drug | Grade | Number of weeks from randomization to last study treatment dose | Number of weeks from onset of event to resolution |
|---|---|---|---|---|---|---|---|
| **Levofloxacin** | | | | | | | |
| 1 | 2.0 | 0.4 | Skin - Rash, urticaria | probably | 3 | 0.7 | 11.6 |

**S9.4 Additional safety analyses**

**Table S9.12 Grade 1 or 2 adverse events at least possibly associated with study drug, by body system classification**

| | **Levofloxacin** | **Placebo** | **total** |
|---|---|---|---|
| All participants receiving at least one dose of study treatment | 452 | 469 | 921 |
| **Total number of events [Number of participants with [3] event(s)]** | **96 [66]** | **92 [59]** | **188 [125]** |
| Biochemical | 2 [2] | 7 [4] | 9 [6] |
| CNS | 11 [3] | 7 [5] | 18 [8] |
| Gastrointestinal | 57 [41] | 45 [31] | 102 [72] |
| Hematological | 1 [1] | 10 [6] | 11 [7] |
| Musculoskeletal | 4 [3] | 2 [1] | 6 [4] |
| Oral | 0 [0] | 1 [1] | 1 [1] |
| Other | 1 [1] | 0 [0] | 1 [1] |
| Skin | 17 [13] | 19 [10] | 36 [23] |
| Systemic | 2 [2] | 0 [0] | 2 [2] |
| Upper respiratory | 1 [0] | 1 [1] | 2 [1] |

CNS: central nervous system

**Table S9.13 All Serious Adverse Events (SAEs) up to 30 days after last study drug dose, including related to TB events**

| | **Levofloxacin** | **Placebo** | **total** |
|---|---|---|---|
| All participants receiving at least one dose of study treatment | 452 | 469 | 921 |
| **Total number of SAEs [Number participants with >= 1 event(s)]** | **14 [10]** | **17 [14]** | **31 [24]** |
| Total number of SAEs for TB [Number participants with >= 1 event(s)] | 4 [2] | 7 [6] | 11 [8] |
| Total number of non-TB SAEs [Number participants with >= 1 event(s)] | 10 [9] | 10 [8] | 20 [17] |

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