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Multicentre controlled open randomised clinical trial to assess efficacy and safety of an anti-tuberculosis drug combination based on optimised-dose rifampicin, optimised-dose moxifloxacin and optimised-dose linezolid for TB: the RML-TB trial protocol

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ABSTRACT

Introduction International organisations, scientists and the tuberculosis (TB) community have been advocating for a shorter, safer treatment for drug-susceptible (DS)-TB with equal or better efficacy than current regimens. A promising approach to achieve this is the combination of dose-optimised repurposed drugs.

Methods and analysis The RML-TB trial is a phase IIb, randomised, non-inferiority, controlled, open-label, multicentre clinical trial. It compares an experimental regimen (optimised-dose rifampicin (R) at 30mg/kg/day, moxifloxacin 600mg/day and linezolid (L) 600 mg/day) with the standard fixed-dose combination regimen of R, isoniazid, pyrazinamide and ethambutol. In the experimental arm, L is administered at 600 mg two times per day for 2 weeks, then once daily for 6 weeks. The primary efficacy outcome is the proportion of patients with negative culture at 8 weeks. Sputum samples will be collected at screening visit, randomisation visit and 1 week, 2 weeks, 4 weeks, 6 weeks and 8 weeks post randomisation. The primary safety outcome is the incidence of grade 3–4 adverse events or a change in treatment regimen within 8 weeks. Safety assessment will be done using the Common Terminology Criteria for Adverse Events classification version 5. Participants must be at least 18 years old, with smear-positive, DS pulmonary TB. Exclusion criteria include corrected QT interval (QTc) prolongation, HIV positive status, severely impaired blood counts or the use of QTc-prolonging drugs. The study will enrol 120 patients (60 per arm) over a 2.5-year period across 13 TB units in Spain.

Ethics and dissemination The study was approved by the ethics committee from Vall d'Hebron University Hospital on the meeting held on 18 March 2022 and The Spanish Drug Agency. Patients will provide informed consent and can withdraw from the trial at any time without giving any reason. This decision will not affect their medical care. Data collection is minimal, and analysis will be blinded. Personal data will be restricted to principal investigators or authorised personnel. Results will be shared via the European Union Drug Regulating Authorities Clinical Trials Database (EUDRACT) website and published in an open-source medical journal, guiding future TB clinical trials and treatment development.

Trial registration number EUDRACT number: 2021-001626-22. CTIS: 2023-509075-17-00.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some trials have demonstrated the non-inferiority of short-course treatment for drug-susceptible tuberculosis (DS-TB).

WHAT THIS STUDY ADDS

⇒ Knowledge on safety and efficacy of an anti-TB combination regimen consisting of optimised-dose rifampicin, optimised-dose moxifloxacin and optimised-dose linezolid versus the standard of care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ May serve as the basis for future clinical trials, providing greater knowledge to advance in the task to obtain safe, effective, inexpensive and shortened treatment regimens for DS-TB.

INTRODUCTION

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* complex (MTBC). According to the WHO, there were 10.6 million new TB cases and 1.3 million TB deaths in 2022 (WHO report 2023), making it the leading cause of death from a single infectious agent worldwide.[1]

The current first-line TB treatment was designed more than 40 years ago and remains unchanged to this day. The success rate of the current treatment varies widely depending on the country and patient subgroup. In 2022, treatment success in the WHO European region was 88% for people treated for drug-susceptible (DS) and 63% for people with multidrug-resistant TB (MDR-TB).[1] The standard treatment for DS-TB is a combination of several drugs, including rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E). This combination of drugs provides bactericidal activity based on H and R, and activity against persistent bacilli provided by R and Z (activity in acid medium). The duration of DS-TB treatment varies between 6 months and 18 months, depending on disease burden, location and clinical response to treatment.[2]

A shortened effective treatment against TB could improve patient adherence, resulting in less TB transmission and better TB outcomes, with positive consequences to the resistance development and health system expenses.[3 4] On the other hand, shortening the treatment regimen can reduce the adverse events (AEs), which is important because AEs are responsible for treatment discontinuations.[5] Community engagement and trust in the TB national programmes will be reinforced, increasing the commitment to eliminate TB.

Hepatotoxicity is one of the main challenges of the first-line treatment, since it includes three potent hepatotoxic drugs. Treatment discontinuation due to hepatotoxicity ranges between 5% and 30%.[6] The risk associated with liver damage can be minimised by switching drugs such as H and Z with non-hepatotoxic alternatives.[7] However, new drugs may introduce other AEs. Understanding patients' preferences, along with the intensity, severity and frequency of AEs associated with alternative drugs, can aid in designing more effective drug combination regimens to combat TB.

Monoresistance to H is the most common form of resistance and requires modification of the treatment regimen.[8] Some regions of the world have reported resistance to H in 12–16% of people newly diagnosed with TB.[9 10] The WHO estimates that approximately 8% of people with TB have resistance to H.[11] It is the first step to develop MDR-TB and can compromise the treatment of latent TB. A new treatment combination that could cover both DS and H-resistant TB may improve treatment outcomes and reduce the amplification of acquired resistance to other TB drugs.

R is a cornerstone of first-line TB treatment due to its potent bactericidal and sterilising properties. The standard dose of 10 mg/kg has been effectively used for decades in programme settings. Recent studies have shown that higher doses of R, up to 35 mg/kg, significantly increase the proportion of patients achieving sputum culture conversion after 12 weeks without increasing the risk of severe toxicity.[12–14] The long-term effects of high-dose R, particularly on relapse rates in pulmonary TB, remain to be fully established.[15–17]

Moxifloxacin (M) inhibits the DNA synthesis of MTBC and exhibits high bactericidal activity. The favourable pharmacokinetic (PK) profile of M and the intracellular activity makes it a very attractive drug to use in TB. In fact, it is a key component for the treatment of drug-resistant TB and is part of the shortened 4-month rifapentine-M containing regimen for DS-TB.[5 18] In most studies, M has been administered at a dose of 400 mg per day. However, R decreases M plasma levels, decreasing the 24-hour area under the curve (AUC) 24 by 30%,[19 20] although the clinical significance of this reduction is unknown.[21]

Linezolid (L) has shown potent activity against *M. tuberculosis* both in vitro and in vivo.[22 23] Furthermore, there appears to be a synergistic effect when combined with M.[24] L, at 600 mg every 12 hours administered for long periods, can produce high rates of AEs.[25] When the dose is reduced to 600 mg per day, the AUC/minimum inhibitory concentration (MIC) ratio remains above 100 (considered optimal for its anti-TB activity), and its anti-TB efficacy is not affected in vivo.[26 27] Toxicity, on the contrary, is significantly decreased, even in treatments of more than 20 months.[28] L doses of 300 mg daily have also shown to be effective in patients with MDR-TB, with a very good safety profile.[23] However, recent studies suggested that R may interact with L and decrease its AUC by up to 30%, although the clinical significance of this reduction has not yet been studied.[29–31]

The aim of the manuscript is to describe the key aspects of the RML-TB study protocol, a randomised clinical trial designed to assess the efficacy and safety of a drug combination to treat people with pulmonary TB based on optimised dose of R, optimised dose M and optimised dose L.

METHODS AND ANALYSIS

Study design

RML-TB trial is a phase IIb non-inferiority, multicentre, randomised, controlled, open-label clinical trial comparing a new anti-TB regimen based on optimised dose R, optimised-dose M and optimised-dose L compared with standard of care treatment for 8 weeks in participants with acid-fast bacillus (AFB) smear-positive

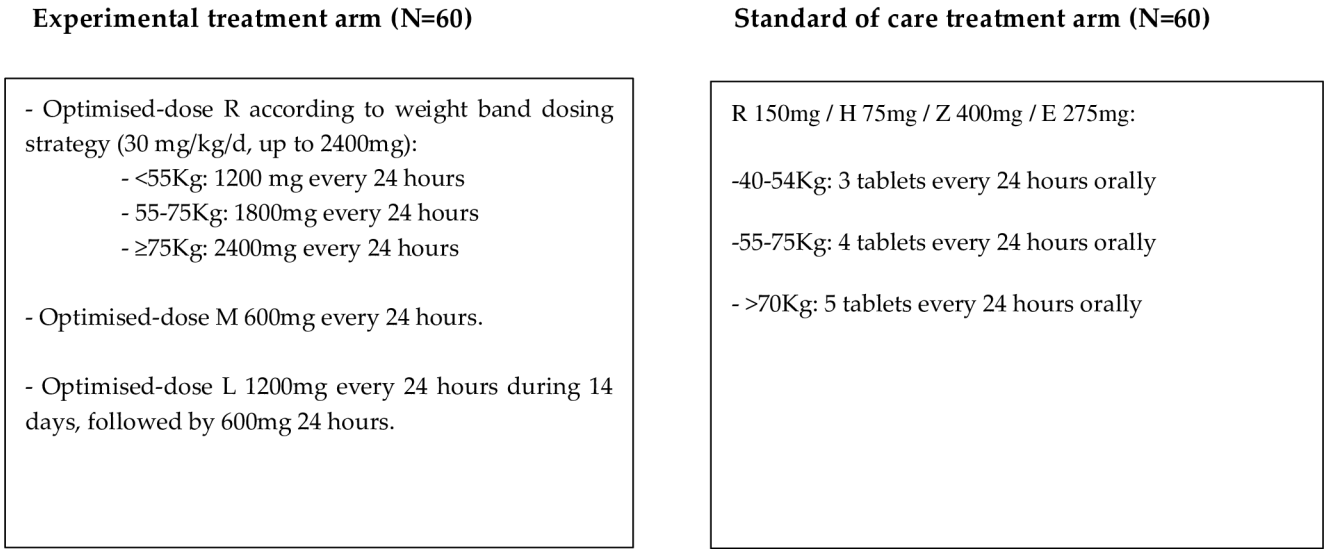

Figure 1 It shows the doses of the different drugs in the two treatment arms. E, ethambutol; H, isoniazid; L, linezolid; M, moxifloxacin; R, rifampicin; Z, pyrazinamide.

DS pulmonary TB (figure 1). Study procedures are summarised in table 1.

Objectives

Primary efficacy objective

To evaluate the proportion of participants with negative sputum culture in liquid media at 8 weeks after randomisation.

Primary safety objective

To evaluate the proportion of participants experiencing Grade 3–4 AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) classification version 5 during the 8 weeks of study participation.

Secondary objectives

1. To assess tolerability, defined as the proportion of participants with any AE.
2. To evaluate the time-dependent decline in sputum smear bacterial load and the time-dependent increase in time-to-positivity () of sputum culture between study arms.
3. To determine the time to culture conversion to negative.
4. To analyse the correlation between the AUC/MIC values for R, M and L with efficacy outcomes.
5. To evaluate quality of life () using the short form 12 health survey questionnaire (SF-12) and St George's Respiratory Questionnaire.
6. To analyse genomic changes in MTBC during the study period in both arms.
7. To conduct a cost-effectiveness study to explore the feasibility of implementing the experimental regimen in national TB programmes.

Substudies

Microbiological evaluation

Sputum samples will be collected from participants on both the screening and randomisation days. If these days coincide, only one sample will be collected. Additional samples will be collected at weeks 1, 2, 4, 6 and 8. We recommend the collection of the overnight sputum the same day of the visit. These samples will be used to compare baseline bacterial load with bacterial load at each specified time point.[32] Bacterial load will be estimated using AFB smear microscopy and TTP in liquid media culture.[33] Time to sputum negativity will also be recorded and compared among interventions for efficacy. All microbiology laboratories will adhere to a shared standard operating procedures.

Drug susceptibility testing will be conducted for R, H, Z, E, M and L using the BACTEC mycobacteria growth indicator tube (MGIT) 960 SIRE Kit and BACTEC MGIT 960 PZA kits. Susceptibility results for M and L will be manually interpreted using TB eXiST software. Critical concentrations are: H 0.1 µg/mL, R 1.0 µg/mL, E 5.0 µg/mL, Z 100 µg/mL, M 0.25 µg/mL and L 1.0 µg/mL.

Whole genome sequencing will be performed on all MTBC isolates (initial and subsequent positive culture samples) from all participants. Bioinformatic analyses will follow the methodology described by Cacino-Muñoz *et al*.[34] Resistance prediction will be performed based on the WHO catalogue of mutations associated with antimicrobial resistance, considering both resistance-associated and predictable variants.[35]

PK and pharmacodynamic analysis

Blood samples will be drawn from participants before taking their daily dose of treatment and at 2 hours, 4 hours and 6 hours post tablet intake, 2 weeks after

Table 1 Scheduled study procedures

	Screening*	Randomisation*	W1	W2	W4	W6	W8
Visit	0	1	2	3	4	5	6
Day	−1 or 2	0	7±2	14±2	28±2	42±4	56±4
Signed IC	X						
Identification card	X						
Medical History	X						
Abuse drugs	X						
Incl./excl. criteria	X	X					
Prior medications	X	X					
Concomitant medication	X	X	X	X	X	X	X
ECG	X		X	X	X	X	X
Barthel	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Physical examination††	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X
Weight (height)‡‡	X	X	X		X	X	X
Symptoms	X	X	X	X	X	X	X
Pregnancy test	X						
Blood count	X§		X	X			X
Biochemical analysis	X§		X	X			X
HIV/C and B hepatitis	X§						
X-ray	X¶						X
Sputum	X[f**]	X[f]	X	X	X	X	X
Dispense study drug		X (TB treatment initiation)		X	X	X	
Drug accountability			X	X	X	X	X
QoL assessment		X		X			X
Cost substudy		X		X			X
PK substudy				X			
Host-related biomarkers	X			X			X
MTB genetic substudy		X	X	X	X	X	X

*The screening and randomisation visits can be performed on the same day.
†We recommend a complete neurological examination, including pin-prick testing and monofilament testing for pain detection thresholds and coin testing for thermal examination for early detection of neuropathy signs.
‡Height will only need to be recorded during the screening visit.
§If the participant has had a blood test within the last 48 hours with the required parameters, there will be no need to repeat them.
¶If the participant has had an X-ray within the last 72 hours, there will be no need to repeat the test.
**[f]If screening and randomisation are performed on the same day, only one sputum sample will be required.
IC, informed consent; MTB, *Mycobacterium tuberculosis*; PK, pharmacokinetic; QoL, quality of life; W, week.

treatment initiation. Serum will be handled, aliquoted, labelled and stored at −80°C at the site facility before being sent to a collaborating laboratory. Concentrations of M, R and L in the experimental arm and H, R, Z and E in the control arm will be measured using high-performance liquid chromatography. PK analysis will employ a Bayesian approach (PK compartment models). Parameters to be calculated include the area under the plasma concentration-time curve over the last 24-hour dosing interval (AUC0-24 or total exposure), the highest plasma concentration observed (Cmax), half-life, volume of distribution, clearance, absorption rate constant, elimination rate constant and time to peak drug concentration. A modified limited sampling strategy (four time points) will be used to predict total exposure, based on excellent prediction adjustment for AUC0-24 with an R^2>95 for R and M.[36–39] This strategy balances cost and complexity while retaining valuable information.

Health economics and QoL analysis

The study will assess both direct and indirect costs, as well as the incidence of catastrophic costs, defined as total TB-related expenses exceeding 20% of the household's annual income prior to the TB episode. Additionally, changes in QoL and respiratory symptoms associated with the study interventions will be evaluated. The capture of the costs related to the TB episode will be based on the WHO handbook survey.[40] QoL will be evaluated using the SF-12 and St George's Respiratory Questionnaire at randomisation, 2-week and 8-week visits.

Assessment of study outcomes

Efficacy assessment

Participants with negative sputum culture results at 8 weeks are defined as follows:

- Participants with positive sputum culture at the screening visit who have a negative sputum culture at 8 weeks post randomisation.
- Participants with positive sputum culture at the screening visit who have no signs or symptoms of active pulmonary TB at 8 weeks post randomisation and are unable to produce sputum samples.

Persistent positive sputum culture (or non-negative sputum culture) participants are defined as

- Participants with positive sputum culture at the screening visit who die of TB progression within 8 weeks of randomisation.
- Participants who modify the study treatment combination for any reason will be considered as having persistent positive sputum culture at 8 weeks post randomisation. A dose reduction of L to 300 mg per day is allowed and will not be considered a treatment modification.
- Participants with temporary suspension due to AEs will be considered treatment failures. Suspensions of less than 3 days for surgical interventions or interventional procedures will not be considered temporary suspensions, and the participant may be evaluated according to microbiological and clinical criteria.
- Participants with a persistent positive sputum culture at 8 weeks post randomisation.

Non-assessable participants

Non-assessable participants are defined as:

- Participants referred to another centre who cannot be evaluated at the recruiting centre.
- Participants lost to follow-up during the study before the 8-week evaluation.
- Participants who die from a cause unrelated to TB or the study treatment within 8 weeks of randomisation.

A data and safety monitoring board (DSMB) has been established to monitor study safety and will evaluate participant records blindly to assign them to a final outcome group if they do not fulfil the protocol definitions. The DSMB will consist of 3 independent experts in TB (one clinician, one epidemiologist and one pharmacist).

Safety assessment

Safety will be assessed by ensuring a standardised evaluation of AEs according to CTCAE version 5.[41] All grade 3 or higher AEs and serious AEs will be for the safety analysis. Tolerability will be measured based on any AE (grades 1–4), treatment dropout rate and any dose reduction.

Subgroup analysis according to adherence to the protocol is shown in table 2.

Study setting

The study will be carried out at 13 different TB units located in Spain. Each centre has previous experience in clinical trials.

Table 2 Analysis populations and endpoints

Assessment	Primary safety	Primary efficacy
Per protocol population	Includes those participants who completed assigned follow-up and were at least 75% adherent to study treatment.	Includes those participants who complete assigned follow-up and were at least 75% adherent to study treatment.
Modified per protocol population	Includes a subset of the per protocol population in which the AEs can be reasonably attributed to the study medication.	Includes those participants who complete assigned follow-up and were at least 75% adherent to study. Participants who die from any cause will be considered as non-negative at 8 weeks post randomisation.
Intention to treat population	Includes all the participants that received at least one dose of assigned treatment.	Includes all the participants enrolled in the study. Non-assessable participants will be considered as non-negative at 8 weeks post randomisation.
Modified intention to treat population	Includes a subset of the intention-to-treat population in which the AEs can be reasonably attributed to the study medication	Includes all the participants enrolled in the study. Non-assessable participants will not be included in the analysis.

AEs, adverse events.

Table 3 Study population and eligibility

Inclusion criteria	Exclusion criteria
1.Age ≥18 years 2.Diagnosis of smear-positive pulmonary tuberculosis by sputum sample Signed IC 4.Negative pregnancy test for women of childbearing age (defined as women who have had menarche and have not yet reached menopause, with the exception of sterile women, including among other situations women with a hysterectomy, women with double salpingectomy and women with double oophorectomy).	1. Recent contact with a person with MDR-TB 2. MDR or mono-resistance to any first-line drugs (except for E) 3. Positive smear microscopy with negative mycobacterial culture 4. Barthel Index <60 or considered by the investigator to have a poor prognosis in the following months 5. Weight <40 kg 6. Treatment with drugs that can prolong QTc in the last month before randomisation for more than 7 days (azithromycin, chloroquine, chlorpromazine, cisapride, clarithromycin, domperidone, droperidol, erythromycin, halofantrine, haloperidol, lumefantrine, mefloquine, methadone, pentamidine, procainamide, quinidine, quinine, sotalol, sparfloxacin, thioridazine, amiodarone) 7. Child-Pugh class C cirrhosis 8. Abuse of illicit drugs according to the investigator's criteria 9. Solid organ or bone marrow transplant recipient 10. Treatment with TNF or other immunosuppressive drugs 11. Patients with oncohaematologic diseases 12. Advanced lung disease according to the investigator's criteria 13. Unstable epilepsy or psychiatric illness 14. History of ischaemic heart disease or severe arrhythmia within the past 6 months 15. Long QTc syndrome or family history of sudden death 16. Patient diagnosed with HIV 17. Breastfeeding women 18. Allergy or intolerance to any of the study drugs 19. History of TB in the previous year 20. Any of the following laboratory abnormalities: (a) AST or ALT>3 times the upper limit of normal; (b) Total bilirubin >3 times the upper limit of normal; (c) Hb <6.5 g/dL; (d) platelets<40 000/mm³; (e) potassium <3.2 mmol/L; (f) eGFR <30 mL/min/1.73 m² 21. Any of the following ECG abnormalities: (a) QTc >0.5 s; (b) other clinically relevant changes in ECG according to the investigator criteria. Treatment with any of the trial drugs for more than 7 days in the last month.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; E, ethambutol; eGFR, estimated glomerular filtration rate; Hb, Haemoglobin; IC, informed consent; MDR-TB, multidrug-resistant tuberculosis; QTc, corrected QT interval; TNF, anti-tumour necrosis factor.

Study population and eligibility

People with pulmonary TB attending each participating TB unit will be assessed against inclusion/ exclusion criteria and be invited to participate in the clinical trial. Detailed inclusion and exclusion criteria are described in table 3.

Recruitment

Participants who meet all inclusion criteria and none of the exclusion criteria and consent in writing to participate will be randomly allocated to one of the two arms (the experimental arm vs standard of care arm). No advertising activities will be performed to attract participants to the sites.

Recruitment is expected to take 34–36 months from the enrolment of the first participant. Monthly online investigator meetings will be held to inform recruitment rates.

Intervention

Randomisation: Randomisation will be performed using a Research Electronic Data Capture (REDCAP) module, with stratification based on cavity presence and sputum

Table 4 Number of tablets according to weight in experimental arm

	<55 kg	55–75 kg	≥75 kg
R (300 mg tablets)	Four tablets	Six tablets	Eight tablets
M (400 mg tablets)	1.5 tablets	1.5 tablets	1.5 tablets
L (600 mg tablets)	One tablet*	One tablet*	One tablet*
Total	6.5 tablets	8.5 tablets	10.5 tablets

*During the first 14 days the participants will receive two tablets of L.
L, linezolid; M, moxifloxacin; R, rifampicin.

smear status. The trial includes the following two interventions:

Experimental arm

- *Optimised R:* dosing will be adjusted according to weight bands, with a maximum dose of 2400 mg/day:
  - *<55 kg:* 1200 mg daily.
  - *55–75 kg*: 1800 mg daily.
  - *≥75 kg*: 2400 mg daily.
- *Optimised M*: 600 mg daily.
- *L*: 1200 mg daily for the first 14 days, then reduced to 600 mg daily.

Figure 1 and table 4 show detailed information according to the weight band.

Standard of care arm (weight band dosing strategy)

Fixed combination tablets: the treatment will prioritise the use of tablets containing a fixed combination of drugs. The most common brand in Spain is Rimstar, which contains:

- R 150 mg.
- H 75 mg.
- Z 400 mg.
- E 275 mg.

The Rimstar dosage per weight band will be:

- *40-54 kg*: three tablets every 24 hours orally.
- *55-75 kg*: four tablets every 24 hours orally.
- *>75 kg*: five tablets every 24 hours orally.

Intravenous treatments: if oral medication cannot be administered, intravenous treatments lasting less than 1 week are permitted.

Treatment Transition: after clinical trial completion, participants will transition to the standard continuation phase according to Spanish national guidelines.

Sample size assumptions and justification

Hypothesis: a non-inferiority hypothesis is established with the lower limit of the 95% CI for the difference in efficacy outcomes set at 7 percentage points. It is assumed that the proportion of patients with a negative culture at 8 weeks post randomisation will be 80% in the experimental arm and 70% in the control arm.[42]

Sample Size: a total of 120 participants, with 60 per group, is calculated, assuming a 5% rate of non-assessable participants. Alpha risk was set at 0.1 and power at 80%. Randomisation will be performed with a 1:1 ratio between study arms, with stratification according to the presence of cavities and bacterial load measured by sputum smear grading.

Statistical analysis plan and monitoring activities

Analysis: the study regimen will be considered inferior to the control arm if the proportion of participants with a negative sputum culture (efficacy outcome) in the experimental arm compared with the control arm after 8 weeks of treatment does not meet the non-inferiority criteria.

Data Collection: a standardised electronic data collection questionnaire (DCQ) will be used. The data management system (Elsevier Macro) complies with all security and protection requirements for clinical trials.

Statistical analysis

- *Descriptive variables:* means and SD or medians and IQRs for continuous variables; frequencies and percentages for categorical variables.
- *Efficacy and safety:* χ^2 test to compare the proportion of patients with culture sterilisation at 8 weeks post randomisation. Absolute risk reduction, relative risk reduction and number needed to treat will be reported, along with their respective CIs.
- *Survival analysis:* Kaplan-Meier curves and Cox proportional hazards regression analysis to study risk factors associated with early sputum culture sterilisation.
- *Bacterial load reduction:* measured as the time it takes for the culture to become positive over time (repeated measures) and correlated with the assigned treatment.
- *Sensitivity analysis:* Based on body mass index, age, sex and Barthel scale.
- *Interim analysis:* an interim analysis is planned when the first 10 participants finish their participation in the clinical trial, focusing on safety outcomes. An additional interim analysis is planned when the first 30 participants finish their participation. Results will be reported for intention-to-treat, modified intention-to-treat, per protocol and modified per protocol analyses.

Monitoring: the monitoring plan includes online and/or on-site monitoring visits, a minimum set of items to monitor. Monitoring activities and communication with the regulatory body will be centralised by Spanish Clinical Research Network (SCReN).

Patient and public involvement

Patients or the public were not involved in the design or conduct of our research.

DISCUSSION

This study is a multicentre, randomised, controlled, open-label clinical trial of non-inferiority design (phase IIb) that aimed at providing knowledge on safety and efficacy of an anti-TB combination regimen consisting of

optimised-dose R, optimised-dose M and optimised-dose L versus the standard of care. Our future ambition is to use the current clinical trial results to leverage the design of a shortened regimen to treat DS-TB.[5 15 43 44]

While regimens containing M and dose-optimised R have shown a more rapid initial decrease in bacterial load compared with the control group, the exact role of M and dose-optimised R in relapse prevention is uncertain.[45] In most of the studies, M has been administered at a dose of 400 mg daily; however, R reduces the plasma levels of M, resulting in a 30% reduction in AUC24.[12 46] In our study, we will administer high doses of M, taking into account the interactions between R and M. Furthermore, the combination of L and M has been shown to exhibit synergistic effects in vitro against clinical isolates from both MDR and non-MDR TB patients.[24 47]

Moreover, previous PK/pharmacodynamic (PD) studies suggest that a daily dose of 300 mg of L is both effective and safe.[48 49] However, the interaction between L and R represents a challenge. Co-administration of R has been shown to significantly reduce L's AUC and Cmax values by an average of 32% and 21%, respectively. This interaction is likely due to R's induction of P-glycoprotein, which increases the intestinal secretion and clearance of L.[30] To mitigate this effect, we have decided to maintain an L dose of 600 mg per day.[50]

We have decided to use optimised doses of L at 600 mg every 12 hours during the first two weeks when the bacterial load is higher to take advantage of its bactericidal effect, followed by 600 mg daily until the end of the study to avoid associated toxicity. This strategy of reducing the dose of L after an initial period has been successfully implemented in other studies.[51]

From a public health perspective, it is important to highlight that this drug combination, if effective, could address both DS-TB and H-resistant TB. One of the possible threats associated with a new treatment regimen is the amplification of resistances to the drugs composing the treatment. *De novo* resistance to fluoroquinolones is both rare and generally low.[52] Furthermore, the proposed drug combination is based on repurposed drugs with expired intellectual property protection, available at a fair and affordable price.

However, if we are able to demonstrate the non-inferiority of our regimen, resistance to R and fluoroquinolones should ideally be ruled out before starting the treatment, at least genotypically. Molecular rapid testing has shown a sensitivity of between 80-90% and specificity (Sp) over 98% to detect R resistance.[53] For fluoroquinolones, the sensitivity for M is 87% and the Sp is 91%, while for levofloxacin they are 84% and 98%, respectively.[53] One limitation of the proposed regimen is the lack of rapid molecular testing to detect L-associated resistance.

Lastly, it should be noted that this is a phase IIb study, and phase III research must be conducted before any changes in clinical practice can be widely recommended.[32] As preliminary efficacy and safety evidence of this new regimen becomes available, interest might increase worldwide, making it easier to obtain funding for the next development stages.

Strengths and weaknesses of the design

Strengths

The study proposes a novel regimen using optimised doses of repurposed drugs with both early bactericidal and sterilising activity. The proposed drug combination is expected to cause less liver toxicity, a major reason for treatment discontinuation, and can be used to treat H-resistant TB, which is not always detected by current rapid molecular assays in low- and middle-income countries and contributes to further resistance amplification. The results of this trial may guide future clinical trials aiming to shorten TB treatment with an inexpensive and readily available drug combination, addressing the main limitation of the 4-month first-line treatment based on optimised doses of rifapentine and M.[54]

Limitations

The open design of the study may introduce biases, though blinding is challenging due to the nature of the drugs and budget constraints. The 7% non-inferiority margin was selected to balance sample size, acquisition of scientifically sound data and ensure participants' safety. Correlation between the 2-month culture status and relapse-free survival during follow-up has not been demonstrated. Self-administered treatment is chosen due to high adherence rates at the participating TB units, with directly observed treatment offered only to participants with risk factors for poor adherence. QTc prolongation due to optimised M dosing will be closely monitored with frequent ECGs. R may reduce M and L exposure, and a PK/PD study may help refine the regimen further.

Ethics and dissemination

IC

All patients included in the study will receive IC both orally and in writing, with written consent obtained in duplicate. Participants will have the right to withdraw from the study at any time without any impact on their medical care and without providing an explanation.

Data collection and protection

Only the minimum necessary data will be collected to fulfil the study objectives, using a coding system for identification. Data will be anonymised for the analysis team and the DSMB, and pseudoanonymised for the rest of the team. Only study investigators and/or authorised personnel will have access to the complete dataset. Participant data will be handled according to current European and national data protection regulations. The databases will meet rigorous security requirements, including a logging system to track access and modifications. Research data will be retained by the institutions

for the duration mandated by applicable regulations. SCReN acts as an External Contract Research Organization and will audit and monitor the trial. The monitoring plan will include an opening visit, a mid-term visit and a final/closing visit. Study personnel will receive training in Good Clinical Practice.

Sharing of trial findings

Both primary results (safety and efficacy) and secondary outcomes will be summarised in the final report and submitted to regulatory authorities and ethics committees. Additionally, the clinical trial results will be summarised in a scientific manuscript and submitted for publication.

Participant and public engagement

No structured community engagement was conducted during the design of this trial. At the end of the trial, engagement with TB community advisory groups will occur to discuss study results and ensure the outreach and impact of the findings.

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Ethics approval This study involves human participants and the study was approved by the ethics committee from Vall d'Hebron University Hospital on the meeting held on 18 March 2022 and the Spanish Drug Agency (AEMPS, Spanish

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