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DRTB-HDT: a randomized controlled trial of two adjunctive host-directed therapies in rifampin-resistant tuberculosis

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Abstract

Background Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide. Current TB treatments are inadequate, requiring participants closely adhere to multi-drug regimens that are long, complex, and often poorly tolerated. In addition to these well-recognized shortcomings, current TB treatments, particularly those for rifampicin-resistant tuberculosis, leave a majority of cured participants with permanent, clinically significant lung impairment and radiographic evidence of bronchiectasis and fibrosis. This project will determine if two adjunctive host-directed therapies (HDTs) can prevent these poor outcomes.

Methods Three hundred thirty participants with RIF-R TB and baseline risk factors for poor outcome will be enrolled in a randomized, controlled, 3-armed multi-centre trial, with clinical sites in Romania, Moldova, Georgia, Mozambique, and South Africa. All participants will receive standard multidrug therapy according to national guidelines. Those participants randomized to the experimental arms will in addition receive either CC-11050 (dovramilast) or metformin. Co-primary efficacy endpoints will examine effects on lung function (measured by spirometry) and infection (measured as time to stable sputum culture conversion). A sub-study will examine quantitative change in lung radiodensity by CT scan.

Discussion These selected host-directed therapies candidates represent two complementary strategies: reducing inflammation vs inducing host cell anti-microbial activity, respectively. Both candidates are supported by data from preclinical and clinical studies. If successful, this ground-breaking project will increase Europe's capacity to control drug resistant tuberculosis by developing new treatments that increase the likelihood of cure and reduce the risk of life-long disability.

Trial registration EudraCT Number: 2020–004295-18. South African National Clinical Trial Registration (SANCTR) Number: DOH-27–042021-8345.

Keywords Tuberculosis, Drug Resistant Tuberculosis (DR-TB), Rifampicin-resistant tuberculosis (RR-TB), Host-directed therapies, Clinical trial, Metformin, Dovramilast (CC-11050)

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Administrative information

Note: the numbers in brackets in this paper refers to the SPIRIT checklist item numbers. The order of the items were modified according to the group similar items (see https://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	A phase 2 randomized, controlled trial of two adjunctive host-directed therapies in rifampicin-resistant tuberculosis.
Trial registration {2a and 2b}	Trial is registered at: 1. South African National Clinical Trial Registration (SANCTR) Number: DOH-27–042021-8345 Registration authorized on: 21 APR 2021 2. European Union Drug Regulating Authorities Clinical Trials Database EudraCT Number: 2020–004295-18 Registration authorized on: 21 NOV 2022 3. Clinical Trials Information System – EMA – European Union EUCT Number: 2025–520745-80–00 Registration authorized on: 30 JAN 2025
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Role of sponsor {5c}	The Sponsor (The Aurum Institute) has no ownership or intellectual property interest in either of the two trial interventions. Prof. Robert Wallis, MD, is the project leader and acts as main investigator of the CT. He conceived the CT in collaboration of the other authors as reported in names and roles of protocol contributors. The Swiss Tropical and Public Health Institute serves as Coordinator of the H2020 funded project under Grant Agreement (GA) 847465). The funders of the CT have had no role in the study design, collection, management, analysis and interpretation of the data. The funder recommends the submission of protocol for publication encouraging the Open Science publication.

Introduction

Background and rationale {6a}

Four hundred thousand cases of rifampicin-resistant tuberculosis (RR-TB) occurred worldwide in 2023, directly resulting in 150,000 deaths [1]. RR-TB participants must closely adhere to multi-drug treatment regimens that are complex and require several months depending on the regimen. Despite major improvements in regimens for RR-TB in the last five years, only 63% of participants who began RR-TB treatments worldwide in 2020 were cured [1]. Even if cured, pulmonary tuberculosis leaves a majority of participants with permanent, clinically significant lung impairment and radiographic evidence of bronchiectasis and fibrosis, regardless of drug susceptibility [2–5]. RR-TB participants are at greatest risk of these residual defects [6, 7]. This presumably reflects delayed eradication of infection and delayed resolution of pulmonary inflammation. The resulting disability reinforces poverty, shortens longevity, and increases mortality due to pneumonia and other non-TB infections [8, 9].

We planned a randomized, controlled, multicentre trial in participants with RR-TB, intended to test if host-directed therapy (HDT) can avert poor outcomes by augmenting the antimicrobial activity of host phagocytic cells and accelerating eradication of infection, and/or by reducing lung inflammation and preventing permanent loss of function. TB-HDT has a long and perhaps checkered history, dating to claims by Koch in 1890 for the therapeutic use of tuberculin. In 2014, a ground-breaking two-day international workshop jointly sponsored by US NIH and the Bill and Melinda Gates foundation (BMGF) helped transform the field, taking inspiration from the remarkable advances in cancer immunotherapy of the past decade. The workshop identified potential cellular targets and molecular

candidates for TB HDTs and charted clinical and regulatory development pathways. Some of the proposed candidates were drugs already approved for other indications. The large existing safety and pharmacology databases for these drugs expedited their clinical evaluation for tuberculosis. The primary publication from the workshop proposed that candidates could be generally classified into two broad categories: those that induced anti-microbial activity in host phagocytic cells, and those that reduced inflammation or targeted specific mechanisms resulting in tissue destruction [10]. The two interventions chosen as investigational products in the current trial (metformin and dovramilast) fall into each of these two categories.

Metformin, a biguanide AMPK activator, is the most widely prescribed drug globally for treatment of type 2 diabetes mellitus. In 2014, Singhal reported that metformin reduced Mycobacterium tuberculosis (*Mtb*) growth in macrophages, and reduced pulmonary immune pathology and enhanced the efficacy of conventional antimicrobials in *Mtb*-infected mice [11]. A study using a mouse model of bleomycin-induced lung fibrosis found metformin accelerates the resolution of established fibrosis by promoting the deactivation and apoptosis of myofibroblasts [12]. Fibrosis is an important underlying factor leading to permanent lung function impairment. These preclinical studies indicate metformin is likely to have important additional effects to protect lung structure and preserve lung function. Diabetes increases TB risk and likely increases the risk of poor TB treatment outcome [13, 14]. Three retrospective studies in nearly 10,000 diabetic participants found that metformin reduced the risk of TB compared to other diabetes treatments [15–17]. Three retrospective studies have found a clinical benefit of metformin vs other diabetes treatments in persons with TB and diabetes, reducing the risk of cavitary disease at diagnosis, and that of death or other poor treatment outcome [11, 18, 19].

Dovramilast (CC-11050) in *M. tuberculosis* infected mice down-regulates genes in multiple inflammatory networks, including those associated with IL-17, IL-23, and NFkB. CC-11050 accelerates the clearance of *Mtb* from the lungs when added to isoniazid therapy in chronic infection models in mice and rabbits [20, 21]. In rabbits, CC-11050 similarly reduces the number and size of sub pleural lesions. In a phase 2 TB-HDT study, 40 HIV-negative participants with moderate or far advanced rifampicin-susceptible tuberculosis (RIF-S-TB), receiving 200 mg CC-11050 for the first 4 months of rifabutin-substituted standard treatment, resulted in improved recovery of FEV1 at month 6 compared to controls, and a trend toward earlier culture conversion was also apparent [22].

Objectives {7}

The primary objective of the trial is to examine the safety, tolerability, and preliminary efficacy of two adjunctive TB-HDTs, metformin and dovramilast (one antimicrobial, and one anti-inflammatory) in participants with rifampin-resistant pulmonary tuberculosis. Efficacy endpoints include measures of recovery of lung function and eradication of *M. tuberculosis* infection.

Trial design {8}

This Phase 2 trial is a randomized, open-label, 3-arm, parallel group trial in RR-TB participants with moderately advanced or far advanced pulmonary disease defined by chest X-ray. A total of 330 participants will be recruited at eight trial sites. Willing participants providing informed consent will undergo screening evaluations to establish eligibility. Participants meeting all the inclusion and none of the exclusion criteria will be randomly assigned to one of three treatment arms, two experimental and one control, within 14 days after starting screening. All participants will receive a full course of the standard treatment for RR-TB administered per established standard of care including directly observed therapy (DOT), video-observed therapy (VOT), video supported treatment (VST) or community-based directly observed therapy (CB-DOT). Those randomized to an experimental arm will concurrently receive adjunctive HDT during the first 6 months of therapy. Participants living with HIV-1 being on antiretroviral therapy (ART) will continue ART. Those not on ART will start ART during the period of study participation. All participants will undergo safety and efficacy assessments no less than monthly, during the study treatment period.

Methods: participants, interventions and outcomes

Study setting {9}

The study is conducted at the following settings: 1. Institutia Medico-Sanitara Publica—Institutul de Pneumologie"Chiril Draganuic"Chisinau, R. Moldova; 2. National Center for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia; 3. Institutul de Pneumoftiziologie Marius Nasta, Bucharest, Romania; 4. Instituto Nacional de Saúde, Marracuene, Mozambique; 5. WITS Health Consortium (PTY), Johannesburg, South Africa; 6. Clinical HIV Research Unit, Sizwe Tropical Disease Hospital, Sandringham, Johannesburg, South Africa 7. Clinical HIV Research Unit, King Dinuzulu Hospital, Durban, South Africa; 8. Isango Lethemba TB Research Unit, Gqeberha, South Africa 9. The Aurum Institute NPC, Tembisa Hospital, South Africa.

Eligibility criteria {10}

Inclusion criteria

Willing to consent, adolescents and adults, 16–65 years old, with Xpert (MTB/RIF or Ultra) and subsequent culture confirmed pulmonary TB and with chest radiograph meeting National TB Association criteria for moderate or far advanced pulmonary tuberculosis; HIV-1 seronegative, or if HIV-1 seropositive, presenting to an African study sites (HIV + participants only enrolled at African sites) with a CD4 T cell count > 100/μl, and either currently receiving ART or willing to start ART during study participation.

Exclusion criteria

Presence of major comorbid conditions which by judgment of the investigator can be a reason of death during trial; RR-TB treatment for > 14 days in the past 12 months prior to randomization; Weight in light clothing < 30 kg; Current pregnancy, breastfeeding or planning pregnancy; Major alterations in laboratory parameters taken prior to randomization; Current treatment with Malaria, requiring treatment with drugs that are strong CYP3 A4 inducers or inhibitors, carbonic anhydrase inhibitors, or OCT2 or MATE inhibitors and co-treatment in the last 28 days prior to randomization, or planned treatment over the course of the trial with systemic corticosteroids; History or clinical record of sensitivity, asthma or allergy that could be attributed to experimental drugs; History or clinical record suggestive of unstable diabetes mellitus that required hospitalization for hyper- or hypo-glycaemia within the past year prior to start of screening, or requiring treatment with metformin; SARS-CoV-2 PCR or antigen test positive during randomization.

The detailed list of inclusion and exclusion criteria described in Table 1.

Who will take informed consent? {26a}

Eligible individuals will be invited to attend the research clinics by recruiters at different sites to obtain IRB/LEC approved informed consent and further assessment of eligibility. Only trained research staff eligible by local regulations will obtain informed consents.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Additional consents are provisioned for the collection and storage of biological specimens for future studies.

Interventions

Explanation for the choice of comparators and intervention description {6b, 11a}

This study will be conducted as a prospective, randomized, controlled, open label, multi-centre trial with 3 parallel arms (2 experimental and 1 control). Newly diagnosed, pulmonary TB participants after enrolment will be randomized at a 1:1:1 ratio (Fig. 1). Randomization will be performed using an online system, stratified according to study site and radiographic extent of disease. All participants will receive recommended treatment for RR-TB according to country specific and WHO guidelines [23]. Participants assigned to one of the two experimental arms will additionally receive either metformin or CC-11050 for the first 6 months.

Efficacy assessments will include measures of lung function and eradication of *M. tuberculosis* (*Mtb*) infection. These assessments will continue through month 18. TB treatment may continue to month 18 or beyond if indicated by national RR-TB treatment guidelines. Participants living with HIV on ART at the time of study entry will continue on ART. The timing of ART initiation for those not yet on ART will depend on baseline CD4 count: day 28 for participants with CD4 + T cells 101–219/μl, and day 56 for those with CD4 ≥ 220/μl, according to CDC/NIH/IDSA guidelines [24].

Criteria for discontinuing or modifying allocated interventions {11b}

Treatment interruptions

Generally, participants experiencing grades 1 and 2 toxicities may continue treatment, at the discretion of the site investigator with careful follow-up, whereas participants experiencing grades 3 and 4 toxicities generally will have study drugs held until signs or symptoms have resolved (or until ≤ Grade 2). Study drugs may be permanently discontinued at the discretion of site investigator. Site investigators will discuss discontinuations and reintroductions of study treatment with the International PI to ensure consistency. Missed TB drug doses will be replaced as per local guidelines.

Discontinuation and withdrawal criteria

Participants are free to withdraw from participation in the study at any time upon request and an investigator may terminate participation in the study.

Most participants will enter this trial based on a rapid molecular test indicating RR-TB. The possibility exists for participants to be enrolled whose baseline cultures fail to show growth of RR *Mtb*. A formal review of baseline *Mtb* culture and drug susceptibility test results will occur on day 84, with a window of ± 6 weeks depending on the time of availability of these results. At this time, the PI will ascertain if baseline cultures will confirm RR-TB. Participants whose cultures do not confirm RR-TB will be excluded from the mITT and PP populations and they may also be excluded from further trial participation if that would be in their best

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Aged 16 to 65 years	Any condition for which participation in the trial, as judged by the investigator, could compromise the well-being of the subject or prevent, limit or confound protocol specified assessments
Able and willing to provide signed written consent or witnessed consent in the case of illiteracy, prior to undertaking any trial-related procedures. In the case of children 16 or 17 years of age, consent of at least one parent or guardian plus assent of the child will be required	Current or imminent (within 24 h) treatment for malaria.
Body weight (in light clothing without shoes) between 30 and 90 kg	Pregnant or breastfeeding/lactating, or with pregnancy planned in the next 9 months NB: urine or serum pregnancy testing may be performed, according to local practices and/or ethics requirements.
Positive sputum Xpert (TB/RIF or Ultra) with subsequent culture confirmation	Is critically ill, such that in the judgment of the investigator, death during the trial is likely.
RIF resistance diagnosed by Xpert OR Hain test OR phenotypic drug susceptibility test	TB meningitis or other forms of severe TB with high risk of a poor outcome as judged by the investigator.
No more than 14 days of RR-TB treatment for this TB episode, provided that a pre-treatment sputum culture can be accessed for study purposes	History of allergy or hypersensitivity to any of the trial therapies or related substances
Chest radiograph meeting National TB Association criteria for moderately advanced or far advanced pulmonary tuberculosis [1]	Having participated in other clinical trials with investigational agents within 8 weeks prior to trial start or currently enrolled in an investigational trial.
If sexually active, and if female of childbearing potential, willing to use effective contraceptive methods for at least the first 9 months of study participation	Prior RR-TB treatment in the preceding 12 months (other than in the 14 days prior to randomization)
HIV-1 seronegative, OR if HIV-1 seropositive, presenting to an African study site with a CD4 T cell count > 100/μl and either currently receiving ART or willing to start ART	Cardiac arrhythmia requiring medication, or any clinically significant ECG abnormality, in the opinion of the investigator
NB: HIV + participants will only be enrolled at African sites	Participants requiring treatment with drugs that are strong CYP3 A4 inducers or inhibitors (eg, ketoconazole, lopinavir, or cobicistat), carbonic anhydrase inhibitors (eg, acetazolamide), or organic cationic transporter-2 (OCT2) and/or multidrug and toxin extrusion (MATE) inhibitors (eg, cimetidine, pyrimethamine).
	Use of systemic (oral or parenteral) corticosteroids within the past 28 days.
	History of unstable Diabetes Mellitus that required hospitalization for hyper- or hypoglycaemia within the past year prior to start of screening, or requiring treatment with metformin.
	Subjects with any of the following abnormal laboratory values: a. creatinine > 2 mg/dL b. haemoglobin < 8 g/dL c. platelets < 100 × 109 cells/L d. serum potassium < 3.5 IU/L e. alanine aminotransferase (ALT) ≥ 2.0 × ULN f. alkaline phosphatase (AP) > 5.0 × ULN g. total bilirubin > 1.5 mg/dL h. positive hepatitis B surface antigen i. random blood glucose > 140 mg/dL (7.8 mmol/L) j. positive SARS-CoV-2 PCR or antigen test

interests (*ie*, if continued participation would represent an unfavourable risk–benefit balance). At the request of the site PI, such cases will be reviewed and will be subject to approval by the International PI. The total study enrolment will be also increased by 1 to account for each participant removed under these circumstances. The added participant will undergo randomization, and need not enter the same treatment arm or be enrolled at the same site as the participant removed.

Any discontinuation or withdrawal will be properly documented.

Relevant concomitant care permitted or prohibited during the trial {11 d}

Use of concomitant medications will be reviewed and recorded at baseline and at each follow-up visit. These will include drugs for RR-TB treatment, HIV ART, and

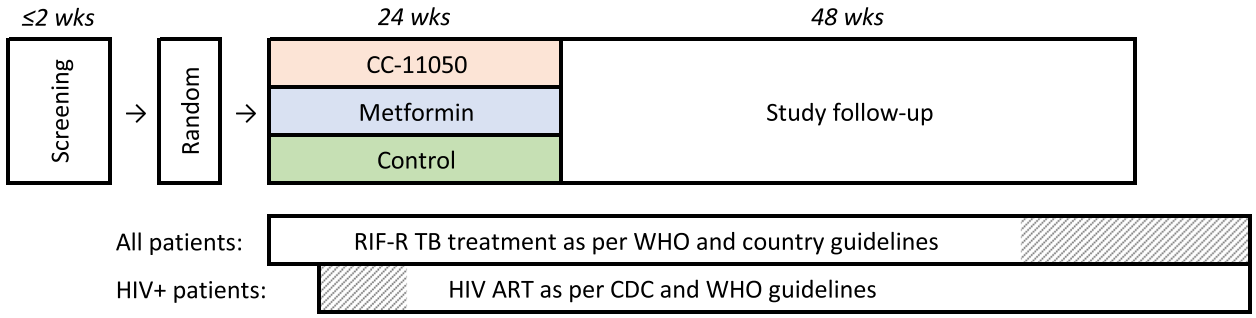

Fig. 1 Study Schematic. RR-TB treatment may continue past week 72 if indicated by national policies. HIV + patients already on ART at the time of randomization will continue on ART. Participants enrolled during the final 18 months of the project funding period will have their final study visit (nominal month 18) during the final 1–2 months of funding

trimethoprim-sulfamethoxazole (or other) prophylaxis for HIV-related opportunistic infection.

Metformin will be temporarily suspended for any surgical procedure (except minor procedures that do not require restricted intake of food and fluids) and will not be restarted until the participant's oral intake has resumed and renal function has been evaluated as normal. A similar approach will be taken if participants coincidentally develop manifestations of sepsis or other critical illness from any cause. Use of metformin will be temporarily suspended if radiological studies involving intravenous iodinated contrast materials are advised for any trial participant, due to potential effects of iodinated contrast on renal function. Metformin will be temporarily discontinued prior to the procedure and restarted no sooner than 48 h after the procedure and only when renal function has been re-evaluated and found to be normal. This protocol includes a CT scan sub-study. These scans will be performed without iodine contrast, to mitigate potential concerns regarding iodine effects on renal function.

Renal elimination of metformin occurs due to membrane-bound cation transporters (OCTs) and multidrug and toxin extrusion transporter (MATEs). A number of commonly used drugs may inhibit the activity of these transporters. Caution is advised for concomitant use of furosemide, nifedipine or cationic drugs eliminated by renal tubular secretion (amiloride, digoxin, morphine, procainamide, quinidine, qui-nine, ranitidine, triamterene, trimethoprim, or vancomycin). Although the effect of any single one of these medicines on metformin elimination may be modest, effects may accumulate if multiple drugs are administered. Of these drugs, study participants are most likely to have trimethoprim (in cotrimoxazole) as a conmed.

Hormonal contraceptives (oral or parenteral) may be used to meet the requirement for contraceptive use during the period of study participation. Use of effective contraception is a requirement for enrolment if study participants are sexually active and of childbearing potential or if their sexual partners are women of childbearing potential.

Efavirenz, dolutegravir, and NRTIs are permitted. All class A-C drugs for treatment of RR-TB are permitted. Rifabutin is permitted (only for participants with *M tuberculosis* isolates demonstrated to be rifabutin susceptible).

Gatifloxacin is prohibited in participants receiving metformin, as gatifloxacin can cause hypoglycaemia. Other fluoroquinolones appear to have a reduced risk of hypoglycaemia.

Ketoconazole, lopinavir, cobicistat, and other strong CYP3 A4 inhibitors, are prohibited in participants receiving CC-11050 or bedaquiline, both of which are metabolized by CYP3 A4.

Strategies to improve adherence to interventions {11c}

Participants will be counselled regarding the importance of following the instructions for medication dosing, including the time of day and ingestion with food. Participants will be counselled regarding potential side effects and the circumstances under which study drugs should be discontinued. Self-reported adherence will be assessed and reinforced at every scheduled participant contact.

Study drugs will be dispensed in numbers sufficient for 1 additional week beyond the next scheduled visit. In the case of planned travel or other circumstances, additional study drug may be dispensed. At each follow up visit, the participant will return all unused tablets to the pharmacy. A pill count will be done, and returns are entered on an accountability log. The number of remaining tablets is counted at each visit with the exception of the day 2 visit. If the pill count does not match the prescribed use, participants will be questioned regarding the reason and receive intensified counselling. If participant does not

return their study drug containers, this will be followed up by the site and feedback tracked by pharmacy.

CC-11050 and metformin tablets will be counted for participants assigned to those treatment arms. Fluoroquinolone tablets (moxifloxacin or levofloxacin, or if necessary, a designated alternative) will be counted for participants in the control arm.

Provisions for post-trial care {30}

Provision for post-trial care ordinarily refers to the continuation of a beneficial treatment in a study of a chronic condition requiring extended or indefinite treatment. In this trial, it may be considered relevant for those individuals requiring RR-TB treatment of a duration greater than the period of trial participation. In such cases, continuation of TB treatment will be ensured by referral to and communication with the local TB control programs that have provided TB treatment during the period of trial participation. As much as the objectives of the trial are to assess HDT effects on the microbiologic and pulmonary outcomes of TB treatment, effects of HDT administered after the conclusion of TB treatment are not within the scope of the study.

No-fault trial insurance is arranged by the Sponsor meeting the requirements outlined by the Association of the British Pharmaceutical Industry. In case of an injury occurring to the participant during the CT, the participants will be provided with free medical management as long as required or until such time it is established that the injury is not related to the CT.

There is also potential for incidental findings (IF) concerning individual trial participants since the planned clinical evaluations, including physical examinations, clinical laboratory tests, chest X-rays and pulmonary function tests far exceed the standard of usual care for TB participants in the local communities. If such finding are determined by study staff to possibly warrant additional investigation or treatment, they will notify the participant without delay and, with permission from the participant, ensure referral to the appropriate community provider (eg, public health clinic) as indicated by the nature of the incidental finding.

Outcomes, plans for assessment and collection of outcomes {12, 18a}

Primary endpoints

The study will have 2 co-primary endpoints. Both endpoints must be met for a treatment to be considered successful. The CC-11050 and metformin arms will each be compared to the control arm in the analysis.

The first co-primary endpoint will assess lung function, as the 1-s forced expiratory volume (FEV1) at month 6, expressed as a percent of its predicted value based on age, sex, height, and race (FEV1%).

The second co-primary endpoint will assess eradication of infection, as the hazard ratio of time to stable culture conversion during treatment (HR-SCC). Time to stable culture conversion will be defined as the time from treatment initiation to the first of two sequential cultures of sputum obtained at least two weeks apart that fail to show growth of *Mtb* in liquid (MGIT) and solid (LJ) medium. The endpoint will first be assessed by a non-inferiority comparison vs the control arm, to test that HDT does not delay the response to standard RR-TB treatment. If criteria for non-inferiority are met, a superiority comparison will follow.

Rationale FEV1 is an independent predictor of all-cause mortality in the general population [9]. It is the most widely used single measurement to assess disease progression or response to treatment in persons with chronic obstructive pulmonary disease (COPD), with a change of 100 ml described as the minimal clinically important effect [53]. FEV1 is also an important determinant of pulmonary disability in COPD. TB causes permanent loss of FEV1 [4, 6, 8]. The magnitude of the loss correlates with the radiographic extent of disease and volume of sputum produced at diagnosis [3]. Although other spirometric parameters are also affected post-TB, only FEV1 shows a relationship to initial burden of disease [3]. Our preliminary data from the Gates TB HDT study in participants with RIF susceptible (RIF-S) TB indicate FEV1% is the most sensitive measure of HDT effects on lung function. This endpoint will be evaluated as a superiority comparison vs control. The depth and breadth of knowledge regarding FEV1 as a clinical biomarker of lung disease gives us confidence that effects seen in TB will translate to clinically significant long-term outcomes.

HR-SCC has been proposed by Profs Davies and Wallis as the endpoint with greatest statistical power to detect a treatment-shortening benefit of new MDR-TB regimens. Its main shortcoming is that only limited data are available to predict the likelihood of successful treatment shortening based on HR-SCC, with one study finding that a value of 1.17 was insufficient to support a 4-month regimen, and a second finding that 1.3 was sufficient.

Secondary endpoints

Secondary efficacy endpoints include other measures of lung function and *Mtb* infection:

1. FEV1 and FVC at 2, 6, 12 and 18 months
2. FEV1 and FVC slope over time

3. Proportions of participants with negative sputum cultures after 2 and 6 months of treatment
4. The proportion of participants with new TB drug resistance
5. The proportion of participants whose treatment is considered unsuccessful due to failure, relapse, or death (individually and in total)

Rationale Spirometry will be performed at multiple time points during and after treatment to broadly assess changes in respiratory function over time. This will assess the extent to which HDT benefits are sustained after treatment is stopped, as they appear to be in the Gates TB-HDT study. Summary measures of these endpoints over time will include slope and random effects modelling. Secondary microbiologic efficacy endpoints will include culture status after 2 and 6 months of treatment, and the proportions of participants whose treatment is unsuccessful (i.e., who experience treatment failure, relapse, or death, with or without acquisition of new resistance).

Secondary safety and tolerability endpoints:

6. Treatment-emergent serious adverse event (TE-SAEs), categorized according to severity, treatment relatedness, and leading to early withdrawal
7. Quantitative and qualitative clinical and laboratory safety measurements, including observed and change from baseline
8. Proportion of participants with disease exacerbation (paradoxical reactions or IRIS)

Exploratory endpoints:

1. Lung radiodensity by chest CT, measured at baseline and month 4
2. PK/PD analysis based on sparse sampling

Rationale The endpoint will be measured by computed tomography CT and analysed centrally using MIM software. Prof. Wallis personally evaluated this endpoint in the Gates TB-HDT study, and will do so in this trial. Quantitative CT will be conducted as a sub-study, at sites with CT capability, and in participants providing additional consent for this procedure. Sparse PK sampling will be performed to examine the relationship of drug exposure to clinical outcomes.

Participant timeline {13}

The schedule of events with planned visits and study procedures can be found in the full protocol included in the supplementary materials.

Sample size {14}

Power calculations are done for each of the two co-primary endpoints to define final sample size.

1. FEV1% at month-6 will be measured by ANCOVA in a superiority comparison to control. We found baseline FEV1% to be an important predictor of change to month 6 in the Gates TB HDT study, with $R = -0.5173$ across all 5 arms. The negative value indicates that higher baseline FEV1% values were associated with smaller improvements during treatment. In this situation, the statistical power of the endpoint increases with the correlation to baseline values. Borm et al. described a method to calculate statistical power using ANCOVA, based on the sample size (N), the square of the correlation between baseline and final values (R2), treatment effect size to be detected, and alpha [25]. Figure 2 shows power calculations using this method. A study with 73 evaluable participants per arm would have 80% power to detect a difference vs control in FEV1% of 6%, as we observed in 2 arms of interest in the Gates TB HDT study. This estimate is a conservative one, in that it does not include any additional precision conferred by the proposed 2 baseline measurements on days 1 and 2.
2. HR-SCC

Power calculations for this endpoint are shown in Fig. 3. Trial simulations indicate that with 100 evaluable participants per arm, and delta $= 0.15$, non-inferiority (NI) could be demonstrated with 80% power at a hazard ratio of 1.36 (left panel); this is similar that observed in the CC-11050 and everolimus arms in the Gates TB HDT study [22]. Delta in this case indicates the maximum deleterious effect on HR-SCC that would be considered acceptable as a trade-off for improved lung function. If delta is reduced to 0.125, the HR for 80% power increases modestly to 1.40. If we are able to demonstrate NI, we will proceed to a superiority comparison (right panel). These simulations indicate that with 100 evaluable participants per arm, the study would have 80% power to detect superiority for this endpoint at a hazard ratio of 1.59.

Sample size calculations indicate that with 330 total participants (100 evaluable per arm), this study will have $\geq 80\%$ power to detect treatment effects similar in size to those observed by Prof. Wallis in the Gates

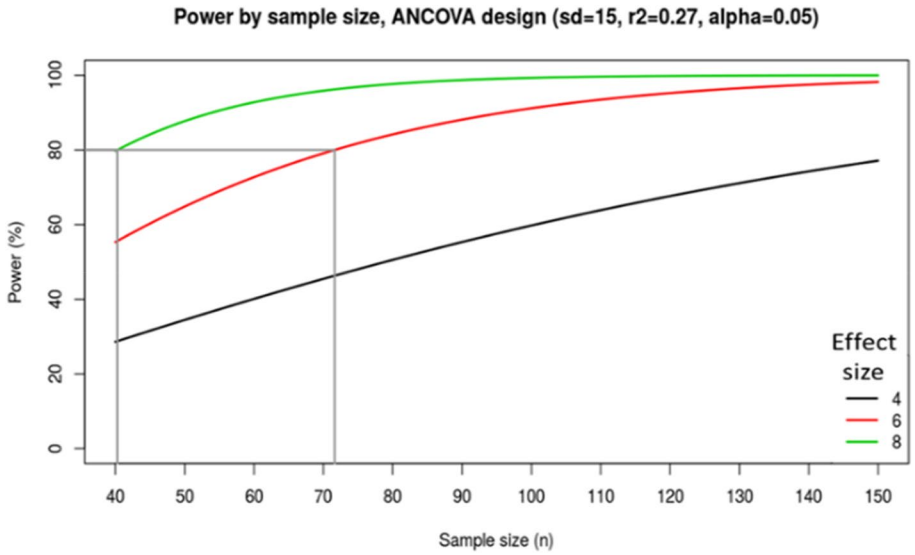

Fig. 2 Power calculations for FEV1

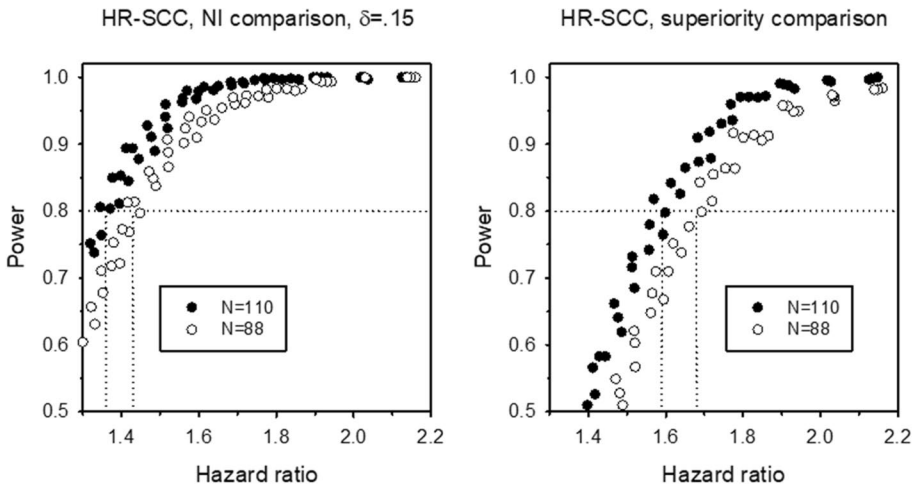

Fig. 3 Power calculations for HR-SCC. Values for N include 10% not evaluable

TB-HDT study for both co-primary endpoints. In addition, the study will have 80% power to detect the superiority of an experimental treatment with regard to HR-SCC, at somewhat higher threshold (1.59).

Recruitment {15}

Recruiters at each site will identify trial participants. Written informed consent to participate in the study, using institutional review board (IRB) and Local Ethics Committees (LECs)—approved consent forms and assent forms, will be obtained by trained study personnel prior to performing any study-specific procedures.

Assignment of interventions: allocation

Sequence generation, concealment mechanism and implementation {16a, 16b, 16c}

For each site different randomization lists will be created. The random allocation sequence will be available for the clinical sites and those enrolling participants into the study.

Assignment of interventions: blinding

Who will be blinded, Procedure for unblinding if needed {17a, 17b}

This study will be conducted as a prospective, randomized, controlled, open label, multi-centre trial.

Several factors led to the decision to conduct the trial as an open-label study:

1. The requirement for up to 7 placebo tablets would substantially increase the pill burden for participants, potentially reducing adherence to TB therapy and HIV ART;
2. Our inability to identify a manufacturer capable of providing metformin and matching placebo tablets would force the study to rely on over-encapsulation of study tablets. This approach is vulnerable to unblinding by participants opening and examining the contents of the capsules;
3. The relatively large size of the metformin tablets (500 mg) additionally makes over-encapsulation impractical.

Methods: data collection and management

Plans to promote participant retention and complete follow-up {18b}

Sites will maintain current lists of contact information for participants and alternative members (family, neighbours, etc.). Participants will be contacted in advance of each scheduled visit as a reminder and at some sites, an SMS reminder will follow the phone call one day prior to the scheduled visit. If an appointment is missed, the participant is contacted via phone and an alternative convenient date is arranged. In some cases participant will be visited at home and transportation arranged, if necessary. Participants will be reimbursed according to recommendations of local ethics panels, in South Africa reimbursement is per local regulator (SAPHRA).

Data management and confidentiality {19, 27}

All clinical and laboratory information required by this protocol is to be present in the source documents and entered into the database (eCRF). Tecro, a South African Clinical Research Organization specializing in data management, will take responsibility for creation and management of the trial database. It will prepare CRF completion guidelines and the study randomization lists, and will create and maintain the study database. The database structure will be compliant to CDISC SDTM, TB treatment area user guide (TAUG), and other applicable database format standards that are required by regulators. Data will be validated on entry, using range and consistency checks. Quality control procedures will include review of CRFs for completion and correctness. Study records (source documents, signed informed consent forms, IRB/IEC correspondence and approval letters, and screening logs) will be kept in a secure location accessible only to authorised study staff, investigators, and monitors. All records will be archived in a secure storage facility for at least fifteen years after the completion of the study.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

All biological samples will be collected strictly per schedule of events (Supplementary materials: study protocol). Study participants will vary with respect to the extent of drug resistance of their *Mtb* isolate and the number and types of effective drugs they receive as treatment. These factors can affect study outcomes. To help control for these effects, whole genome sequence (WGS) analysis will be performed on participant isolates. The purposes will be (1) to determine the drug resistance profiles of the infecting strains to calculate the number and type of effective drugs each participant received, (2) account for Mtb drug resistance profile as a covariate in the analysis of treatment response, (3) in cases of treatment failure distinguish between prolonged infection with the same strain (poor response to treatment), acquisition of drug resistance and reinfection, and (4) in cases of relapse, establish whether it is due to relapse with the same strain or reinfection with another Mtb strain. For these purposes, isolates will be stored at sites and shipped periodically to two central labs, in Borstel and Stellenbosch.

After clinical trial completion, all residual biological samples shipped to central laboratories will be kept and used for the future studies.

Statistical methods

Statistical methods for primary and secondary outcomes, interim analyses, methods for additional analyses and methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20a, 21b, 20b, 20c}

Both experimental arms will be compared individually to the control arm, *i.e.*, as separate studies sharing a common control arm. Since the success or failure of each experimental treatment is assessed only once, and since each treatment might be advanced independently to a phase 3 trial based on study data, there will be no adjustment for multiple comparisons.

Both co-primary endpoints: FEV1% at month 6 (a superiority comparison *vs* control), and HR SCC through month 6 (a non-inferiority comparison *vs* control) as described above, must be achieved for an experimental arm to be considered successful. Under these circumstances, no adjustment is required for type 1 error [26, 27]. This design increases the risk of a type 2 error (failing to find a difference when one indeed is present). EMA advises against relaxing alpha from 0.05 to 0.075 to account for this [28]. We concur, and believe this modest increase in type 2

error risk is acceptable, as it reflects the predominant view of researchers that interventions to improve post-TB lung function must not have a large negative effect on the likelihood of microbiologic cure.

A hierarchical superiority comparison *vs* control is included for HR-SCC. This superiority comparison will be performed only if non-inferiority is demonstrated for that experimental arm. Adjustment for multiple comparisons is not required for such one-dimensional (non-branching) hierarchical testing [27].

All confidence intervals (CIs) will be reported as two-sided at the 95% confidence level. All testing for significance will be two-sided, using a threshold of $P = 0.05$. Demographic and baseline characteristics of the randomized participants will be summarised by (i) study arm and (ii) site and study arm. Any imbalances of baseline characteristics across treatment arms will be noted. Data will be examined for normality; data that are not normally distributed will be transformed if possible, or tested by non-parametric methods. Differences in proportions will be tested by the chi-square or Fisher's exact tests, and continuous measures by t test or ANCOVA. Analyses will be adjusted for baseline differences affecting outcome measures, as described below.

FEV1 at months 2, 6, 12, and 18 will be analysed by ANCOVA. We have found in the Gates-funded TB HDT study that baseline FEV1 and infection burden (measured as log of time-to-positivity in automated liquid culture [MGIT TTP]) are potential covariates of FEV1 at these time points; we will adjust for them as covariates in this study. Missing values at these time points will not be imputed or otherwise estimated. A secondary analysis will examine change in FEV1 over the full period of treatment by random effects modelling. This will be described in detail in the Statistical Analysis Plan. FEV1% (expressed as a percentage of that predicted based on age, sex, height, and race or ethnicity) will be used in initial analyses. Other spirometry variables, including FVC%, FEV1%/FVC%, TLC%, RV%, RV%/TLC%, and corresponding values expressed absolute volumes and as Z scores, will be examined similarly.

Time from first dose (day 1) to stable culture conversion (SCC) will be analysed by Cox proportional hazards regression. Participants not reaching this event will be censored on the date of their last sputum culture result. We have found baseline log MGIT TTP to be an important covariate of time to stable culture conversion in the Gates TB HDT study, and will adjust for this. We will also adjust for the number of effective anti-TB drugs in the treatment regimen, as determined by whole genome sequencing, with weighting based on WHO category and the extent to which assigned treatments were completed. The first comparison for HR-SCC will be a NI comparison, using a delta of 0.15, meaning that the experimental treatment would be considered non-inferior to control if the 95%CI of the HR excludes 0.85 (1-delta). The value of delta in this case represents the maximum trade-off that might be considered clinically acceptable in the event that an HDT protected lung function but slowed the eradication of infection. It is important to note that among the 4 HDT candidates evaluated in the Gates TB HDT study, none showed such a profile: the agents either were inactive (vitamin D and auranofin), or appeared to show a benefit with regard to both parameters (CC-11050 and everolimus).

Plans to give access to the full protocol, participant-level data and statistical code {31c}

The protocol is available as an online supplement to this manuscript. After the conclusion of the trial and publication of the primary results, anonymized participant level data will be made available to qualified investigators through the NIH TB Portals system. Leftover biological samples will be kept for the maximum duration of 5 years at central laboratories, and if not used during this period will be destroyed.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5 d}

The Trial Steering Committee (TSC), will be chaired by international PI, Prof Wallis. TSC membership will include one representative of each of the Consortium organizations. Additional members may be invited by the TSC to address particular aspects of study activities. TSC responsibilities include the monitoring of trial conduct and progress, review of information from external sources relevant to the design and conduct of the study, and consideration of recommendations from the DMC and SAC. The TSC will meet in person once annually and by teleconference weekly.

The Scientific Advisory Committee (SAC), will be comprised of external experts in the field of host-directed tuberculosis therapy, tuberculosis clinical trials, and treatment of drug-resistant tuberculosis. It will provide scientific advice to the TSC with regard to advances in the field (including basic and clinical studies) as they might affect the objective and conduct of the trial. The SAC will meet once annually.

Composition of the data monitoring committee, its role and reporting structure {21a}

A Data Monitoring Committee (DMC), composed of external experts in the field of tuberculosis clinical trials will be provided study data regularly to examine emerging differences among study arms. The chair of the DMC

will have experience with serving on another DMC. The members will be selected to not be involved with the trial in any way or have a competing interest that could impact on the trial. The DMC will function independently of and make recommendations to the Trial Steering Committee. All potential DMC members will be provided with the protocol prior to joining the committee. Members will be reimbursed for travel, accommodation and a per diem only. The DMC will meet periodically by web-based meeting. The frequency of meetings will be determined by the pace of study activity. The DMC will review summaries of enrolment and exclusion rates, demographic and baseline data, and key study endpoints, including, TE-SAEs, Suspected Unexpected Serious Adverse Reactions (SUSARs), deaths, and discontinuations. Additionally, other Immediately Reportable Events (IREs) are those causing an interruption in HDT treatment. The Committee will give specific attention to the proportions of subjects with serious adverse events or adverse clinical outcomes. The DMC will be directed to recommend discontinuation of enrolment and potentially discontinuation of treatment for arms in which safety or efficacy appears likely to be worse than in the control arm.

Adverse event reporting and harms {22}

This study will use the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS AE Grading Table), Version 2.1, July 2017. All AEs are recorded in the trial database. SAEs and IREs are additionally reported using specific forms. Clinical research sites must report SAEs and SUSARs no later than 1 reporting day (24 h) (excluding Saturday and Sunday) after the site becomes aware of an event that meets protocol-defined criteria for reporting, or earlier if so required by local or national policies.

Frequency and plans for auditing trial conduct {23}

Trial monitoring will be conducted by two organizations independently of the Sponsor. The frequency of monitoring will be risk-based, such that sites with a greater likelihood of missing or incorrect entries will receive greater scrutiny, according to ICH-GCP E6 (R2). Informed consents will be 100% source data verified. Half of the participating subjects will have source data verification (SDV) on key data (eg, inclusion/exclusion criteria, AE data and primary endpoints). Additionally, a smaller proportion of study participants will have their data fully SDV'ed. Source data verification will be based on site experience and risk assessment and follow a mutually agreed monitoring plan. Centralised monitoring activities will include check for CRF completeness, check for correct timing of biological sample collection, consistency checks and will be performed on a regular basis throughout the study period.

The Clinical Operations Unit (COU) of Swiss TPH will conduct on-site and centralised monitoring activities for study sites in Romania, Moldova and Georgia (each one study site). Monitoring of African sites (South Africa and Mozambique) will be performed by FHI Clinical (formerly TCD/Triclinium). The same monitoring parameters will be used for both northern and southern hemisphere sites.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Several protocol modifications were made till current version (Table 2) and any further modification will be discussed and approved by the International PI/Sponsor and site Principal Investigators similar to previous modifications. All substantial amendments were discussed by study PI on steering committee meetings and upon agreement submitted to the Ethics Committees and to the competent authorities for approvals. Non-substantial amendments were also agreed on steering committee meetings and submitted to the corresponding authorities and ethics committees as notification.

Dissemination plans {31a}

The results of the trial will be submitted for publication in open-access peer-reviewed scientific journal. Preliminary and final research data will be discussed among consortium members, agreed and made accessible in accordance with the FAIR principles. Results will be shared to the scientific community through conferences and other relevant events, and to the national community advisory groups and key stakeholders.

Table 2 List of protocol amendments

N	Protocol version number and date
1	v1.0–05 DEC 2020
2	v2.0–01 MAR 2021
3	v3.0–03 FEB 2022
4	v4.0–06 MAY 2022
5	v5.0—21 MAR 2023
6	v6.0 (only Southern Hemisphere)—09OCT2023
7	v7.0–26 APR2024

Table 3 List of ethics committees, which approved study protocol

Partner	Location	Ethics committee	Date of initial approval
1. LMU University Hospital	Germany	• Ethikkommission bei der LMU Muenchen	9 th of June 2022
2. Aurum	South Africa	• Wits Human Research Ethics Committee (Wits HREC)	24 th of March 2021
3. UAntwer-pen	Belgium	• Ethics committee of Antwerp University Hospital	1 st of August 2022
4. NCTLD	Georgia	• Local Ethics Committee of the National Center for Tuberculosis and Lung Diseases (NCTLD)	9 th of September 2022
5. IFP CD	Moldova	• National Committee for Ethical Expertise of Clinical Trial (NCEECT) • Agency for Medicines and Medical Devices	10thof November 2022
6. IPMN	Romania	• Comisia Națională de Bioetică a Medicamentului și Dispozitivelor Medicale (CNBMDM) • Agenția Națională a Medicamentului și Dispozitivelor Medicale (ANMDM)	8 th of September 2022
7. WHC	South Africa	• Wits Human Research Ethics Committee (Wits HREC)	Initial approval—24 th of March 2021 Re-Certification Approval – 28 th of January 2022
8. INS	Mozambique	• Comité Institucional de Bioética para a Saúde (CIBS) • Comité Nacional de Bioética para a Saúde (CNBS) • Autoridade Nacional Reguladora de Medicamentos (ANARME)	28 th February 2023

Discussion

Several unexpected factors affected trial execution. During the grant agreement negotiation process, the Aurum Institute was notified by Horizon 2020 that an African organization could not serve as Coordinator. The Swiss Tropical and Public Health Institute graciously agreed to accept this responsibility, with the Aurum Institute retaining scientific leadership of the project. At the same time, Celgene (the original pharma developer of CC-11050 and Aurum's initial pharma partner for the project) was acquired by BMS, with the requirement by the US Federal Trade Commission that the company divest its ownership of the apremilast (Otezla) franchise. CC-11050 was developed as a backup compound for apremilast. Apremilast was sold to Amgen, taking CC-11050 with it. Nearly a year elapsed before Medicines Development for Global Health, an Australian non-profit drug developer, acquired rights to CC-11050 for tuberculosis and leprosy. The manufacturing of a new batch of drug became necessary, as the original supply no longer had a sufficient expiration date. The hospital in Germany that was to serve as a clinical site was closed by the German Federal government as an economy measure. Two additional sites in South Africa were brought on to account for these changes. In total, these activities delayed the start of the trial by nearly 3 years. Fortunately, H2020 was able to grant the project a 2 year no-cost extension to partly account for these delays. To stay within the funding period constraints, the protocol amended to shorten the period of observation of participants enrolled during the project's final 18 months. This modification ensures that all participants would be evaluable for the primary endpoints, and that all would have at least 1 month of trial follow-up after the period of HDT treatment is completed. The project ensures that any participant requiring additional TB treatment after the period of trial participation ends will receive this care outside the trial, through local TB control programs (Table 3).

Trial status

The current trial protocol version is 7.0, issued on 26 th April 2024. Participant recruitment started on 30 January 2023 and as projected with current enrolment plan will continue until April 2025, when 330 participants are enrolled.

Abbreviations

AE	Adverse event
ART	Antiretroviral therapy
CRF	Case report forms
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CT	Clinical trial
DSMB	Data safety management board
DOT	Directly observed therapy
EOT	End of TB treatment
eCRF	Electronic case report forms
FEV1	1 second forced expiratory volume
FU	Followed-up
HDT	Host-Directed Therapies
IP	Investigational product
IRE	Immediately Reportable Events
Mtb	*Mycobacterium tuberculosis*
MDR	Multidrug-resistant
RR-TB	Rifampicin resistant tuberculosis
SoC	Standard of care
SCC	Stable culture conversion
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reactions
TSC	Trial steering committee
TB	Tuberculosis
ULN	Upper limit of normal
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11072-5.

Supplementary Material 1. Trial protocol v7.0 dated 26.04.2024

Supplementary Material 2

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Authors' contributions {31b}
RW conceived the CT and designed it, obtained funding. RW wrote the first version of the protocol draft. NT wrote the initial draft of the manuscript. All co-authors SM, AJ, TN, NH, AR, VC, ET, LG, EI, CK, PH, SR, KN, SN and KR contributed to the protocol revisions including last v7 and reviewed the final draft of the manuscript for important intellectual content, and approved it to be published.

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Data availability {29}
Any data required to support the protocol will be provided on request with an relevant Ethics Committees approval.

Declarations

Ethics approval and consent to participate {24}
The study protocol, the informed consent forms, and investigator brochures were submitted and approved by all relevant ethics committees listed in Table 3.

Consent for publication {32}
All authors consent for publication.

Competing interests {28}
The authors declare no competing interests.

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