ISRCTN18086293 https://doi.org/10.1186/ISRCTN18086293

Safety and effectiveness of a 6-month all-oral treatment regimen for the treatment of rifampicin-resistant tuberculosis in Vietnam

Submission date
12/06/2024

Recruitment status
No longer recruiting

Registration date
01/07/2024

Overall study status
Ongoing

Last Edited
01/07/2024

Condition category
Infections and Infestations

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and aims
Tuberculosis or TB is treatable; however, some TB bacteria stop responding to commonly used anti-TB medicines, and this is called drug-resistant TB (DR-TB). Thus, treatment of DR-TB takes longer and causes more side effects with less chance of cure. Therefore, new TB drugs and novel regimens are urgently required to enable faster, safer and better treatment for persons with drug-resistant TB. A new shorter regimen for only 6 months with fewer drugs has been recommended by the World Health Organization. It has been found to work well, and the side effects are manageable. The purpose of this study is to evaluate the ability of this short regimen to kill TB bacteria and the safety of this regimen in DR-TB patients in Vietnam.

Who can participate?
Patients ≥ 15 years old who have been diagnosed with rifampicin-resistant tuberculosis and are eligible for treatment

What does the study involve?
Two regimens (so-called BPaL-M and BPaL-Lf regimens) will be studied. Both will last 6 months, but there is a difference in 1 out of 4 drugs between 2 regimens. However, both drugs used are effective anti-TB drugs and are highly recommended by the World Health Organization for the treatment of DR-TB. The choice of the treatment regimen will be made by chance.

What are the possible benefits and risks of participating?
Benefits:
There is a greater chance that patients will be cured of DR-TB with the study regimens BPaL-M /Lf compared to the routinely used regimens. Patients will possibly be cured sooner with a shorter duration of only 6 months of treatment and a lower pill burden, however, this cannot be guaranteed. The information from this study may help us to treat future patients with drug-resistant TB better.

Risks:
All the different procedures will be carried out according to the medical protocol. There may be

risks associated with participation, but all necessary measures will be taken, and close monitoring will be carried out accordingly by the medical and research team. The treatment may fail. In this case, the treatment will be adjusted accordingly. Treatment failure is also possible with standard treatment. Participants may also experience side effects, which can sometimes be serious. The side effects will be monitored regularly and at each visit to ensure signs are detected early and treated accordingly. The study team will ensure that patient data remains confidential without identifying a name.

Where is the study run from?
The study will be led from the Viet Nam National Lung Hospital and conducted at 5 sites (provinces)

When is the study starting and how long is it expected to run for?
April 2023 to August 2026

Who is funding the study?
This study is conducted by the Vietnam National TB Programme and Interactive Research and Development Viet Nam (IRD VN), who collaborated to implement this study, with support from the Institute of Tropical Medicine Antwerp in Belgium.

Who is the main contact?
Principal investigator: Dr. Nguyen Thi Mai Phuong, phuong.nguyen@ugent.be

Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
Dr Thi Mai Phuong Nguyen

ORCID ID
https://orcid.org/0000-0002-1521-3872

Contact details
National Lung Hospital, 463 Hoang Hoa Tham Street
Ha Noi
Viet Nam
100000
+84949357999
phuong.nguyen@ugent.be

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Ver.4 26/12/23

Study information

Scientific Title
Stage IV pragmatic randomized clinical trial to compare 6 month all oral BPaLLf (bedaquiline, pretomanid, linezolid and levofloxacin) regimen with WHO-recommended BPaLM (bedaquiline, pretomanid, linezolid and moxifloxacin) regimen in term of safety and effectiveness for the treatment of rifampicin-resistant tuberculosis in Vietnam

Acronym
BPaL-M/Lf

Study objectives
The mean QTcF (QT interval corrected for heart rate using Fridericia's formula) prolongation is higher for BPaL-M than for BPaL-Lf in patients treated for RR-TB with similar TB treatment effectiveness.

Bdq or B: bedaquiline; Pa: pretomanid; Lzd or L: linezolid; Mfx or M: moxifloxacin; Lfx of Lf: levofloxacin; RR-TB: rifampicin resistant tuberculosis

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 06/09/2023, Institutional Review Board (IRB) - Institute of tropical medicine Antwerp (Nationalestraat 155, Antwerp, 2000, Belgium; +32410057701; IRB@itg.be), ref: 1703 /23

2. approved 26/12/2023, Science and Ethics committee - National lung hospital (463 Hoang Hoa Tham street, Ha Noi, 100000, Viet Nam; +842438326249; hoidongdaoducbvptw@gmail.com), ref: 656/2023/NCKH

Study design
Phase IV pragmatic monthly-block randomized clinical trial

Primary study design
Interventional

Study type(s)
Treatment, Safety, Efficacy

Health condition(s) or problem(s) studied
Treatment of fluoroquinolones susceptible rifampicin-resistant TB patients

Interventions

In Vietnam, a pragmatic randomized clinical trial will be conducted to compare two standardized rifampicin-resistant TB (RR-TB) regimens: BPaL-M with BPaL-Lf (levofloxacin replaces moxifloxacin in the interventional arm) in terms of safety (QT-prolonging effect) and clinical effectiveness (treatment success versus death, treatment failure or recurrence).

Methodology:
A before-and-after design will not be used as the overall quality of care may change over time and introduce bias. On the other hand, a stepped-wedge design or a randomized clinical trial, with randomization of individual patients, seems not feasible under programmatic conditions. Therefore, in this study, to ensure that patients in the same clinic are treated with both the BPaL-M regimen and the BPaL-Lf regimen during the trial study period, the randomization will be done by monthly blocks, whereby the regimen used changes every month. Allocation to a monthly block, and thus one of both regimens, is defined by the date of RR-TB diagnosis. The use of the month of RR-TB diagnosis as a stratifying variable seems a better option than the month of RR-TB treatment start (the month of diagnosis is not controlled by the clinician who oversees treatment start). A coin toss will determine which regimen will be used during the first monthly block. Patients diagnosed with RR-TB during the subsequent month will be treated with the other regimen. Hence, the choice of regimen will be determined by the month in which RR-TB was diagnosed.

Regimens use orally administered drugs recommended by WHO for RR-TB treatment:
Regimen 1 (control arm, WHO recommended regimen): (26 weeks) BPaL-M, which contains bedaquiline, pretomanid, linezolid and moxifloxacin.
Regimen 2 (interventional arm): (26 weeks) BPaL-Lf, which contains bedaquiline, pretomanid, linezolid and levofloxacin.

The primary objective is to compare the mean QTcF prolongation between BPaL-M and BPaL-Lf.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Bedaquiline, pretomanid, linezolid, moxifloxacin and levofloxacin

Primary outcome(s)
QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation (difference between baseline QTcF interval and highest value during treatment for the QTcF interval) measured using electrocardiogram (ECG) at baseline, 2 weeks after treatment starts and monthly until treatment completes

Key secondary outcome(s))
1. Compare safety between BPaL-M and BPaL-Lf
1.1. QT interval corrected for heart rate using Fridericia's formula (QTcF) > 500 ms during treatment measured using ECG is at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.2. QTcF increase ≥ 60ms from baseline measured using ECG at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.3. Any TB treatment change due to adverse event (AE) measured using linezolid's dose change,

linezolid's temporary interruption, linezolid's permanent interruption, temporary or permanent interruption of full regimen due to adverse events at any time during treatment
1.4. Treatment failure due to AEs measured using permanent interruption of full regimen due to adverse events at any time during treatment
1.5. Max grade of QT-prolongation and its timing measured using ECG at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.6. Max grade of peripheral neuropathy and its timing measured using clinical screening of symptoms, and brief peripheral neuropathy screening (BPNS) at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.7. Max grade of myelosuppression and its timing measured using full blood count at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.8. Max grade of optic neuritis and its timing measured using vision and color acuity testing at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.9. Max grade of hepatotoxicity and its timing measured using liver enzymes assessed at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.10. Any grade 3-4 AE measured using clinical assessment, blood tests, BPNS, vision and color acuity testing at baseline, 2 weeks after treatment starts, and monthly until the end of treatment
1.11. Any serious adverse event (SAE) measured using clinical assessment, blood tests, BPNS, vision and color acuity testing at baseline, 2 weeks after treatment starts, and monthly until the end of treatment

2. Compare effectiveness between BPaL-M and BPaL-Lf:
2.1. Clinical effectiveness: ("therapeutic success" being defined as "cure" or "treatment completed" without recurrence 12 months after the end of treatment) of the two regimens, versus clinically adverse outcomes (death, failure, relapse) measured using outcomes (based on clinical progression and sputum culture results) at 12 months after completing the treatment.
2.2. Programmatic effectiveness (therapeutic success versus programmatically adverse outcomes (death, failure, relapse, loss to follow-up)) measured using outcomes (based on clinical progression and sputum culture results) at the end of treatment
2.3. Sputum culture conversion at different timepoints during treatment measured using sputum cultures at baseline and monthly until the end of treatment, at 6 and 12 months after completing treatment
2.4. Month of sputum culture conversion measured using sputum cultures at baseline and monthly until the end of treatment, at 6 and 12 months after completing treatment
2.5. Time to treatment failure (due to lack of conversion or due to AE) or relapse measured using permanent interruption of full regimen due to adverse events at any time during treatment or lack of culture conversion at the end of treatment
2.6. Acquired resistance measured using phenotypic drug susceptibility testing (DST) with drugs used in the regimen at baseline and with positive culture at any time during treatment

Completion date
31/08/2026

Eligibility

Key inclusion criteria
1. Diagnosed with pulmonary TB by a microbiological test (molecular or phenotypic), and has laboratory-confirmed resistance to at least rifampicin by either molecular or phenotypic drug susceptibility test
2. Fluoroquinolone resistance excluded either on phenotypic or genotypic DST
3. Aged 15 years or above, regardless of HIV status, at the time of enrolment

4. Willing and able to give informed consent to be enrolled in the trial and adhere to the trial procedures and follow-up schedule (signed or witnessed consent if illiterate)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
15 years

Sex
All

Key exclusion criteria
1. Known allergies, hypersensitivity, or intolerance to any of the BPaL-M/Lf component drugs
2. Pregnant or breast-feeding
3. Liver enzymes >3 times the upper limit of normal (AST or ALT)
4. Taking any medications contraindicated with the medicines in the trial
5. QTcF > 450ms
6. Peripheral neuropathy of Grade 3–4
7. Any baseline biochemical laboratory value consistent with Grade 4 toxicity
8. Has DST showing infection with a strain resistant to any of the study regimens' component drugs (Bdq, Pa, Lzd, Mfx or Lfx) or delamanid (Dlm)
9. Has been previously exposed to any of the BPaL-M/Lf drugs (Bdq, Pa, Lzd, Mfx or Lfx) or Dlm for more than four weeks, unless DST confirms susceptibility to these drugs
10. The clinical DR-TB committee decides that it is not in the best interest of the patient to be enrolled on the BPaL-M/Lfx due to the necessity of an individualized TB treatment regimen

Date of first enrolment
01/03/2024

Date of final enrolment
28/02/2025

Locations

Countries of recruitment
Viet Nam

Study participating centre
Hanoi Lung hospital
44 Thanh Nhan street, Hai Ba Trung district

Hanoi
Viet Nam
-

Study participating centre
Hai Phong lung hospital
560 Tran Tat Van street, Kien An district
Hai Phong
Viet Nam
188140

Study participating centre
Khanh Hoa TB and lung diseases hospital
Vinh Hai street
Nha Trang
Viet Nam
-

Study participating centre
Can Tho TB and lung diseases hospital
QL 91 Phuoc Thoi, O Mon district
Can Tho
Viet Nam
-

Study participating centre
An Giang CDC
28 Alley Nguyen Du
Long Xuyen
Viet Nam
-

Sponsor information

Organisation
Vietnam National Lung Hospital

Funder(s)

Funder type
Research organisation

Funder Name
Global Fund to Fight AIDS, Tuberculosis and Malaria

Alternative Name(s)
Global Fund, The Global Fund, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Fonds mondial de lutte contre le sida, la tuberculose et le paludisme, Fonds mondial, Le Fonds mondial, Globalen Fonds, Der Globalen Fonds, GFATM

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Switzerland

Funder Name
Interactive Research and Development Viet Nam (IRD VN)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from (contact Thi Mai Phuong Nguyen, email: phuongnguyen1186@gmail.com). The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary
Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			14/06/2024	No	Yes