

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

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<b>Registration date</b> 01/07/2024	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 01/07/2024	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Individual participant data <input type="checkbox"/> 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  $\geq 15$  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](mailto:phuong.nguyen@ugent.be)

## Contact information

### Type(s)

Public, Scientific, Principal Investigator

### Contact name

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## Additional identifiers

### EudraCT/CTIS number

Nil known

### IRAS number

### ClinicalTrials.gov number

Nil known

## Secondary identifying numbers

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

## Secondary study design

Randomised controlled trial

## Study setting(s)

Hospital, Medical and other records

## Study type(s)

Treatment, Safety, Efficacy

## **Participant information sheet**

See study outputs table

## **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

## **Pharmaceutical study type(s)**

Not Applicable

## **Phase**

Phase IV

## **Drug/device/biological/vaccine name(s)**

Bedaquiline, pretomanid, linezolid, moxifloxacin and levofloxacin

## **Primary outcome measure**

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

## **Secondary outcome measures**

### **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  $\geq 60$ ms 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

**Overall study start date**

17/04/2023

**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

**Age group**

Mixed

**Lower age limit**

15 Years

**Sex**

Both

**Target number of participants**

400

**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

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**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

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**Study participating centre**

**Can Tho TB and lung diseases hospital**

QL 91 Phuoc Thoi, O Mon district

Can Tho

Viet Nam

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**Study participating centre**

**An Giang CDC**  
28 Alley Nguyen Du  
Long Xuyen  
Viet Nam  
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## Sponsor information

### Organisation

Vietnam National Lung Hospital

### Sponsor details

463 Hoang Hoa Tham street  
Ha Noi  
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100000  
+842438326249  
vietnam\_ntp@yahoo.com

### Sponsor type

Hospital/treatment centre

### Website

<https://benhvienphoitrunguong.vn/>

## Funder(s)

### Funder type

Research organisation

### Funder Name

Global Fund to Fight AIDS, Tuberculosis and Malaria

### Alternative Name(s)

Global Fund, Fonds mondial, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Fonds mondial de lutte contre le sida, la tuberculose et le paludisme, The Global Fund, Le Fonds mondial, 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**

**Publication and dissemination plan**

Interim analysis 1: as soon as the safety data for 97 patients in each arm (194 in total) are available, an interim analysis will be carried out for both primary and secondary endpoints.  
Interim analysis 2: as soon as end-of-treatment outcomes are available for all 400 patients enrolled, the interim analysis will be repeated.  
Final analysis: as soon as post-treatment follow-up outcomes are available for all 400 patients enrolled the final analysis will be conducted.

**Intention to publish date**  
30/06/2025

**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?
<a href="#">Participant information sheet</a>			14/06/2024	No	Yes