ISRCTN11881662 https://doi.org/10.1186/ISRCTN11881662

Doxycycline to improve lymphedema due to podoconiosis

Submission date	Recruitment status	[X] Prospectively registered
25/07/2017	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/07/2017	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
19/06/2025	Injury, Occupational Diseases, Poisoning	[X] Record updated in last year

Plain English summary of protocol
Background and study aims
Podoconiosis (endemic non-filarial elephantiasis) is a non-infectious disease that occurs in barefoot farmers who are in long-term contact with irritant red clay soil of volcanic origins. Current treatment practices of lymphedema (swelling) due to podoconiosis (PodoLE) rely on decreasing the number of acute attacks by improving the hygiene of the affected limbs. While this treatment package has been shown to be effective in halting the progression of PodoLE, it requires sustained access to resources required for limb care and strict adherence to the prescribed procedures. In two previous studies doxycycline 200 mg for 6 weeks was given to patients with lymphedema due to lymphatic filariasis (LF), a parasitic disease caused by worms. This oral antibiotic treatment led to improvement or halt of the progression of the lymphedema in most of the treated patients, whether their filarial infections were active or not. This led to the assumption that the same effect could also be expected in patients with PodoLE. Therefore, the aim of this study is to find out whether doxycycline (200 mg/d for 6 weeks) is effective in patients with PodoLE.

Who can participate?
Patients aged 18 – 60 years with a lymphedema due to podoconiosis of the leg
Follow-up: Those who participated in screening during the TAKeOFF PodoLEDoxy Cameroon clinical trial

What does the study involve?
Participants are randomly allocated to be treated with either doxycycline 200 mg or a placebo for 6 weeks. Treatments are given in addition to the standard methods of hygiene. At the start of the study and 6, 12, 18 and 24 months later, participants undergo measurements of the legs. A questionnaire about the occurrence of acute attacks is carried out every 2 months after the start of treatment. Participants also undergo lymphedema management training at the start of the study and after 4, 6, 12, 18 and 24 months.
All people seen by the team at the study start (those who received treatment and those who had to be excluded) will be asked to consent to an additional follow-up around 2-4 years after last patient last follow-up. Similar procedures as the 24-month follow-up will be done. All participants will receive another round of lymphedema management training, including the necessary supplies.

What are the possible benefits and risks of participating?
Benefits to the participant include thorough medical evaluation, intensified hygiene training, free supplies for local care of lymphedema and free medical treatment for common illnesses during the treatment period and follow-up. The risks to participants are side effects caused by the licensed study drug doxycycline and infection during blood sampling. In the event of side effects caused by the study drugs or treatments, participants are treated and followed up by the research team until they are resolved.

Where is the study run from?
University of Buea (Cameroon)

When is the study starting and how long is it expected to run for?
January 2017 to June 2026

Who is funding the study?
Research Networks for Health Innovations in Sub-Saharan Africa sponsored by the Federal Ministry of Education and Research (BMBF) (Germany)

Who is the main contact?
1. Prof. Samuel Wanji (public)
swanji@yahoo.fr
2. Prof. Achim Hoerauf (scientific)
achim.hoerauf@ukbonn.de

Contact information

Type(s)
Public

Contact name
Prof Samuel Wanji

Contact details
Public Health Parasitology and Entomology
Department of Microbiology and Parasitology
University of Buea
PO Box 63
Buea
Cameroon
00000
+237 (0)77 72 43 84
swanji@yahoo.fr

Type(s)
Scientific

Contact name
Prof Achim Hoerauf

Contact details

Institute for Medical Microbiology
Immunology and Parasitology
University Hospital of Bonn
Sigmund-Freud-Str. 25
Bonn
Germany
53105
+49 (0)228 2871 5673
achim.hoerauf@ukbonn.de

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
TAKeOFF-5-0517

Study information

Scientific Title
Doxycycline for treatment of non-filarial lymphedema due to podoconiosis (PodoLE): a randomized, placebo-controlled trial

Acronym
TAKeOFF - PodoLEDoxy

Study objectives
To show efficacy of a 6-week course of daily doxycycline 200 mg on lack of progression of lymphedema due to podoconiosis (PodoLE).

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 03/05/2019, Comite Ethique de la Recherche pour la Sante Humaine (CNERSH), Yaounde, Cameroon, ref: 2018/05/1002/CE/CNERSH/SP.
2. Approved 04/05/2018, The Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, Bonn, Germany, ref: 139/18.

Follow-up:
1. Approved 02/05/2025, Comite Ethique de la Recherche pour la Sante Humaine (CNERSH), Yaounde, Cameroon, ref : 2025/04/1801/CE/CNERSH/SP.
2. Submitted in Bonn pending approval: The Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, Bonn, Germany.

Previous ethics approval:
Documents will be submitted in September 2017 to the following boards for approval:
1. Comite Ethique de la Recherche pour la Sante Humaine (CNERSH), Yaounde, Cameroon
2. University of Buea, Faculty of Health Sciences Institutional Review Board
3. The Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, Bonn, Germany

Study design
Interventional randomized double-blind placebo-controlled Phase II trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Podoconiosis (Podo)

Interventions
Current interventions as of 07/05/2019:
The study involves daily observed treatment with either doxycycline 200mg for 6 weeks or placebo matching doxycycline for 6 weeks (42 days). Participants with lymphedema due to pododconiosis (PodoLE) stage 2-3 will be randomized (block randomisation) to one of the two treatment regimens:
1. DOX 200: Doxycycline 200 mg/d for 6 weeks (2 100 mg tablets/day orally)
2. Placebo (control): Placebo matching Doxycycline for 6 weeks (2 tablets/day orally)

Treatment will be administered ad personam by the trial clinician directly in the villages in the form of daily observed treatment (DOT). All treatment regimens will be administered on top of the standardized methods of hygiene ("standard of care"). Treatment will be carried out in a blinded manner, meaning that neither the patients nor the caregiver will know to which treatment arm the patients belong.

At baseline as well as 6, 12, 18 and 24 months after treatment onset, participants will undergo lymphedema-specific measurements (circumference measurements of the leg, volume measurement of the legs). A questionnaire regarding the occurrence of acute attacks (ADLA) will be carried out every 2 months after treatment onset. Participants will also undergo lymphedema management training at baseline and after 4, 6, 12, 18 and 24 months.

Added 19/06/2025:
Follow-up:
Around 2-4 years after last patient last follow up, participants who consent in a separate form will again undergo lymphedema-specific measurements (staging, circumference measurements of the leg, volume measurement of the legs). A questionnaire regarding the occurrence of acute attacks (ADLA) and about hygiene and lymphedema management will be carried out. Participants will also undergo another lymphedema management training.

Original interventions:
The study involves daily observed treatment with either doxycycline 200mg for 6 weeks or placebo matching doxycycline for 6 weeks (42 days). Participants with lymphedema due to pododconiosis (PodoLE) stage 2-4 will be randomized (block randomisation) to one of the two treatment regimens:
1. DOX 200: Doxycycline 200 mg/d for 6 weeks (2 100 mg tablets/day orally)
2. Placebo (control): Placebo matching Doxycycline for 6 weeks (2 tablets/day orally)
Treatment will be administered ad personam by the trial clinician directly in the villages in the form of daily observed treatment (DOT). All treatment regimens will be administered on top of the standardized methods of hygiene ("standard of care"). Treatment will be carried out in a blinded manner, meaning that neither the patients nor the caregiver will know to which treatment arm the patients belong.

At baseline as well as 6, 12 and 24 months after treatment onset, participants will undergo lymphedema-specific measurements (circumference measurements of the leg, volume measurement of the legs, ultrasound measurement of the skin thickness at the ankles). A questionnaire regarding the occurrence of acute attacks (ADLA) will be carried out every 2 months after treatment onset. Participants will also undergo lymphedema management training at baseline and after 4, 6, 12, 18 and 24 months.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Doxycycline

Primary outcome measure
Lack of progression of lymphedema due to podoconiosis (PodoLE) (stage reduction or same stage as pre-treatment using the 5-point scale staging according to Tekola et al, 2008), examined 24 months after treatment onset

Added 19/06/2025:
Follow-up:
Level of adherence to lymphedema self-care practices since the final (24-month) evaluation in the prior PodoLEDoxy study, quantified through structured questionnaires (this will range from 2-4 years depending on the participant’s initial PodoLEDoxy enrolment)

Secondary outcome measures
Current secondary outcome measures as of 07/05/2019:
1. Lack of progression of PodoLE (stage reduction or same stage as pre-treatment using the 5-

point scale staging according to Tekola et al, 2008), examined 6, 12 or 18 months after treatment onset
2. Improvement of PodoLE, i.e. stage reduction (at least one stage compared to pre-treatment), examined 6, 12, 18 and 24 months after treatment onset
3. Change of PodoLE stages (reduction or increase) compared to baseline, assessed at 6, 12, 18 and 24 months after treatment onset
4. Changes (reduction or increase) of the circumference of the affected limbs compared to baseline circumferences, measured by tape measure at 6, 12, 18 and 24 months after treatment onset
5. Changes of the circumference of the affected limbs compared to baseline circumferences, measured with an infrared scanner (LymphaTech®) at 6, 12, 18 and 24 months after treatment onset
7. Changes of the volume of the affected limbs compared to baseline volume, measured with an infrared scanner (LymphaTech®) at 6, 12 and 24 months after treatment onset
8. Changes in the duration of acute attacks compared to pre-treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
9. Changes in the frequency of acute attacks compared to pre-treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
10. Absence of acute attacks, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
11. Changes of the hygiene level compared to pre-treatment, assessed by using a hygiene survey especially developed for this study at 6, 12 and 24 months
12. Changes in the quality of life (QoL) compared to pre-treatment at 12 and 24 months after treatment onset
13. Levels of angiogenic, lymphangiogenic, pro-fibrotic or pro-inflammatory biomarkers (such as VEGF, CECAM-a, MMPS) in blood and/or urine as a measure for prognostic effects, measured using ELISA and/or Luminex Multiplex Assay technique at baseline, 6, 12 and 24 months after treatment onset

Assessment of safety:
Adverse events (AE) assessed and described in the scope of the daily observed treatment (DOT). This involves:
1. Occurrence of AE
2. Intensity of AE (Grade 0 [none], Grade 1 [mild], grade 2 [moderate] grade 3 [severe])
3. SAE
4. Relation to treatment (definite, probable, possible, remote, not related)
5. Outcome of AE (restored, improved, unchanged, deteriorated, death, unknown, overcome with sequelae)
6. Intervention

Added 19/06/2025:
Follow-up (this will range from 2-4 years depending on the participant's initial PodoLEDoxy enrolment):
1. Change of LE stage (reduction or increase) compared to pre-treatment (V1/V2; all screened participants) and 24 months after treatment onset (V15; treated participants only).
2. Changes (reduction or increase) of the circumference measured by tape measure of the affected limbs compared to baseline (V2; all screened participants, if baseline measurements are available) and 24 months after treatment onset (V15; treated participants only).
3. Changes in the duration of acute attacks compared to pre-treatment (V1/V2; all screened participants) and 24 months after treatment onset (V15; treated participants only).

4. Changes in the frequency of acute attacks compared to pre-treatment (V1/V2; all screened participants), and 24 months after treatment onset (V15; treated participants only).
5. Changes in hygiene level compared to pre-treatment (V2; all screened participants, if baseline measurements are available), and 24 months after treatment onset (V15; treated participants only)
6. Differences in hygiene level of treated participants compared to participants who were not enrolled in the PodoLEDoxy study (controls).
7. Changes in quality of life (QoL) compared to pre-treatment (V2; all screened participants, if baseline measurements are available), and 24 months after treatment onset (V15; treated participants only).
8. Differences in quality of life (QoL) of treated participants compared to participants not enrolled in the clinical study (controls).
All endpoints will be compared between treated participants and controls.

Original secondary outcome measures:
1. Lack of progression of PodoLE (stage reduction or same stage as pre-treatment using the 5-point scale staging according to Tekola et al, 2008), examined 6 or 12 months after treatment onset
2. Improvement of PodoLE, i.e. stage reduction (at least one stage compared to pre-treatment), examined 6, 12 and 24 months after treatment onset
3. Change of PodoLE stages (reduction or increase) compared to baseline, assessed at 6, 12 and 24 months after treatment onset
4. Changes (reduction or increase) of the circumference of the affected limbs compared to baseline circumferences, measured by tape measure at 6, 12 and 24 months after treatment onset
5. Changes of skin thickness of the affected limbs compared to baseline values, measured by ultrasound at 6, 12 and 24 months after treatment onset
6. Changes of the circumference of the affected limbs compared to baseline circumferences, measured with an infrared scanner (LymphaTech®) at 6, 12 and 24 months after treatment onset
7. Changes of the volume of the affected limbs compared to baseline volume, measured with an infrared scanner (LymphaTech®) at 6, 12 and 24 months after treatment onset
8. Changes in the duration of acute attacks compared to pre-treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
9. Changes in the frequency of acute attacks compared to pre-treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
10. Absence of acute attacks, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
11. Changes of the hygiene level compared to pre-treatment, assessed by using a hygiene survey especially developed for this study at 6, 12 and 24 months
12. Changes of the quality of life (QoL) compared to pre-treatment, assessed using the 12-item version of the WHODAS 2.0 at 12 and 24 months after treatment onset
13. Levels of angiogenic, lymphangiogenic, pro-fibrotic or pro-inflammatory biomarkers (such as VEGF, CECAM-a, MMPS) in blood and/or urine as a measure for prognostic effects, measured using ELISA and/or Luminex Multiplex Assay technique at baseline, 6, 12 and 24 months after treatment onset

Assessment of safety:
Adverse events (AE) assessed and described in the scope of the daily observed treatment (DOT). This involves:
1. Occurrence of AE

2. Intensity of AE (Grade 0 [none], Grade 1 [mild], grade 2 [moderate] grade 3 [severe])
3. SAE
4. Relation to treatment (definite, probable, possible, remote, not related)
5. Outcome of AE (restored, improved, unchanged, deteriorated, death, unknown, overcome with sequelae)
6. Intervention

Overall study start date
01/01/2017

Completion date
01/06/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 07/05/2019:
1. Lymphedema of at least one leg grade 2-3 measured on a 5-point scale (Tekola et al, 2008)
2. Age ≥ 18 years and ≤ 60 years
3. Men or non-pregnant women. If women of childbearing potential, they must use an approved, effective method of contraception (including abstinence) before, during and for at least 2 weeks after the completion of the active intervention with doxycycline or placebo
4. Negative pregnancy test
5. Body weight ≥40 kg
6. Resident in endemic area for podoconiosis for ≥ 2 years
7. Able and willing to give informed consent/ to provide assent to participate in the trial
8. Ability to use established standardized methods of hygiene and effectively applying it prior to the initiation of the drug treatment
9. Negative test for lymphatic filariasis (LF)

Added 19/06/2025:
Follow-up:
1. Participated in screening during the TAKeOFF PodoLEDoxy Cameroon clinical trial
2. Able and willing to give informed consent/to provide assent to participate in the current follow-up study

Original participant inclusion criteria:
1. Lymphedema of at least one leg grade 2-4 measured on a 5-point scale (Tekola et al, 2008)
2. Age ≥ 18 years and ≤ 65 years
3. Men or non-pregnant women. If women of childbearing potential, they must use an approved, effective method of contraception (including abstinence) before, during and for at least 2 weeks after the completion of the active intervention with doxycycline or placebo
4. Negative pregnancy test
5. Body weight ≥ 40 kg
6. Resident in endemic area for podoconiosis for ≥ 2 years
7. Able and willing to give informed consent/ to provide assent to participate in the trial
8. Ability to use established standardized methods of hygiene and effectively applying it prior to the initiation of the drug treatment
9. Negative test for lymphatic filariasis (LF)

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
N = 200

Total final enrolment
203

Key exclusion criteria
Current participant exclusion criteria as of 07/05/2019:
1. No lymphedema
2. Stage 1, 4 or stage 5 lymphedema due to podoconiosis
3. Lymphedema due to lymphatic filariasis (LF)
4. Age < 18 years or > 60 years
5. Body weight < 40 kg
6. Pregnant or breastfeeding women
7. Women of childbearing potential not using an agreed method of contraception (including abstinence; oral contraceptives are not allowed because of interaction with trial drugs)
8. Clinical or biologic evidence of hepatic or renal dysfunction or disease of the central nervous system (CNS)
9. Evidence of severe comorbidities except for features of filarial disease
10. Alcohol or drug abuse
11. History of adverse reactions to doxycycline or other tetracyclines
12. Any significant condition (including medical and psychological/ psychiatric disorder) which in the opinion of the study investigator might interfere with the conduct of the study
13. History of photosensitivity reactions after taking drugs.
14. Concomitant medication with antacids containing aluminium, magnesium or sucralfate and not able to discontinue
15. Concomitant medication with other antibiotics than doxycycline and not able to discontinue
16. Concomitant medication with diuretics or sulfonylurea
17. Concomitant medication with coumarin
18. Haemoglobin < 8 gm/dL
19. Neutrophil count <1 100/mm3
20. Platelet count <100 000/mm3
21. Creatinine > 2 times upper limit of normal
22. AST (GOT) > 2 times upper limit of normal
23. ALT (GPT) > 2 times upper limit of normal
24. Gamma-GT > 2 times upper limit of normal
25. Positive urine pregnancy test
26. Positive test for W. bancrofti

Added 19/06/2025:
Follow-up:
1. Individuals who are seriously sick at the time of study.

Original participant exclusion criteria:
1. No lymphedema, stage 1 or stage 5 lymphedema due to podoconiosis
2. Lymphedema due to lymphatic filariasis (LF)
3. Age <18 years or >65 years
4. Body weight <40 kg
5. Pregnant or breastfeeding women
6. Women of childbearing potential not using an agreed method of contraception (including abstinence; oral contraceptives are not allowed because of interaction with trial drugs)
7. Clinical or biologic evidence of hepatic or renal dysfunction or disease of the central nervous system (CNS)
8. Evidence of severe comorbidities except for features of filarial disease
9. Alcohol or drug abuse
10. History of adverse reactions to doxycycline or other tetracyclines
11. Any significant condition (including medical and psychological/psychiatric disorder) which in the opinion of the study investigator might interfere with the conduct of the study
12. History of photosensitivity reactions after taking drugs.
13. Concomitant medication with antacids containing aluminium, magnesium or sucralfate and not able to discontinue
14. Concomitant medication with other antibiotics than doxycycline and not able to discontinue
15. Concomitant medication with diuretics or sulfonylurea
16. Concomitant medication with coumarin
17. Haemoglobin <8 g/dL
18. Neutrophil count <2 000/mm3
19. Platelet count <100 000/mm3
20. Creatinine >2 times upper limit of normal
21. AST (GOT) >2 times upper limit of normal
22. ALT (GPT) >2 times upper limit of normal
23. Gamma-GT >2 times upper limit of normal
24. Positive urine pregnancy test
25. Positive wb123 or TBF or qPCR for W. bancrofti

Date of first enrolment
01/05/2019

Date of final enrolment
31/12/2019

Locations

Countries of recruitment
Cameroon

Study participating centre
University of Buea
PO Box 63

Buea
Cameroon
00000

Sponsor information

Organisation
University of Buea

Sponsor details
PO Box 63
Buea
Cameroon
00000

Sponsor type
University/education

Website
http://www.ubuea.cm/

ROR
https://ror.org/041kdhz15

Funder(s)

Funder type
Government

Funder Name
Research Networks for Health Innovations in Sub-Saharan Africa sponsored by the Federal Ministry of Education and Research (BMBF), Germany

Results and Publications

Publication and dissemination plan
The publication of the study results is planned in a high-impact peer reviewed journal.

Intention to publish date
30/09/2023

Individual participant data (IPD) sharing plan

The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		30/03/2020	02/04/2020	Yes	No
Other publications		23/08/2023	19/06/2025	Yes	No
Other publications		17/07/2023	19/06/2025	Yes	No
Other publications		01/12/2020	19/06/2025	Yes	No