

Protocol

Dovramilast for Erythema Nodosum Leprosum in Patients With Leprosy in Nepal: Protocol for a Phase 2 Open-Label Pilot Study

Mahesh Shah¹, MD; Divya RSJB Rana², MSc; Kapil Dev Neupane², BS; Preeti Maharjan², MPH; Suwash Baral¹, MD; Reejana Shrestha¹, MD; Jivan Shakya², PhD; Binod Aryal², MSc; Bishwanath Acharya², PhD; Indra Bahadur Napit², MD, PhD; Deanna A Hagge³, PhD

¹Department of Dermatology, Anandaban Hospital, The Leprosy Mission Nepal, Lalitpur, Nepal

²Research Department, Anandaban Hospital, The Leprosy Mission Nepal, Lalitpur, Nepal

³Zero Leprosy Pathfinder Consulting, Baton Rouge, LA, United States

Corresponding Author:

Mahesh Shah, MD
Department of Dermatology
Anandaban Hospital, The Leprosy Mission Nepal
Godawari-06, Tikabhariav
Lalitpur 151
Nepal
Phone: 977 9841203417
Email: MaheshS@tlmnepal.org

Abstract

Background: Erythema nodosum leprosum (ENL) is an immunological complication affecting up to 10% of borderline lepromatous and 50% of lepromatous leprosy cases with a high bacterial index (3-6+). Current treatments often require prolonged therapy over years and cause significant long-term side effects, highlighting the need for new therapies. Therefore, it is imperative to identify new therapies for ENL. Phosphodiesterase 4 inhibitors are a class of compounds that mediate immune homeostasis and have the potential to treat ENL with fewer side effects. Dovramilast (formerly CC-11050) is an anti-inflammatory phosphodiesterase 4 inhibitor; to date, it has been shown to be well tolerated in phase 1 human studies. This is the first phase 2 study of dovramilast in ENL.

Objective: This phase 2 pilot study aims to assess the safety and tolerability of dovramilast and to explore preliminary clinical responses in patients with new or recurrent ENL.

Methods: This study was designed in two steps: (1) 28 days of treatment for 10 males to ensure safety and (2) an initial 12-week treatment course, with the option to retreat if further ENL episodes occur (up to 48 wk of treatment), for up to 40 males or females, as required on a case-by-case basis. Demographic, clinical, and laboratory data will be collected longitudinally, along with the ENL International Study Group ENL Severity Scale, Brief Pain Inventory, and Douleur Neuropathique 4 questionnaire for the identification of neuropathic pain. Patients will be followed for 12 months for ENL recurrence after cessation of the study drug. Safety will be evaluated through adverse event reporting and laboratory monitoring, while efficacy will be assessed using descriptive and trend-based analyses of changes in ENL severity, pain, and clinical outcomes over time.

Results: The initial safety evaluation (step 1) of this phase 2 pilot study was completed and reviewed by an independent Data Safety Monitoring Board, which did not identify safety concerns that would preclude continuation of the study. Based on the step 1 results, the study proceeded to step 2, which evaluates longer-term administration of dovramilast in male and female participants. As of April 2026, a total of 15 participants have been recruited. All study data are anticipated to be collected by September 2027, with publication of the main trial results expected by December 2027.

Conclusions: This phase 2 pilot study is designed to generate preliminary data on the safety, tolerability, and potential clinical signals of dovramilast in patients with new or recurrent ENL. Findings from this exploratory trial will inform the feasibility, outcome measures, and design of future adequately powered randomized controlled studies and do not directly support changes to current clinical practice at this stage.

Trial Registration: ClinicalTrials.gov NCT03807362; <https://clinicaltrials.gov/study/NCT03807362>

International Registered Report Identifier (IRRID): DERR1-10.2196/88069

JMIR Res Protoc 2026;15:e88069; doi: [10.2196/88069](https://doi.org/10.2196/88069)

Keywords: CC-11050; clinical trial; doxycycline; erythema nodosum leprosum; ENL severity scale; leprosy; Nepal

Introduction

Leprosy and Leprosy Reactions

Leprosy is an important but neglected global disease. Effective multidrug therapy (MDT) has resulted in a reduced prevalence of the disease, and leprosy case detection rates have stagnated over recent decades, as reported by the World Health Organization (WHO) [1,2]. Leprosy is caused by the acid-fast bacteria *Mycobacterium leprae* or *M. lepromatosis* and primarily affects the skin and peripheral nerves [3,4].

In 2023, 72.9% of new leprosy cases detected were multibacillary [1] presenting with one or more cardinal signs, including greater than 5 lesions, detectable *M. leprae* bacilli, or peripheral nerve involvement, compared to paucibacillary presenting with less than 5 lesions and no detectable bacilli [5]. Delayed diagnosis or treatment of leprosy can lead to permanent nerve damage and disabling deformities. Neuropathy may develop before, during, or long after treatment due to persistent mycobacterial antigens that drive immunological reactions and accelerate nerve injury. Consequently, leprosy reactions are a major contributor to long-term disability in affected individuals [6-12].

Two major types of leprosy reactions occur, affecting up to 30% to 50% of all leprosy cases at some point: type 1 reaction (T1R, reversal reaction) and erythema nodosum leprosum (ENL, also called type 2 reaction) [7,13-15]. T1R typically involves increased cell-mediated immunity toward leprosy antigens and most often develops in borderline tuberculoid, borderline borderline, and borderline lepromatous (BL) cases. However, ENL develops only in BL and lepromatous leprosy (LL) cases, with high bacterial loads associated with reduced T cells and increased antibody responses to leprosy antigens. ENL may occur before the start of leprosy treatment but can also develop during or years after MDT [6,7]. After treatment for leprosy, people may experience episodes of ENL for years because mycobacterial antigens persist despite bactericidal MDT [6-8,16]. Neuritis can occur either alone or

in combination with T1R or ENL. Some patients experience reaction cases typical of T1R and ENL in succession or in combination [17,18].

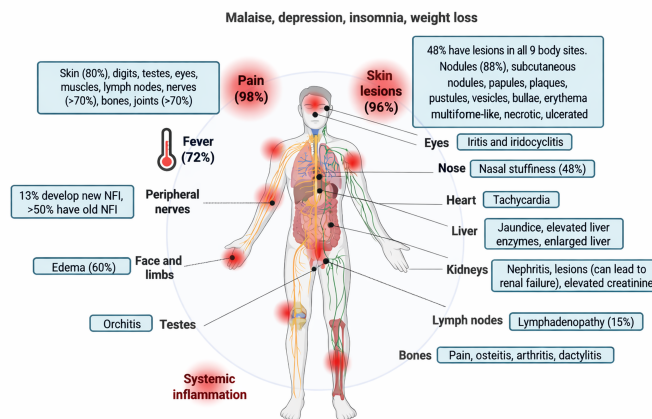
Characteristics of ENL

ENL presents as new, red, painful nodules, usually on the legs, arms, face, and sometimes on the trunk, and it varies in severity [8,19-22]. It is characterized by the rapid appearance of successive crops of painful and erythematous subcutaneous nodules that may ulcerate [19]. ENL may be present at the time of leprosy diagnosis or develop within the first few years after starting MDT [6-8].

Individual ENL episodes can last months or years, with a significant proportion of patients experiencing recurrent episodes [6,8]. Recurrent ENL reactions are defined as more than 1 ENL episode with the same characteristics as acute ENL. Chronic ENL is defined as an episode lasting for more than 6 months of treatment. The main risk factors for ENL are LL or BL leprosy with high bacterial load and a bacterial index greater than or equal to 3+ [11,19,23]. Of these, 10% of patients with BL and 50% of patients with LL develop the first ENL episode coincident with leprosy diagnosis, during MDT, or in the years after MDT completion. Other less well-defined factors that increase risk include pregnancy, lactation, puberty, intercurrent infection, vaccination, and stress [16].

Systemic signs and symptoms, such as fever, anorexia, and malaise, signal its occurrence; however, these symptoms are not always recognized in association with leprosy and can be initially misdiagnosed [19]. See [Figure 1](#) for symptoms and organ systems that are variably associated with ENL. The ENL International Study Group ENL Severity Scale (EESS) focuses on a subset of 10 major symptoms as severity indicators common to both males and females: pain, fever, number of ENL lesions, inflammation of ENL lesions, extent of ENL lesions, peripheral edema, bone pain, inflammation of joints and/or digits, lymphadenopathy, and nerve tenderness [19,24].

Figure 1. Symptoms and organ involvement associated with erythema nodosum leprosum (ENL). The peripheral nervous system is shown on the left and the lymphatic system on the right. Symptoms and incidence are consolidated from reviews and ENL cohort reports [19,25]. Created in BioRender by author DAH [26].



When the reaction is mild, only the skin is affected, often in combination with a low-grade fever. When the reaction is severe, the nodules are multiple and may ulcerate, there may be a high fever, and other organs such as the nerves, eyes, joints, testes, and lymph nodes may be inflamed. Typically, recurrence in these patients presents with the emergence of red subcutaneous swelling, often associated with fever and pain.

Apart from disability and stigma, ENL can cause devastating psychosocial, physical, and economic hardship [9,27,28] and multiple hospitalizations in affected patients. Moreover, the side effects of treatments create vulnerabilities to other diseases, prevent patients from leading normal social or emotional lives or engaging with others, cause loss of employment or cessation of schooling, or degrade their enthusiasm to struggle against these obstacles.

Potential Causes of ENL

The pathogenesis of ENL is poorly understood [14,29,30]. ENL was previously considered to be an immune complex-mediated phenomenon; however, very limited and sometimes contradictory evidence is available to support this [31].

As is common in BL or LL cases, studies have indicated that ENL patients have high levels of anti-*M. leprae* antibodies, as well as persistent levels of *M. leprae* antigens. The most characteristic feature of the lesions is the presence of a neutrophilic infiltrate. Immunoglobulin and complement deposition are present in the skin lesions. Serum complement levels are decreased, and the expression of interleukin (IL)-6, IL-8, IL-10, IL-4, and IL-5 is increased. Activation of both toll-like receptor 2 and fragment crystallizable receptors has been shown to induce IL-1 β , which upregulates the expression of E-selectin and neutrophil binding in endothelial cells. Additionally, neutrophils can be stimulated by *M. leprae* to secrete tumor necrosis factor (TNF)- α and IL-8, thereby increasing inflammation [14,29,30].

Cell-mediated immune responses also contribute to the pathogenesis of ENL. Several studies have supported the association of a T-helper 1-type response with high levels of interferon-gamma and IL-12 [30]. CD4⁺ T cells have been shown to outnumber CD8⁺ T cells by 2 to 1. On the other hand, other studies have suggested that a T-helper 2-type response dominates, with high levels of TNF- α and IL-6 detected in the serum and skin lesions [10,32]. More recently, single nucleotide polymorphisms in the IL-6 gene were found to be associated with ENL [33]. Soil-transmitted helminth-induced immunomodulation across many shared cellular and cytokine pathologies may also be relevant to the development of neuritis, T1R, and ENL reaction episodes in coendemic populations [34].

Treatment for ENL

Prednisolone, thalidomide, and clofazimine are currently recommended by the WHO as treatment for ENL; however, ENL treatment has been controversial for decades [20,21,28,35,36]. Prednisolone is the most common first-line treatment in most low- or middle-income countries and leprosy-endemic countries (except Brazil, which uses thalidomide). Prednisolone is generally available and affordable, but, as ENL may require years of treatment, patients can develop severe consequences such as diabetes, cardiovascular problems, blindness, and osteoporosis leading to bone fractures [37-39].

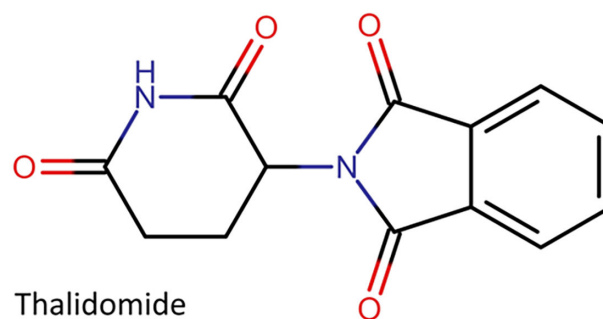
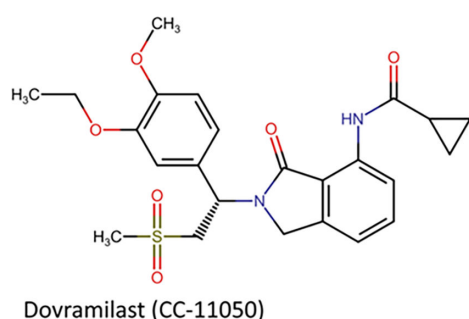
Thalidomide, the most recently recommended therapeutic agent for the treatment of ENL, was developed more than 50 years ago and has both immunoregulatory and sedative activity [40]. However, owing to the teratogenicity and related consequences in the 1960s, thalidomide is often restricted or unaffordable for most ENL cases in endemic countries. High-dose clofazimine has anti-inflammatory properties and can be given in combination with prednisolone. Studies, however, have not indicated a significant impact, and patients rarely tolerate clofazimine due to skin pigmentation [41].

Both high-dose prednisolone and thalidomide are sometimes insufficient to control severe refractory ENL [42-44]. Many cases are chronic and experience ENL symptom relapse soon after the decrease in dosage or cessation of drugs [35]. Thus, a safe and effective drug that can be used for a shorter duration and imparts long-term remission has always been envisioned [28]. These problems are compounded by the lack of alternative treatments with established efficacy for ENL. Various efforts have been made to develop alternative ENL treatments, most notably pentoxifylline, azathioprine, cyclosporine, methotrexate, and anti-TNF biologics such as etanercept and infliximab [45-59].

Dovramilast in Relevance to ENL

Dovramilast has been evaluated as an adjunct host-directed therapy in HIV, tuberculosis, and SARS-CoV-2 infection

Figure 2. Chemical structures of dovramilast and thalidomide. Figures were drawn using the RCSB PDB Chemical Sketch Tool with chemical Simplified Molecular-Input Line-Entry System (SMILES) from PubChem.



Therefore, the primary objective of this phase 2, open-label clinical trial is to evaluate the safety and preliminary efficacy of dovramilast in adults with new or recurrent ENL. The primary research question is whether dovramilast is safe and well tolerated when administered for short- and longer-term treatment cycles in patients with ENL. Secondary research questions address whether dovramilast treatment is associated with improvements in ENL severity, pain, and clinical manifestations over time, and whether repeated treatment cycles can reduce recurrence without the need for prolonged corticosteroid or thalidomide use. We hypothesize that dovramilast will demonstrate a favorable safety profile and lead to clinically meaningful reductions in ENL severity and symptom burden, supporting its further evaluation as an alternative therapeutic option for ENL.

This protocol is written based on SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Checklist 1) [70].

Methods

Research Question and Hypothesis

The primary research question of this phase 2 pilot study is whether dovramilast is safe and well tolerated in patients with new or recurrent ENL. Secondary research questions explore whether dovramilast treatment is associated with improvements in ENL severity, pain, and clinical manifestations over time and whether repeated treatment cycles may

models and clinical studies, demonstrating immunomodulatory effects and a favorable safety profile [60-67]. Preclinical studies in rabbit and mouse models of tuberculosis showed improved bacterial clearance and reduced lung inflammation and fibrosis. Phase 1 and phase 2 clinical trials in HIV and tuberculosis patients confirmed good tolerability with no serious adverse events (AEs) and evidence of improved clinical outcomes [60,64,67]. Although previously studied as an adjunct host-directed therapy in infectious diseases, ENL represents a distinct immunological complication, supporting the rationale for evaluating dovramilast as a novel therapeutic option distinct from thalidomide [36,68,69]. The structural difference between dovramilast and thalidomide is presented in Figure 2.

reduce recurrence. Given the exploratory nature of this pilot study, formal hypothesis testing is not planned; instead, the study is designed to generate preliminary safety, feasibility, and clinical trend data to inform future randomized controlled trials.

Aims and Objectives

The primary objective of this study is to evaluate the safety and tolerability of short- and longer-term administration of dovramilast in adults with new or recurrent ENL. Secondary objectives include assessing preliminary clinical signals of efficacy, including changes in ENL severity, pain, and neurological symptoms, as well as documenting patterns of remission and recurrence. Exploratory objectives include evaluating biological correlations of treatment response using plasma and skin biopsy samples to support mechanistic understanding.

Study Setting and Sites

The study will be conducted at Anandaban Hospital, The Leprosy Mission Nepal, located in Lalitpur District, Nepal, along with its affiliated satellite clinics. Anandaban Hospital is a national referral center for leprosy and leprosy-related complications and provides specialized clinical and research infrastructure for ENL management and follow-up.

Sample Size and Justification

The planned sample size includes 10 male participants in step 1 and up to 40 additional male and female participants in

step 2. Anandaban Hospital is a tertiary referral center for the management of leprosy reactions and related complications, with approximately 60 to 70 patients with ENL presenting annually. A target sample size of 40 participants was selected based on feasibility considerations, recognizing that not all presenting patients would meet the study’s inclusion criteria or be eligible for enrollment.

Moreover, as this is an observational pilot study, no formal statistical power calculation was performed. The selected sample size is intended to allow assessment of feasibility, safety, and variability in clinical outcomes and to generate preliminary evidence to inform the design and sample size estimation of a future multicenter randomized controlled trial.

ENL Case Definition

ENL definitions are aligned with the ENL International Study Group definitions [19] and the EESS [24]. ENL is defined as occurring when an individual diagnosed with BL or LL leprosy and a bacterial index >3+ develops 10 or more tender papular or nodular or both types of skin lesions. Other ENL symptoms may also be included but not be limited to those listed in the EESS.

There are 3 clinical patterns by which ENL is described [24]:

1. Acute for a single episode lasting less than 24 weeks
2. Recurrent if a patient experienced a second or subsequent episode of ENL occurring 28 days or more after stopping treatment for ENL
3. Chronic if occurring for 24 weeks or more during which a patient has required ENL treatment either continuously or where any treatment-free period had been 27 days or less

This initial phase 2 clinical trial will focus on acute and recurrent forms of ENL.

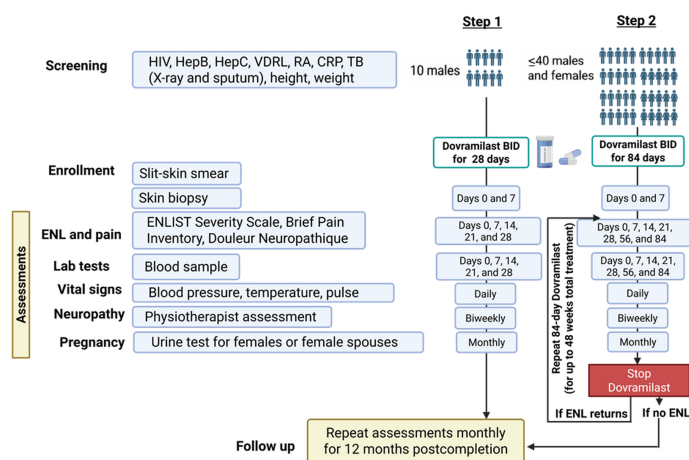
The EESS [24] will be used to establish the presence and severity of ENL symptoms during the trial.

Study Design

Overview

This study will be a single-center, single-arm, phase 2, open-label trial to evaluate the safety and efficacy of 200 mg dovramilast administered twice daily and consumed with fatty food in participants with moderate-to-severe ENL. As outlined in Figure 3, the study will be performed in 2 steps.

Figure 3. Overall study design showing treatment decision process and treatment durations. CRP: C-reactive protein; ENL: erythema nodosum leprosum; ENLIST: Erythema Nodosum Leprosum International Study Group; HepB: hepatitis B; HepC: hepatitis C; RA: rheumatoid arthritis; TB: tuberculosis; VDRL: Venereal Disease Research Laboratory test for syphilis. Created in BioRender [26].



- Step 1: 10 male participants with new or new episode ENL.
- Step 2: Up to 40 participants, including male and female patients with new or new episode ENL.

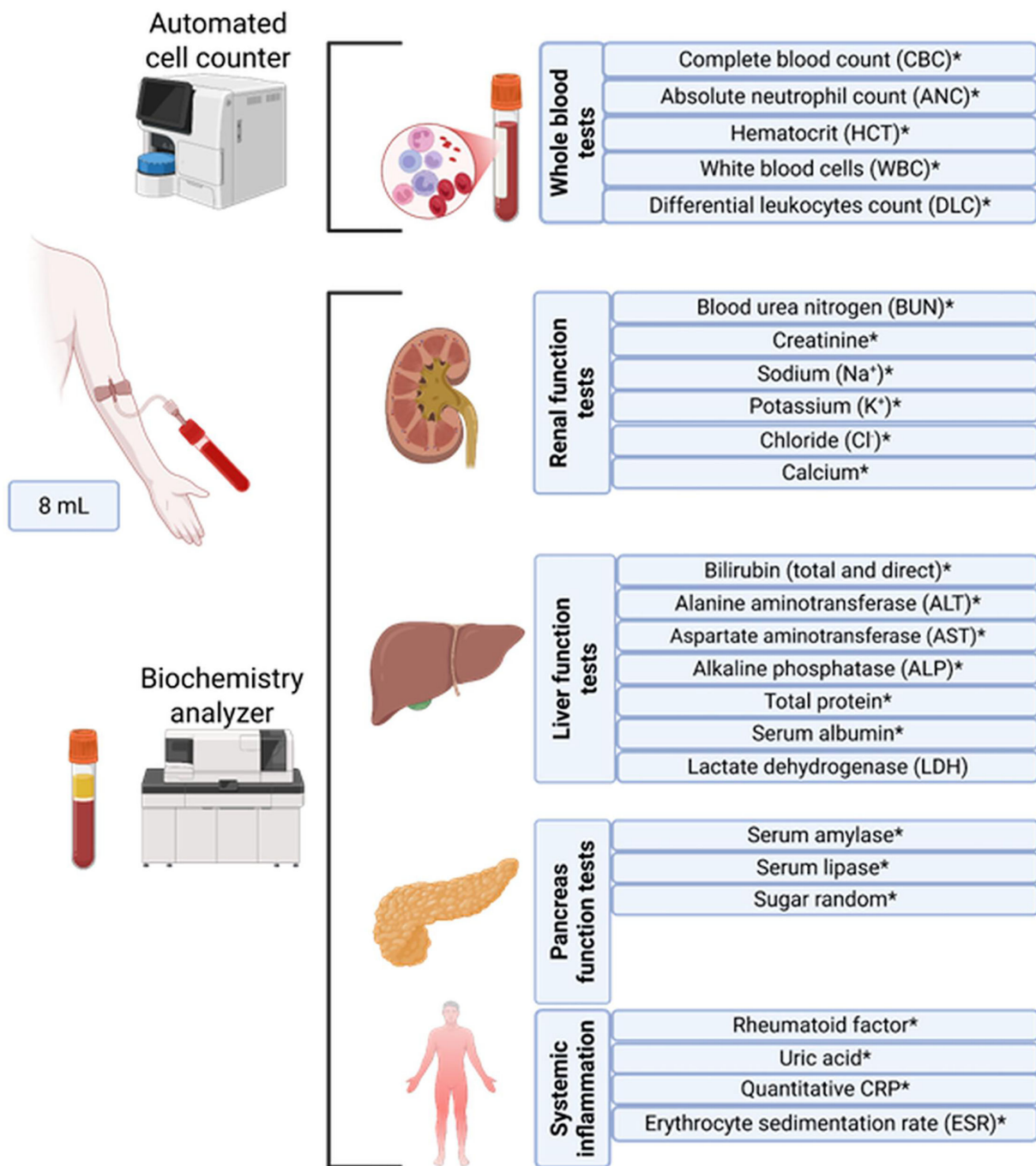
The primary aims of step 1 and step 2, respectively, are as follows:

1. To evaluate the immediate effect on the safety and efficacy of 28 days (1 mo) of dovramilast treatment in 10 males with a new or recurrent episode of ENL
2. To evaluate a 12-week treatment cycle of dovramilast, with the provision for further 12-week treatment cycles

of dovramilast for up to 48 weeks (12 mo), in up to 40 participants, including males and females presenting with new or recurrent ENL

A safety analysis will be conducted on all participants who received at least 1 dose of the study drug and will include the frequency of all AEs and laboratory abnormalities (Figure 4), as well as the frequency of dose interruptions, dose reductions, and treatment discontinuations.

Figure 4. List of laboratory tests to be performed during the trial. The asterisk (*) indicates the subset of tests performed in step 1. All tests will be performed in step 2. Created in BioRender [26].



Study participants will be eligible for any concomitant treatment, including, but not limited to, WHO-recommended MDT, antipyretics, and analgesics. No standard ENL treatment regimens of prednisolone or thalidomide, or both, will be provided during the study drug treatment. In step 1, any new ENL episodes after the cessation of the study drug will be managed with standard ENL care. In step 2, any new ENL episodes will be managed with a repeat 12-week treatment cycle with doxramilast.

Step 1: Evaluation of the Immediate Effects

To evaluate the immediate effects of doxramilast, 10 male participants with moderate to severe, new, or recurrent ENL

will receive an initial 10 days of treatment with 200 mg of doxramilast twice daily. The physician has the discretion to determine whether individual prospective participants with severe neuropathy or other severe symptoms should be enrolled. Participants will be males aged 18 to 65 years and weigh greater than or equal to 40 kg. The initial 28-day safety evaluation (step 1) was limited to male participants as a precautionary measure to minimize potential reproductive and pregnancy-related risks during early exposure to doxramilast in patients with ENL. Although doxramilast has demonstrated an acceptable safety profile in previous phase 1 and phase 2 studies in other disease settings, comprehensive reproductive safety data in ENL populations are limited. Restricting early enrollment to males allowed

close monitoring of short-term safety and tolerability before broader inclusion. Upon confirmation of acceptable safety by the Data Safety Monitoring Board (DSMB), enrollment was expanded in step 2 to include both male and female participants, with appropriate exclusion of pregnant or breastfeeding women. Safety and efficacy monitoring assessments will be performed by DSMB representative clinicians during the initial 7- to 10-day treatment period. If assessments during the 10-day initial treatment trial indicate poor safety or efficacy, participants may be removed from the treatment no later than day 10. If assessments during the 10-day initial treatment period indicate that the drug is well tolerated and the participant's ENL symptoms are responding, the treatment will be continued until day 28. If the drug treatment is not well tolerated, or if assessments for efficacy fail to demonstrate ENL symptom relief, participants may be removed from the treatment.

Upon review of the 10- and 28-day assessments, the DSMB will recommend that another cohort of 40 participants be enrolled for up to 12 months of treatment (step 2).

Step 2: Evaluation of the Long-Term Effects

Participants will be either male or female, aged 18 to 65 years, with a new or newly recurrent ENL episode and will receive 200 mg of doxycycline twice daily. Male weights will be aligned with step 1 requirements (≥ 40 kg), whereas females should weigh at least 35 kg.

In a subset of participants during step 2, pharmacokinetic assessments of drug levels in the blood will be performed using plasma collected at appropriate times on day 1 and day 10 (predose and 3 hours postdose) after doxycycline treatment.

As in step 1, participants will be enrolled for an initial 7 to 10 days of treatment. If patients tolerate the drug well and respond, they will continue to receive doxycycline for 12 weeks.

Every 12 weeks of treatment, doxycycline will be discontinued to determine if ENL symptoms recur or if the ENL episode has fully recovered. If symptoms recur after 28 days within the 1-year follow-up period, doxycycline will be administered again for another 12 weeks, as indicated by individual patient needs, for up to 1 year of total doxycycline treatment duration (12 wk \times 4=48 wk total). Based on individual patient clinical needs, this discontinuation test will be repeated at 6 and 9 months for a total treatment period of up to 52 weeks. While clinical care may occur more frequently as indicated by individual ENL symptoms, participants will be evaluated on days 10 and 28 and monthly during treatment, and monthly for 1 year after discontinuation of the drug (final visit).

Inclusion Criteria

Study participants must satisfy the following criteria for enrollment in the study:

1. Must be 18 to 65 years old, weighing ≥ 35 kg for women and ≥ 40 kg for men.

2. In step 1, the participants must be male. In step 2, the participants can be either male or female.
3. Understand and voluntarily sign an informed consent document prior to any study-related assessment or procedure.
4. Have signs or symptoms of new episodes of ENL.
5. Able to adhere to the study schedule and other protocol requirements. Patients with stable and well-managed diabetes and hypertension can be included in the study.
6. Women of childbearing age can be enrolled in step 2 following confirmation of safety in the initial male-only cohort, provided they are not pregnant or breastfeeding, have a negative pregnancy test at screening, comply with protocol-specified pregnancy testing, and agree to pregnancy prevention counseling (including abstinence where contraception is not culturally acceptable) during treatment and for 4 weeks after the last dose of study medication.

Exclusion Criteria

The presence of any of the following will exclude a potential participant from enrollment:

1. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the participant from participating in the study.
2. Daily rifampicin treatment will be excluded with a minimum washout period of 2 weeks prior to doxycycline administration. However, if rifampicin is taken only once a month as part of MDT, this will not be used as an exclusion criterion.
3. Any condition, including the presence of laboratory abnormalities, that places the participant at an unacceptable risk if they were to participate in the study.
4. Any condition that confounds the ability to interpret data from the study (ie, HIV, chronic hepatitis B, chronic hepatitis C, or tuberculosis in patients under active treatment). Patients with resolved tuberculosis will not be excluded from the study.
5. Use of systemic corticosteroids or thalidomide within 7 days of study medication initiation.
6. Pregnant or nursing females.

Primary and Secondary Outcomes

The primary outcome is the proportion of participants achieving a complete clinical response by day 10 of doxycycline treatment. Complete clinical response is defined as a clinically meaningful improvement or resolution of ENL manifestations based on standardized clinical criteria rather than a binary presence or absence. This includes a reduction in the number, tenderness, and inflammation of ENL skin nodules, assessed clinically and supported by changes in the EESS score; resolution of ENL-associated fever based on clinical assessment and temperature recordings; and improvement or resolution of nerve pain and tenderness evaluated through neurological examination and validated pain assessment tools. Safety outcomes include the frequency and severity of AEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 [71], as well

as laboratory abnormalities and neurological assessments. In addition, plasma and skin biopsy samples will be collected at predefined time points for exploratory evaluation of biological responses to doxramilast, including inflammatory and immunological markers relevant to ENL pathogenesis (such as circulating cytokines, acute-phase reactants, and immune cell-associated markers), and histopathological features of ENL lesions. These exploratory analyses will be descriptive and are intended to provide mechanistic insights into treatment response.

Secondary outcomes include the proportion of participants who achieve and maintain remission of ENL symptoms during treatment and for up to 12 months following cessation of the study drug. Longitudinal changes in disease severity, pain, and neurological symptoms will be assessed over time using validated instruments, including the EESS, Brief Pain Inventory, and Douleur Neuropathique 4 questionnaire. In addition, the frequency of ENL recurrence and the need for repeat doxramilast treatment cycles during the follow-up period will be documented.

Discontinuation of Treatment or Removal From the Study

A participant can be discontinued from ongoing drug treatment upon the occurrence of AEs related or unrelated to the drug treatment. If a participant fails to return for 1 or more follow-up appointments, data may still be collected upon attendance of the remaining appointments for up to 1 year after the last date of drug administration.

Interventional Methods

Step 1: twice-daily administration of 200 mg of doxramilast to be taken with fatty food. The treatment will be for 10 days, with a rollover for a total of 28 days if safety and efficacy demonstrate benefit by day 10 for the patient. Step 2: twice-daily administration of 200 mg of doxramilast in patients to be taken with fatty food for 12 weeks, with additional 12-week treatment cycles (week 48) depending on individual clinical needs.

Safety and Efficacy

Primary and secondary end points for efficacy, as explained above, will be assessed on day 0, day 28, and 1 year after study drug cessation. The severity of any toxicity will be graded according to version 5.0 of the NCI CTCAE. Summaries of demographics, disposition, study drug exposure, protocol violations, and AEs will also be made.

An independent DSMB oversees trial conduct and participant safety. The DSMB reviewed safety data from the initial safety cohort (step 1) prior to progression to the expanded treatment phase (step 2). Ongoing safety oversight includes periodic review of AEs, protocol deviations, and overall study conduct. Study monitoring is conducted in accordance with Good Clinical Practice and NHRC ethical guidelines to ensure data quality, protocol adherence, and participant protection.

Data Analysis

This study is designed as an exploratory phase 2 pilot trial; therefore, analyses will be primarily descriptive and longitudinal rather than inferential. All analyses will be conducted according to the intention-to-treat principle, including all participants who receive at least 1 dose of doxramilast, regardless of treatment duration, protocol deviations, or withdrawal.

Primary outcome analysis will focus on estimating the proportion of participants achieving a complete clinical response by day 10 of treatment, based on predefined clinical criteria encompassing skin, systemic, and neurological manifestations of ENL. This proportion will be summarized with descriptive statistics and corresponding confidence intervals to provide an estimate of response frequency and variability. Secondary outcomes will be assessed through longitudinal evaluation of ENL severity, pain, and neurological symptoms using validated instruments (EESS, Brief Pain Inventory, and Douleur Neuropathique 4). Changes in these measures over time will be summarized descriptively using means, medians, ranges, and graphical trend displays to assess patterns of improvement, remission, and recurrence during treatment and follow-up. The frequency and timing of ENL recurrences and the need for repeat doxramilast treatment cycles will be documented to characterize treatment durability. Exploratory laboratory and tissue outcomes derived from plasma and skin biopsy samples will be analyzed descriptively to evaluate trends in inflammatory, immunological, and histopathological markers over time.

In addition to clinical and exploratory outcomes, feasibility will be assessed as a key objective of this pilot study. Feasibility indicators include the ability to recruit and retain participants according to the protocol, adherence to study medication and follow-up schedules, completeness of clinical and patient-reported outcome data, and acceptability of study procedures. These feasibility measures, together with observed variability in outcomes and safety findings, will be used to inform decisions regarding the design, operational requirements, and scalability of a future adequately powered randomized controlled trial.

Given the pilot nature of the study, missing data will not be imputed; analyses will be based on available data, and the extent and reasons for missing data will be described and considered in interpretation.

Ethical Considerations

Ethical approval was obtained from the Government of Nepal, Nepal Health Research Council (NHRC reference number 409 for step 1 and 1485 for step 2) and the Department of Drug Administration (DDA reference number 2802 for step 1 and 58,900 for step 2). This study's protocol adheres to all relevant ethical guidelines for research involving human participants.

Informed consent will be obtained prior to any study-related procedures. During the consent process, participants will receive comprehensive information about this study,

including its objectives, procedures, potential benefits, travel fares, and any associated risks or discomforts. Participants will also be informed of their rights, including the option to withdraw from the study at any point, ensuring that participation is entirely voluntary.

Participant safety is a primary objective of this study. Potential harms associated with doxramilast are assessed through regular clinical evaluations, laboratory monitoring, neurological assessments, and systematic AE reporting. All AEs are graded using the NCI CTCAE version 5.0. Protocol-defined measures, including dose interruption, discontinuation, or withdrawal, are implemented in the event of clinically significant AEs. Clinical trial insurance was secured for all enrolled participants to cover compensation for any study-related injury or AEs, in compliance with NHRC ethical and regulatory guidelines.

To safeguard the privacy of participants, all collected data will be anonymized by assigning each participant a unique study number, ensuring that no personal identifiers are directly associated with the data. Demographic, clinical, and personal details will be securely stored in locked cabinets for all hard copies of the case report forms, as well as in a password-protected REDCap (Research Electronic Data Capture; Vanderbilt University) database. Only authorized research staff will have access to the data, and all information gathered during this study will be used exclusively for research purposes.

Results

The initial safety evaluation (step 1), approved by the IRB on August 16, 2017, was completed in 2020 with enrollment of 10 male participants presenting with new or recurrent moderate-to-severe ENL. Review by the DSMB did not identify safety concerns that would preclude progression of the study, supporting continuation to the expanded treatment phase (step 2), which received IRB approval on February 15, 2024.

Based on findings from step 1, no substantive modifications to the study design, dosing regimen, or safety monitoring procedures were required. Step 2 recruitment procedures were initiated in September 2024, with enrollment planned to continue according to the protocol-specified sample size and follow-up schedule. All data are anticipated to be collected by September 2027, and the main results of the trial are anticipated to be published by December 2027. As of April 2026, a total of 15 participants have been recruited.

Recruitment, retention, and follow-up procedures have been implemented as outlined in the protocol. Any protocol deviations identified were documented and addressed according to Good Clinical Practice guidelines and did not necessitate protocol amendments.

Detailed analyses of safety, efficacy, and exploratory outcomes will be reported in a future results publication upon study completion.

Discussion

Principal Findings

This phase 2 study is designed to evaluate the safety, tolerability, and preliminary clinical effects of doxramilast in patients with new or recurrent ENL. We hypothesize that doxramilast will demonstrate an acceptable safety profile and be associated with clinically meaningful reductions in ENL severity and symptom burden, while reducing reliance on prolonged corticosteroid or thalidomide therapy. If confirmed, these findings would support further evaluation of doxramilast as a novel immunomodulatory treatment option for ENL.

Comparison to Prior Work

Phosphodiesterase 4 (PDE4) inhibition has emerged as a potential immunomodulatory strategy for inflammatory diseases [72]. Apremilast, an oral PDE4 inhibitor approved for psoriasis and psoriatic arthritis [73], has been reported in limited case series and clinical experiences as a treatment option for ENL, particularly in patients with recurrent or steroid-dependent disease [74-76]. These reports suggest that PDE4 inhibition may reduce inflammatory burden and ENL symptoms while avoiding some of the long-term toxicities associated with corticosteroids and thalidomide.

However, evidence supporting apremilast use in ENL is scarce, highlighting the need for prospective clinical evaluation of PDE4 inhibitors in this setting. Doxramilast, a chemically distinct PDE4 inhibitor with demonstrated immunomodulatory effects and a favorable safety profile in other inflammatory and infectious disease studies, represents a rational candidate for systematic investigation in ENL through a structured phase 2 clinical trial.

Strengths and Limitations

Strengths of this study include the use of validated ENL severity and pain scales, longitudinal follow-up for recurrence, and a staged design with independent safety oversight. Limitations include the open-label, single-arm design and inadequate sample size, which preclude formal efficacy comparisons but are appropriate for an exploratory phase 2 protocol.

Future Directions

Findings from this study will inform the design of future randomized controlled trials, including the selection of primary end points, sample size estimation, and treatment duration. If doxramilast demonstrates sustained clinical benefit with acceptable safety, it may represent a steroid-sparing option for ENL, with important implications for long-term disability prevention in leprosy-affected populations.

Dissemination Plan

Study findings will be disseminated through peer-reviewed publications, conference presentations, and reporting to relevant health authorities. Results will also be shared with participating clinicians and, where appropriate, with study

participants and patient advocacy groups to support evidence-based management of ENL.

Conclusions

This protocol describes an exploratory phase 2 study evaluating doxycycline for the treatment of new or recurrent ENL. The study is designed to assess safety, tolerability,

feasibility, and preliminary clinical signals rather than to determine definitive efficacy. The anticipated findings will support the refinement of outcome measures, sample size estimates, and trial design for future randomized controlled studies. As such, this work represents an important step toward, but not yet evidence for, the broader clinical application of doxycycline in ENL management.

Acknowledgments

The authors thank the ENL patients at Anandaban Hospital for their participation in step 1 of this study and the DSMB members—Dr Warwick J Britton (Head, Department of Immunology, University of Sydney Medical School, Australia), Dr Paul Saunderson (Research and Medical Director, American Leprosy Missions/The Leprosy Mission International), Dr KP Dhakal (Dermatologist and Former Country Director, Netherlands Leprosy Relief, Nepal), Dr David Scollard (Representative Clinician, DSMB; Former Head, National Hansen's Disease Program, USA), Dr Bhaskar Mohan Kayastha (Head, Department of Dermatology, Patan Academy for Health Sciences, Nepal; Former Head, Department of Dermatology, Nepal Academy for Medical Sciences), Dr Rabindra Baskota (Chief, Leprosy Control and Disability Management Section, Government of Nepal; Representative Clinician, DSMB), and Dr Prashna Napit (Representative Clinician, DSMB)—for their oversight and guidance. They are also thankful to Dr Vikram Khetani and Dr Ken Arakawa (Celgene Corporation, USA), Dr Mark Sullivan and Dr Lydia Iannazzo (Medicines Development for Global Health, Australia) for their contributions to the study design. They are grateful to the Nepal Health Research Council for ethical review and the Department of Drug Administration for clinical trial licensing support, and to Dr Ramesh Parajuli (Legal Consultant-Medical Ethics) for study protocol review. They acknowledge their collaborators, Dr Jason D Simmons (University of Washington, USA) and Dr Selvakumar Subbian (New Jersey Medical School, Rutgers University, USA), and thank Dr Gilla Kaplan (USA) for advocating continued use of CC-11050/Doxycycline in ENL clinical trials. They appreciate the assistance of Mr Dilip Shrestha, Ms Ruby Thapa, and Ms Jeni Maharjan (Mycobacterial Research Laboratory) with documentation, and Ms Savi Tulsee-Chetty (SCT Consulting, South Africa) for monitoring visits and Good Clinical Practice training. They thank Mr Shovakhar Kandel, the Executive Director, and the executive board of The Leprosy Mission Nepal for understanding the need for a new drug trial in ENL and approving the trial to be conducted at Anandaban Hospital. Finally, their sincere thanks to all staff of Anandaban Hospital and the research team, along with the administration, finance, and country office staff, for their valuable support and coordination during the trial.

The authors declare the use of generative artificial intelligence (GAI) in the research and writing process. According to the GAIDeT taxonomy (2025), the following tasks were delegated to GAI tools under full human supervision: proofreading and editing; summarizing text. The GAI tool used was Paperpal.

Responsibility for the final manuscript lies entirely with the authors. GAI tools are not listed as authors and do not bear responsibility for the final outcomes.

Funding

This study was initially funded by Celgene Corporation, United States. Following the acquisition of Celgene by Bristol Myers Squibb, the rights to the study drug (doxycycline) were transferred to Amgen Inc. Ongoing support for the study, including provision of the study drug, is facilitated through Medicines Development for Global Health (MDGH), Melbourne, Australia. The study drug is supplied by the funder through MDGH, which had no role in the conduct or reporting of this study.

Data Availability

The data generated as part of this study will be made available as supplemental materials with relevant publications.

Authors' Contributions

MS is the principal investigator, and IBN and DAH are coinvestigators of this study. DAH, MS, and IBN conceptualized the study. MS, DAH, IBN, KDN, DRSJBR, and PM were involved in the initial discussion and design of the study. SB, RS, B Aryal, JS, and B Acharya joined later and contributed to study design. MS, DRSJBR, IBN, SB, RS, BA, JS, B Acharya, and DAH contributed to preparation of the original draft. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Checklist 1

SPIRIT checklist.

[\[PDF File \(Adobe File\), 269 KB-Checklist 1\]](#)

References

1. Global leprosy (Hansen disease) update, 2023: elimination of leprosy disease is possible – time to act! [Report in French]. World Health Organization; 2024. URL: <https://iris.who.int/bitstream/handle/10665/378895/WER9937-501-521.pdf?sequence=1> [Accessed 2025-08-20]
2. The global health observatory: leprosy (Hansen's disease). World Health Organization. URL: <https://www.who.int/data/gho/data/themes/topics/leprosy-hansens-disease> [Accessed 2025-08-20]
3. Han XY, Sizer KC, Velarde-Félix JS, Frias-Castro LO, Vargas-Ocampo F. The leprosy agents *Mycobacterium lepromatosis* and *Mycobacterium leprae* in Mexico. *Int J Dermatol*. Aug 2012;51(8):952-959. [doi: [10.1111/j.1365-4632.2011.05414.x](https://doi.org/10.1111/j.1365-4632.2011.05414.x)] [Medline: [22788812](https://pubmed.ncbi.nlm.nih.gov/22788812/)]
4. FAQs: frequently asked questions on leprosy. World Health Organization; 2013. URL: <https://iris.who.int/bitstream/handle/10665/205085/B5044.pdf?sequence=1> [Accessed 2024-11-20]
5. Guidelines for the diagnosis, treatment and prevention of leprosy. World Health Organization; 2018. URL: <https://www.who.int/publications/i/item/9789290226383> [Accessed 2024-11-18]
6. Pocaterra L, Jain S, Reddy R, et al. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg*. May 2006;74(5):868-879. [Medline: [16687695](https://pubmed.ncbi.nlm.nih.gov/16687695/)]
7. Van Brakel WH, Khawas IB, Lucas SB. Reactions in leprosy: an epidemiological study of 386 patients in West Nepal. *Lepr Rev*. Sep 1994;65(3):190-203. [doi: [10.5935/0305-7518.19940019](https://doi.org/10.5935/0305-7518.19940019)] [Medline: [8942150](https://pubmed.ncbi.nlm.nih.gov/8942150/)]
8. Feuth M, Brandsma JW, Faber WR, Bhattarai B, Feuth T, Anderson AM. Erythema nodosum leprosum in Nepal: a retrospective study of clinical features and response to treatment with prednisolone or thalidomide. *Lepr Rev*. Sep 2008;79(3):254-269. [Medline: [19009975](https://pubmed.ncbi.nlm.nih.gov/19009975/)]
9. Raffe SF, Thapa M, Khadge S, Tamang K, Hagge D, Lockwood DNJ. Diagnosis and treatment of leprosy reactions in integrated services--the patients' perspective in Nepal. *PLoS Negl Trop Dis*. 2013;7(3):e2089. [doi: [10.1371/journal.pntd.0002089](https://doi.org/10.1371/journal.pntd.0002089)] [Medline: [23505585](https://pubmed.ncbi.nlm.nih.gov/23505585/)]
10. Rao TD, Rao PR. Serum immune complexes in erythema nodosum leprosum reactions of leprosy. *Indian J Lepr*. Apr 1988;60(2):189-195. [Medline: [3142953](https://pubmed.ncbi.nlm.nih.gov/3142953/)]
11. Saunderson P, Gebre S, Desta K, Byass P, Lockwood DN. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr Rev*. Sep 2000;71(3):285-308. [doi: [10.5935/0305-7518.20000033](https://doi.org/10.5935/0305-7518.20000033)] [Medline: [11105488](https://pubmed.ncbi.nlm.nih.gov/11105488/)]
12. Toh HS, Maharjan J, Thapa R, et al. Diagnosis and impact of neuropathic pain in leprosy patients in Nepal after completion of multidrug therapy. *PLoS Negl Trop Dis*. Jul 2018;12(7):e0006610. [doi: [10.1371/journal.pntd.0006610](https://doi.org/10.1371/journal.pntd.0006610)] [Medline: [29965957](https://pubmed.ncbi.nlm.nih.gov/29965957/)]
13. Balagon MVF, Gelber RH, Abalos RM, Cellona RV. Reactions following completion of 1 and 2 year multidrug therapy (MDT). *Am J Trop Med Hyg*. Sep 2010;83(3):637-644. [doi: [10.4269/ajtmh.2010.09-0586](https://doi.org/10.4269/ajtmh.2010.09-0586)] [Medline: [20810832](https://pubmed.ncbi.nlm.nih.gov/20810832/)]
14. Kahawita IP, Lockwood DNJ. Towards understanding the pathology of erythema nodosum leprosum. *Trans R Soc Trop Med Hyg*. Apr 2008;102(4):329-337. [doi: [10.1016/j.trstmh.2008.01.004](https://doi.org/10.1016/j.trstmh.2008.01.004)] [Medline: [18313706](https://pubmed.ncbi.nlm.nih.gov/18313706/)]
15. Scollard DM, Martelli CMT, Stefani MMA, et al. Risk factors for leprosy reactions in three endemic countries. *Am J Trop Med Hyg*. Jan 2015;92(1):108-114. [doi: [10.4269/ajtmh.13-0221](https://doi.org/10.4269/ajtmh.13-0221)] [Medline: [25448239](https://pubmed.ncbi.nlm.nih.gov/25448239/)]
16. Voorend CGN, Post EB. A systematic review on the epidemiological data of erythema nodosum leprosum, a type 2 leprosy reaction. *PLoS Negl Trop Dis*. 2013;7(10):e2440. [doi: [10.1371/journal.pntd.0002440](https://doi.org/10.1371/journal.pntd.0002440)] [Medline: [24098819](https://pubmed.ncbi.nlm.nih.gov/24098819/)]
17. Moraes MO, Sampaio EP, Nery JA, Saraiva BC, Alvarenga FB, Sarno EN. Sequential erythema nodosum leprosum and reversal reaction with similar lesional cytokine mRNA patterns in a borderline leprosy patient. *Br J Dermatol*. Jan 2001;144(1):175-181. [doi: [10.1046/j.1365-2133.2001.03970.x](https://doi.org/10.1046/j.1365-2133.2001.03970.x)] [Medline: [11167702](https://pubmed.ncbi.nlm.nih.gov/11167702/)]
18. Rea TH, Sieling PA. Delayed-type hypersensitivity reactions followed by erythema nodosum leprosum. *Int J Lepr Other Mycobact Dis*. Sep 1998;66(3):316-327. [Medline: [9934358](https://pubmed.ncbi.nlm.nih.gov/9934358/)]
19. Walker SL, Balagon M, Darlong J, et al. ENLIST 1: an international multi-centre cross-sectional study of the clinical features of erythema nodosum leprosum. *PLoS Negl Trop Dis*. 2015;9(9):e0004065. [doi: [10.1371/journal.pntd.0004065](https://doi.org/10.1371/journal.pntd.0004065)] [Medline: [26351858](https://pubmed.ncbi.nlm.nih.gov/26351858/)]
20. Kaur I, Dogra S, Narang T, De D. Comparative efficacy of thalidomide and prednisolone in the treatment of moderate to severe erythema nodosum leprosum: a randomized study. *Australas J Dermatol*. Aug 2009;50(3):181-185. [doi: [10.1111/j.1440-0960.2009.00534.x](https://doi.org/10.1111/j.1440-0960.2009.00534.x)] [Medline: [19659979](https://pubmed.ncbi.nlm.nih.gov/19659979/)]
21. Ramu G, Girdhar A. Treatment of steroid dependant cases of recurrent lepra reaction with a combination of thalidomide and clofazimine. *Lepr India*. Oct 1979;51(4):497-504. [Medline: [522443](https://pubmed.ncbi.nlm.nih.gov/522443/)]
22. Van Brakel WH, Nicholls PG, Lockwood DNJ, Rao PSS, Smith WCS. A scale to assess the severity of leprosy reactions. *Lepr Rev*. Jun 2007;78(2):161-164. [Medline: [17824489](https://pubmed.ncbi.nlm.nih.gov/17824489/)]

23. Manandhar R, LeMaster JW, Roche PW. Risk factors for erythema nodosum leprosum. *Int J Lepr Other Mycobact Dis*. Sep 1999;67(3):270-278. [Medline: [10575406](#)]
24. Walker SL, Sales AM, Butlin CR, et al. A leprosy clinical severity scale for erythema nodosum leprosum: an international, multicentre validation study of the ENLIST ENL Severity Scale. *PLoS Negl Trop Dis*. Jul 2017;11(7):e0005716. [doi: [10.1371/journal.pntd.0005716](#)] [Medline: [28671966](#)]
25. Drummond PLDM, Santos RMMD, Carvalho GO, Pádua CAMD. Adverse events in patients with leprosy on treatment with thalidomide. *Rev Soc Bras Med Trop*. Apr 11, 2019;52:e20180385. [doi: [10.1590/0037-8682-0385-2018](#)] [Medline: [30994805](#)]
26. List of laboratory tests to be performed during the trial. asterisk (*) indicates the subset of tests performed in step 1. All tests will be performed in the step 2. bioRENDER. URL: <https://BioRender.com/k49w070> [Accessed 2026-05-26]
27. Chandler DJ, Hansen KS, Mahato B, Darlong J, John A, Lockwood DNJ. Household costs of leprosy reactions (ENL) in rural India. *PLoS Negl Trop Dis*. Jan 2015;9(1):e0003431. [doi: [10.1371/journal.pntd.0003431](#)] [Medline: [25590638](#)]
28. Costa PDSS, Fraga LR, Kowalski TW, Daxbacher ELR, Schuler-Faccini L, Vianna FSL. Erythema nodosum leprosum: update and challenges on the treatment of a neglected condition. *Acta Trop*. Jul 2018;183:134-141. [doi: [10.1016/j.actatropica.2018.02.026](#)] [Medline: [29474830](#)]
29. Negera E, Bobosha K, Walker SL, et al. New insight into the pathogenesis of erythema nodosum leprosum: the role of activated memory T-cells. *Front Immunol*. 2017;8:1149. [doi: [10.3389/fimmu.2017.01149](#)] [Medline: [28966621](#)]
30. Polycarpou A, Walker SL, Lockwood DNJ. A systematic review of immunological studies of erythema nodosum leprosum. *Front Immunol*. 2017;8:233. [doi: [10.3389/fimmu.2017.00233](#)] [Medline: [28348555](#)]
31. Singal A. Current concepts and challenges in the management of erythema nodosum leprosum. *Indian Dermatol Online J*. 2020;11(4):479-481. [doi: [10.4103/idoj.IDOJ_69_20](#)] [Medline: [32832432](#)]
32. Moraes MO, Sarno EN, Almeida AS, et al. Cytokine mRNA expression in leprosy: a possible role for interferon-gamma and interleukin-12 in reactions (RR and ENL). *Scand J Immunol*. Nov 1999;50(5):541-549. [doi: [10.1046/j.1365-3083.1999.00622.x](#)] [Medline: [10564558](#)]
33. Sousa ALM, Fava VM, Sampaio LH, et al. Genetic and immunological evidence implicates interleukin 6 as a susceptibility gene for leprosy type 2 reaction. *J Infect Dis*. May 1, 2012;205(9):1417-1424. [doi: [10.1093/infdis/jis208](#)] [Medline: [22459738](#)]
34. Hagge DA, Parajuli P, Kunwar CB, et al. Opening a can of worms: leprosy reactions and complicit soil-transmitted helminths. *EBioMedicine*. Sep 2017;23:119-124. [doi: [10.1016/j.ebiom.2017.08.026](#)] [Medline: [28882756](#)]
35. Van Veen NHJ, Lockwood DNJ, van Brakel WH, Ramirez Jr J, Richardus JH. Interventions for erythema nodosum leprosum. *Cochrane Database Syst Rev*. Jul 8, 2009;2009(3):CD006949. [doi: [10.1002/14651858.CD006949.pub2](#)] [Medline: [19588412](#)]
36. Leprosy/Hansen disease: management of reactions and prevention of disabilities. World Health Organization; 2020. URL: <https://www.who.int/publications/i/item/9789290227595> [Accessed 2025-11-18]
37. Post E, Wagenaar I, Brandsma W, et al. Prednisolone adverse events in the treatment and prevention of leprosy neuropathy in two large double blind randomized clinical trials. *Lepr Rev*. Sep 1, 2021;92(3):236-246. [doi: [10.47276/lr.92.3.236](#)]
38. Siagian JN, Menaldi SL. Analysis of therapeutic effectiveness and adverse effects of long-term corticosteroids among leprosy patients with reactions: a retrospective cohort study. *SAGE Open Med*. 2022;10:20503121221089448. [doi: [10.1177/20503121221089448](#)] [Medline: [35465634](#)]
39. Sugumaran DS. Leprosy reactions--complications of steroid therapy. *Int J Lepr Other Mycobact Dis*. Mar 1998;66(1):10-15. [Medline: [9614834](#)]
40. Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharmacol Ther*. 1965;6:303-306. [doi: [10.1002/cpt196563303](#)] [Medline: [14296027](#)]
41. Maghanoy A, Balagon M, Saunderson P, Scheelbeek P. A prospective randomised, double-blind, placebo controlled trial on the effect of extended clofazimine on erythema nodosum leprosum (ENL) in multibacillary (MB) leprosy. *Lepr Rev*. Jun 1, 2017;88(2):208-2016. [doi: [10.47276/lr.88.2.208](#)]
42. Ramien ML, Wong A, Keystone JS. Severe refractory erythema nodosum leprosum successfully treated with the tumor necrosis factor inhibitor etanercept. *Clin Infect Dis*. Mar 1, 2011;52(5):e133-5. [doi: [10.1093/cid/ciq213](#)] [Medline: [21292656](#)]
43. Chowdhry S, Shukla A, D'souza P, Dhali T, Jaiswal P. Treatment of severe refractory erythema nodosum leprosum with tumor necrosis factor inhibitor Etanercept. *Int J Mycobacteriol*. Jun 2016;5(2):223-225. [doi: [10.1016/j.ijmyco.2016.02.002](#)] [Medline: [27242236](#)]
44. Zhu J, Yang D, Shi C, Jing Z. Therapeutic dilemma of refractory erythema nodosum leprosum. *Am J Trop Med Hyg*. Jun 2017;96(6):1362-1364. [doi: [10.4269/ajtmh.16-0118](#)] [Medline: [28719256](#)]

45. de Barros B, Lambert SM, Shah M, et al. Methotrexate and prednisolone study in erythema nodosum leprosum (MaPs in ENL) protocol: a double-blind randomised clinical trial. *BMJ Open*. Nov 17, 2020;10(11):e037700. [doi: [10.1136/bmjopen-2020-037700](https://doi.org/10.1136/bmjopen-2020-037700)] [Medline: [33203627](https://pubmed.ncbi.nlm.nih.gov/33203627/)]
46. Jaume L, Hau E, Monsel G, et al. Methotrexate as a corticosteroid-sparing agent in leprosy reactions: a French multicenter retrospective study. *PLoS Negl Trop Dis*. Apr 2023;17(4):e0011238. [doi: [10.1371/journal.pntd.0011238](https://doi.org/10.1371/journal.pntd.0011238)] [Medline: [37079647](https://pubmed.ncbi.nlm.nih.gov/37079647/)]
47. Miller RA, Shen JY, Rea TH, Harnisch JP. Treatment of chronic erythema nodosum leprosum with cyclosporine A produces clinical and immunohistologic remission. *Int J Lepr Other Mycobact Dis*. Sep 1987;55(3):441-449. [Medline: [3309088](https://pubmed.ncbi.nlm.nih.gov/3309088/)]
48. Lambert SM, Nigusse SD, Alembo DT, et al. Comparison of efficacy and safety of ciclosporin to prednisolone in the treatment of erythema nodosum leprosum: two randomised, double blind, controlled pilot studies in Ethiopia. *PLoS Negl Trop Dis*. Feb 2016;10(2):e0004149. [doi: [10.1371/journal.pntd.0004149](https://doi.org/10.1371/journal.pntd.0004149)] [Medline: [26919207](https://pubmed.ncbi.nlm.nih.gov/26919207/)]
49. Tapia C, Nessel TA, Zito PM. Cyclosporine. In: *StatPearls*. StatPearls Publishing; 2025. [Medline: [29494057](https://pubmed.ncbi.nlm.nih.gov/29494057/)]
50. Marlowe SNS, Hawksworth RA, Butlin CR, Nicholls PG, Lockwood DNJ. Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg*. Oct 2004;98(10):602-609. [doi: [10.1016/j.trstmh.2003.12.013](https://doi.org/10.1016/j.trstmh.2003.12.013)] [Medline: [15289097](https://pubmed.ncbi.nlm.nih.gov/15289097/)]
51. Lockwood DNJ, Darlong J, Govindharaj P, Kurian R, Sundarrao P, John AS. AZALEP a randomized controlled trial of azathioprine to treat leprosy nerve damage and type 1 reactions in India: main findings. *PLoS Negl Trop Dis*. Mar 2017;11(3):e0005348. [doi: [10.1371/journal.pntd.0005348](https://doi.org/10.1371/journal.pntd.0005348)] [Medline: [28358815](https://pubmed.ncbi.nlm.nih.gov/28358815/)]
52. Durães SMB, Salles SDAN, Leite VRB, Gazzeta MO. Azathioprine as a steroid sparing agent in leprosy type 2 reactions: report of nine cases. *Lepr Rev*. Sep 2011;82(3):304-309. [Medline: [22125939](https://pubmed.ncbi.nlm.nih.gov/22125939/)]
53. Jitendra SSV, Bachaspatimayum R, Devi AS, Rita S. Azathioprine in chronic recalcitrant erythema nodosum leprosum: a case report. *J Clin Diagn Res*. Aug 2017;11(8):FD01-FD02. [doi: [10.7860/JCDR/2017/26536.10499](https://doi.org/10.7860/JCDR/2017/26536.10499)] [Medline: [28969152](https://pubmed.ncbi.nlm.nih.gov/28969152/)]
54. Mohammadi O, Kassim TA. Azathioprine. In: *StatPearls*. StatPearls Publishing; 2025. [Medline: [31194347](https://pubmed.ncbi.nlm.nih.gov/31194347/)]
55. Patel AA, Swerlick RA, McCall CO. Azathioprine in dermatology: the past, the present, and the future. *J Am Acad Dermatol*. Sep 2006;55(3):369-389. [doi: [10.1016/j.jaad.2005.07.059](https://doi.org/10.1016/j.jaad.2005.07.059)] [Medline: [16908341](https://pubmed.ncbi.nlm.nih.gov/16908341/)]
56. Cogen AL, Lebas E, De Barros B, et al. Biologics in leprosy: a systematic review and case report. *Am J Trop Med Hyg*. May 2020;102(5):1131-1136. [doi: [10.4269/ajtmh.19-0616](https://doi.org/10.4269/ajtmh.19-0616)] [Medline: [32157993](https://pubmed.ncbi.nlm.nih.gov/32157993/)]
57. Mendes AFM, Gomes CM, Kurizky PS, Ianhez M. Case report: a case series of immunobiological therapy (anti-TNF- α) for patients with erythema nodosum leprosum. *Front Med (Lausanne)*. 2022;9:879527. [doi: [10.3389/fmed.2022.879527](https://doi.org/10.3389/fmed.2022.879527)] [Medline: [35814767](https://pubmed.ncbi.nlm.nih.gov/35814767/)]
58. Winterfield LS, Menter A. Infliximab. *Dermatol Ther*. 2004;17(5):409-426. [doi: [10.1111/j.1396-0296.2004.04044.x](https://doi.org/10.1111/j.1396-0296.2004.04044.x)] [Medline: [15379776](https://pubmed.ncbi.nlm.nih.gov/15379776/)]
59. Goffe B, Cather JC. Etanercept: an overview. *J Am Acad Dermatol*. Aug 2003;49(2 Suppl):S105-11. [doi: [10.1016/mjd.2003.554](https://doi.org/10.1016/mjd.2003.554)] [Medline: [12894133](https://pubmed.ncbi.nlm.nih.gov/12894133/)]
60. Subbian S, Koo MS, Tsenova L, et al. Pharmacologic inhibition of host phosphodiesterase-4 improves isoniazid-mediated clearance of *Mycobacterium tuberculosis*. *Front Immunol*. 2016;7:238. [doi: [10.3389/fimmu.2016.00238](https://doi.org/10.3389/fimmu.2016.00238)] [Medline: [27379099](https://pubmed.ncbi.nlm.nih.gov/27379099/)]
61. Amgen is supporting advancement of AMG 634 for global health diseases in developing countries. Amgen. URL: <https://www.amgen.com/newsroom/press-releases/2020/06/amgen-is-supporting-advancement-of-amg-634-for-global-health-diseases-in-developing-countries> [Accessed 2026-05-23]
62. Amgen to buy Celgene psoriasis drug Otezla for \$13.4 billion. Reuters. URL: <https://www.reuters.com/article/business/amgen-to-buy-celgene-psoriasis-drug-otezla-for-134-billion-idUSKCN1VG102/> [Accessed 2024-11-18]
63. MDGH acquires a new potential treatment of tuberculosis and leprosy. Medicines Development for Global Health (MDGH). URL: <https://www.medicinesdevelopment.com/news/mdgh-update-march-2021> [Accessed 2024-11-18]
64. Boulougoura A, Gabriel E, Laidlaw E, et al. A phase I, randomized, controlled clinical study of CC-11050 in people living with HIV with suppressed plasma viremia on antiretroviral therapy (APHRODITE). *Open Forum Infect Dis*. Jun 2019;6(6):ofz246. [doi: [10.1093/ofid/ofz246](https://doi.org/10.1093/ofid/ofz246)] [Medline: [31211164](https://pubmed.ncbi.nlm.nih.gov/31211164/)]
65. Subbian S, Tsenova L, Holloway J, et al. Adjunctive phosphodiesterase-4 inhibitor therapy improves antibiotic response to pulmonary tuberculosis in a rabbit model. *EBioMedicine*. Feb 2016;4:104-114. [doi: [10.1016/j.ebiom.2016.01.015](https://doi.org/10.1016/j.ebiom.2016.01.015)] [Medline: [26981575](https://pubmed.ncbi.nlm.nih.gov/26981575/)]

66. Kolloli A, Ramasamy S, Kumar R, Nisa A, Kaplan G, Subbian S. A phosphodiesterase-4 inhibitor reduces lung inflammation and fibrosis in a hamster model of SARS-CoV-2 infection. *Front Immunol.* 2023;14:1270414. [doi: [10.3389/fimmu.2023.1270414](https://doi.org/10.3389/fimmu.2023.1270414)] [Medline: [37854602](https://pubmed.ncbi.nlm.nih.gov/37854602/)]
67. Wallis RS, Ginindza S, Beattie T, et al. Adjunctive host-directed therapies for pulmonary tuberculosis: a prospective, open-label, phase 2, randomised controlled trial. *Lancet Respir Med.* Aug 2021;9(8):897-908. [doi: [10.1016/S2213-2600\(20\)30448-3](https://doi.org/10.1016/S2213-2600(20)30448-3)] [Medline: [33740465](https://pubmed.ncbi.nlm.nih.gov/33740465/)]
68. Villahermosa LG, Fajardo Jr TT Jr, Abalos RM, et al. A randomized, double-blind, double-dummy, controlled dose comparison of thalidomide for treatment of erythema nodosum leprosum. *Am J Trop Med Hyg.* May 2005;72(5):518-526. [Medline: [15891124](https://pubmed.ncbi.nlm.nih.gov/15891124/)]
69. Haslett PAJ, Roche P, Butlin CR, et al. Effective treatment of erythema nodosum leprosum with thalidomide is associated with immune stimulation. *J Infect Dis.* Dec 15, 2005;192(12):2045-2053. [doi: [10.1086/498216](https://doi.org/10.1086/498216)] [Medline: [16288366](https://pubmed.ncbi.nlm.nih.gov/16288366/)]
70. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med.* Feb 5, 2013;158(3):200-207. [doi: [10.7326/0003-4819-158-3-201302050-00583](https://doi.org/10.7326/0003-4819-158-3-201302050-00583)] [Medline: [23295957](https://pubmed.ncbi.nlm.nih.gov/23295957/)]
71. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. National Cancer Institute; 2017. URL: <https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf> [Accessed 2026-04-05]
72. Li H, Zuo J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Front Pharmacol.* 2018;9:1048. [doi: [10.3389/fphar.2018.01048](https://doi.org/10.3389/fphar.2018.01048)] [Medline: [30386231](https://pubmed.ncbi.nlm.nih.gov/30386231/)]
73. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet.* Aug 25, 2012;380(9843):738-746. [doi: [10.1016/S0140-6736\(12\)60642-4](https://doi.org/10.1016/S0140-6736(12)60642-4)] [Medline: [22748702](https://pubmed.ncbi.nlm.nih.gov/22748702/)]
74. Narang T, Kaushik A, Dogra S. Apremilast in chronic recalcitrant erythema nodosum leprosum: a report of two cases. *Br J Dermatol.* Apr 2020;182(4):1034-1037. [doi: [10.1111/bjd.18233](https://doi.org/10.1111/bjd.18233)] [Medline: [31218666](https://pubmed.ncbi.nlm.nih.gov/31218666/)]
75. Narang T, Ashraf R, Kaushik A, Dogra S. Apremilast in multibacillary leprosy patients with chronic and recurrent erythema nodosum leprosum: a prospective single-centre pilot study. *J Eur Acad Dermatol Venereol.* Dec 2021;35(12):e917-e919. [doi: [10.1111/jdv.17585](https://doi.org/10.1111/jdv.17585)] [Medline: [34365679](https://pubmed.ncbi.nlm.nih.gov/34365679/)]
76. Mandloi U, Gogia N, Sonare D, Waghmare S. Apremilast in erythema nodosum leprosum: a case series. *J Dermatol Dermatol Surg.* 2024;28(1):42-45. [doi: [10.4103/jdds.jdds_45_23](https://doi.org/10.4103/jdds.jdds_45_23)]

Abbreviations

- AE:** adverse events
- BL:** borderline lepromatous
- DSMB:** Data and Safety Monitoring Board
- EESS:** ENL International Study Group ENL Severity Scale
- ENL:** erythema nodosum leprosum
- IL:** interleukin
- LL:** lepromatous leprosy
- MDT:** multidrug therapy
- NCI CTCAE:** National Cancer Institute Common Terminology Criteria for Adverse Events
- PDE4:** phosphodiesterase 4
- REDCap:** Research Electronic Data Capture
- SPIRIT:** Standard Protocol Items Recommendations for Interventional Trials
- T1R:** type 1 reaction
- TNF:** tumor necrosis factor
- WHO:** World Health Organization

Edited by Amy Schwartz; peer-reviewed by Paulo R L Machado, Sunil K Gupta; submitted 19.Nov.2025; final revised version received 29.Apr.2026; accepted 30.Apr.2026; published 17.Jun.2026

Please cite as:

Shah M, Rana DRSJB, Neupane KD, Maharjan P, Baral S, Shrestha R, Shakya J, Aryal B, Acharya B, Napit IB, Hagge DA. Dovramilast for Erythema Nodosum Leprosum in Patients With Leprosy in Nepal: Protocol for a Phase 2 Open-Label Pilot Study

JMIR Res Protoc 2026;15:e88069

URL: <https://www.researchprotocols.org/2026/1/e88069>

doi: [10.2196/88069](https://doi.org/10.2196/88069)

© Mahesh Shah, Divya R S J B Rana, Kapil Dev Neupane, Preeti Maharjan, Suwash Baral, Reejana Shrestha, Jivan Shakya, Binod Aryal, Bishwanath Acharya, Indra Bahadur Napit, Deanna Alisa Hagge. Originally published in JMIR Research Protocols (<https://www.researchprotocols.org>), 17.Jun.2026. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Research Protocols, is properly cited. The complete bibliographic information, a link to the original publication on <https://www.researchprotocols.org>, as well as this copyright and license information must be included.