Expression of Interest

The Clinical Studies and Trials Unit, Division of Development Research, Indian Council of Medical Research, New Delhi

Invites Expression of Interest (EoI) from ICMR-INTENT centres for

Collaboration in the design and conduct of a double blind parallel-arm randomized controlled trial to evaluate the efficacy and safety of Bedaquiline in combination with Multi-drug therapy in individuals with Multibacillary Leprosy

Invitation of expression of Interest

The Clinical Studies and Trials Unit, Division of Development Research, Indian Council of Medical Research (ICMR), New Delhi, is pleased to invite Expressions of Interest (EoI) from ICMR Indian Clinical Trial and Education Network (INTENT) centres for the purpose of design and conduct of a double blind parallel-arm randomized controlled trial to evaluate the efficacy and safety of Bedaquiline in combination with Multi-drug therapy in individuals with Multibacillary Leprosy

Schedule of EoI:

- Date of Publication: 28 February 2025
- Last Date of Submission: 21 March 2025

Interested applicants may submit required information through a Google form, the link for which is available at the end of this document. Please note that only shortlisted ICMR-INTENT centres will be contacted for the subsequent steps. ICMR reserves the right to cancel this EoI and/or reissue it with or without amendments, without incurring any liability or obligation. No reason may be provided for such decisions. ICMR reserves the right to amend or add further details to the EoI as deemed necessary by the Competent Authority, which will be duly notified.

Background

An estimated 1,02,200 new cases of leprosy reported by the National Leprosy Eradication Programme in 2022-2023 in India. While there has been a steady decline in leprosy burden, there still remains a substantial number of new cases detected every year in India. The National Strategic Plan and Roadmap for Leprosy 2023-2027 for India aims to achieve interruption of transmission at district for at least five consecutive years.

The current treatment regimens for leprosy had been introduced more than 30 years ago; there is a need for newer efficacious drugs to treat leprosy disease. Bedaquiline (BDQ), a new class of antimicrobials uniquely active against mycobacteria and currently approved only for treatment of drug-resistance Tuberculosis, has shown promising bactericidal activity against Mycobacterium leprae in Animal studies and Phase 1 clinical trials. Addition of BDQ to Rifampicin containing regimens ensures two bactericidal drugs, thus potentially ensuring a sterilizing effect of the regimen, which can interrupt transmission of leprosy. To generate evidence of efficacy of Bedaquiline in leprosy treatment, the Clinical Studies and Trials Unit (CSTU), through the INTENT, plans to conduct a clinical trial to evaluate the efficacy and safety of Bedaquiline in combination with Multi-drug therapy in individuals with Multibacillary Leprosy

Objective

To select institutions within the INTENT that will participate in the design and conduct of an ICMR-funded double blind parallel-arm randomized controlled trial to evaluate the efficacy and safety of Bedaquiline in combination with Multi-drug therapy in individuals with Multibacillary Leprosy

Scope of work

- Selected institutions will co-design a clinical trial protocol for the trial mentioned in the objective. The CSTU, with inputs from experts, has developed a draft protocol synopsis for the same, which is expected to provide a reference for protocol development. The synopsis is available at Annexure 1.

- Selected institutions will conduct the said clinical trial at their institutions, ensuring compliance to ethical requirements and good clinical practices
- Overall trial coordination and trial monitoring will be the responsibilities of the CSTU, ICMR.

Eligibility Criteria:

INTENT Institutes interested in submitting an Expression of Interest (EoI) should provide information regarding the following parameters

1. **Proven Experience:** The applicant must have demonstrated experience in conducting late-phase clinical trials, both in-facility as well as community-based trials. This includes a history of successfully managing and executing such trials, with verifiable outcomes. Experience in conduct of regulation-compliant clinical trials is desirable.

2. **Access to Facilities and Resources:** The applicant must have access to necessary facilities, equipment, and resources required to conduct comprehensive clinical evaluations. This includes, but is not restricted to, clinical trial infrastructure (for e.g., three-room strategy, Investigational Product management facilities, etc.), availability of experienced GCP-certified human resources, availability of Standard Operating Procedures laboratory facilities for leprosy related diagnostics/prognostics, medical care facilities (for SAE/AE management), clinical trial data management resources, DHR-registered Institutional Ethics Committee and any other resource essential for the successful execution of the trial

3. **Access to adequate number of cases/ study participants:** The applicant should demonstrate capacity to enroll eligible study participants from health facilities and community.

4. Multidisciplinary team: The applicant should form a team including investigators from all the required domains (community medicine, dermatology, internal medicine/ infectious disease, microbiology, etc.)

Applicants are required to submit required information in a Google form, the link for which is available at the end of this document. Only those entities that meet these

eligibility criteria will be considered for the subsequent stages of the EoI evaluation process.

Important Points for Submitting the Expression of Interest (EoI): Your submission must thoroughly address each specific question outlined in the Google form. Provide clear, concise, and detailed responses that demonstrate your understanding and alignment with the EoI requirements.

Adherence to these points will be critical in the evaluation of your EoI. Please ensure that your submission is complete and aligned with the objectives.

Review Process

The process for reviewing the Expression of Interest (EoI) submissions will involve the following steps:

1. **Initial Screening by ICMR:** The EoI documents will be evaluated and shortlisted by a team at the Indian Council of Medical Research (ICMR). During this initial phase, the ICMR team will screen the applications for completeness and accuracy of information. Each application will be screened independently, irrespective of the number of applications submitted by a single ICMR-INTENT centre.
2. **Short listing of Applicants:** Applications that meet the eligibility criteria will be reviewed by independent experts based on the information submitted by applicants and shortlisted for further consideration by the Competent Authority of ICMR.
3. **Further steps:** Selected ICMR-INTENT centres for the trial will be informed about their selection and further procedures regarding the trial.

Timeline:

Activities	**Date**
Release of Call	28 February 2025
Last date of Submission of EoI	21 March 2025

Link for Google application form:
https://docs.google.com/forms/d/e/1FAIpQLSds3pQPT6WbcIXMH0_Na7sebI4hPiZOjwGBMlDmBujQXMw6dg/viewform?usp=header

For any queries related to the call, please contact:

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Annexure 1: Clinical Trial Protocol Synopsis

Study Title	A double-blind parallel-arm randomized controlled trial to evaluate the efficacy and safety of Bedaquiline in combination with Multi-drug therapy in individuals with Multibacillary Leprosy
Clinical Phase	Phase 3
Study rationale	An estimated 1,02,200 new cases of leprosy reported by NLEP in 2022-2023 in India. While there has been a steady decline, there still remains a substantial number of new cases detected every year in India. Multibacillary (MB) leprosy cases which represents 61% of total cases, tend to be more infectious than paucibacillary (PB) cases. Among MB cases, those with bacillary index of ≥ 3+ are highly infectious. Around 40% to 60% of MB cases in India have bacillary index of ≥ 3+. Interruption of transmission is essential to reduce burden. Thus, effective treatment of MB cases with ≥ 3+ bacillary index is crucial. A systematic review and meta-analysis published in 2023 that aimed to synthesize evidence on the efficacy and safety of drugs for treating leprosy reported that the WHO regimen may not be effective enough and MDT combined with other drugs may be more effective than MDT alone. Studies reporting viable bacteria in patients even after 2 years of regular treatment, relapse, resistance against Rifampicin shows the need for newer drugs for the treatment of Leprosy. Bedaquiline (BDQ), a new class of antimicrobials uniquely active against mycobacteria is currently approved only for treatment of DR-TB. Animal studies has shown promising bactericidal activity against M leprae. Pharmacokinetics and dynamics are well known from TB related studies. Addition of BDQ to Rifampicin containing regimen ensures two bactericidal drugs, thus potentially ensuring a sterilizing effect of the regimen. This can interrupt transmission of leprosy
Study Objective(s)	**Primary:** To estimate the efficacy of Bedaquiline-containing multi-drug therapy in bacteriological clearance, as assessed by measuring bacillary index and morphological index, in individuals with newly detected multibacillary leprosy compared to standard multi-drug therapy after one year of treatments **Secondary:** **1.** To compare the safety of Bedaquiline-containing multi-drug therapy with standard WHO MB multi-drug therapy up to 12 months of therapy **2.** To test the efficacy of Bedaquiline-containing multi-drug therapy in achieving clinical cure, as assessed by disappearance of/change in lesions, in individuals with newly detected multibacillary leprosy with bacillary index of ≥ 3+/mB positive compared to standard multi-drug therapy after 6 and 12 months of treatment **3.** To compare the incidence and severity of type 1 and type 2 reactions and neuritis between the BDQ-containing regimen and WHO MB standard multi-drug therapy **4.** To estimate the number of relapses, as evidenced by appearance of new lesions or increase in the bacillary score at any skin smear site compared to the previous bacillary score upto five years of follow-up

Investigational products	**Intervention arm**: All-oral regimen of Bedaquiline (200 mg orally once daily for 2 weeks followed by 800 mg once a month for 6 months) plus MDT (Rifampicin 600 mg once a month plus Clofazimine 300 mg once a month and 50 mg daily plus Dapsone 100 mg daily, all for 12 months) **Comparator arm:** Standard all-oral regimen for MB leprosy that includes Rifampicin 600 mg once a month plus Clofazimine 300 mg once a month and 50 mg daily plus Dapsone 100 mg daily, all for 12 months
Indication	Multibacillary leprosy
Study Design	Multi-centre double-blind parallel-arm randomized controlled trial
Subject Population **key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1. Treatment naïve MB smear +ve 2. all adults in the age group of 18-60 years 3. Patient willing to be followed up for 5 years 4. Apparently healthy on the basis of physical examination, medical history, vital signs, and 12-lead electrocardiogram (ECG) performed at screening 5. Results within normal limits of biochemical tests including liver enzymes, blood coagulation, hematology **Exclusion Criteria** 1. Any previous treatment with any anti-leprosy drug for any duration 2. Concomitant Tuberculosis disease or undergoing treatment for Tuberculosis disease 3. Women who are pregnant or breastfeeding at the time of enrollment or unwilling to practice reliable contraception for the period of therapy and 6 months after stopping the therapy 4. Known case of any major cardiac, hepatic renal or systemic diseases 5. Results within normal limits of biochemical tests including liver enzymes, , hematology 6. Any one with following deranged laboratory parameters: Hb<8 gm/dl, >3 times upper level for Bi, liver enz- SGPT , SGOT, G6PD def for dapsone , HbA1c>8, HIV/HCV/HbsAg + ,known alcohol and substance abuse , Any QTc (>450ms) abnormality in baseline ECG, weight <40kg
Number of Participants	800 to 1000 eligible individuals
Study Duration	Recruitment will be completed in 1 to 1.5 years. Each subject will be given treatment for 12 months and will be followed up for another 12 months. i.e duration of participation of each patient will last for 24 months. The total study duration will be between 3 to 3.5 years.
Study Phases	**Screening and enrollment:** Individuals presenting at the clinics of the study centres will be screened for eligibility. Eligible participants will be invited to participate in the study and after providing consent, will be randomly allocated to one of the two study arms.

	Safety Cohort: The first 30 participants enrolled in the trial will be followed till month 6 visit, as mentioned below, for safety-related outcomes. Conditional to evidence of acceptable safety in these 30 participants, as determined by A DSMB and Ethics Committees, the remaining participants will be enrolled. **Study visits:** **Baseline visit:** Participants will undergo a clinical assessment of leprosy disease that includes recording of all hypopigmented or reddish skin lesions with definite loss of sensation as well as definite thickening with loss of sensation and weakness /paralysis of the corresponding muscles of the hands, feet or eyes. Samples for slit skin smears will be collected from at least two sites, earlobe and active (erythematous or infiltrated) lesion and examined for bacillary and morphological indices. They will then be administered the first dose of the IP. **Home visits:** Study personnel will visit homes of participants daily for first 14 days to administer the IP and assess for adverse events **Week 1, 4 and 8 visits:** Participants will be asked to visit the study clinic for clinical assessment. ECG will be performed to detect any abnormality, especially prolonged QTc interval. In addition, at week 8 visit, samples for slit skin smears will be collected from the same sites as in baseline visit and examined for bacillary and morphological indices. **Month 6 visit:** Clinical assessment and ECG will be performed to detect any abnormality. Samples for slit skin smears will be collected from the same sites as in previous visit and examined for bacillary and morphological indices. **Month 12 visit:** Clinical assessment will be performed. Samples for slit skin smears will be collected from the same sites as in previous visit and examined for bacillary and morphological indices. **Month 24 / end of study visit:** Clinical assessment will be performed to check for development of one or more new skin patches consistent with leprosy without evidence of reactions. Samples for slit skin smears will be collected from the same sites as in previous visit and examined for bacillary and morphological indices. Any relapse case will be referred to the NLEP for management. **All visits:** Assessment of adverse events and type 1 & 2 reactions will performed.
Primary endpoint *(can assess composite endpoint)*	**1.** Change from baseline in the bacillary index from ≥ 3+ to 1+ or no bacilli detected at one year after enrollment. **2.** Change from baseline in morphological index to 0 at one year after enrollment
Secondary endpoints	1. Regression in skin lesions at one year after enrollment. This will be assessed as: number, border, size, surface, satellites 2. Change in nerve function impairment 3. Molecular and mouse foot pad viability assay 4. All of the primary endpoints and first three secondary endpoints at 6 months after enrollment 5. Frequency of incidence of severe adverse events and adverse events 6. Quality of life EQL 7. Frequency of disease relapse