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Request for Expression of Interest (EOI)

Clinical Trial for Vorinostat in Duchenne Muscular Dystrophy

Background

Duchenne Muscular Dystrophy (DMD) is a progressive, X-linked neuromuscular disorder characterized by the absence of functional dystrophin protein, leading to irreversible muscle degeneration, loss of ambulation, and premature mortality. Despite advances in genetic diagnosis and supportive care, therapeutic options remain limited in India, and there is an urgent need for disease-modifying therapies.

Vorinostat, an FDA approved histone deacetylase (HDAC) inhibitor for cutaneous T-cell lymphoma, has shown potential in preclinical models of DMD to reduce fibrosis, improve muscle regeneration, and preserve muscle strength. Furthermore, it mitigates cardiac arrhythmias, addressing critical secondary complications. Data from recent studies, including the EPIDYS trial of Givinostat (another HDAC inhibitor), support the therapeutic relevance of epigenetic modulation in DMD pathophysiology.

Phase 1 studies in other indications (e.g., oncology) have established vorinostat's safety profile at doses up to 400 mg/day in adults, with common adverse events including thrombocytopenia, diarrhea, and fatigue. Given its existing safety profile, Vorinostat is a promising candidate for drug repurposing to provide an affordable and accessible intervention for DMD patients in India.

This proposal seeks to evaluate the safety and efficacy of Vorinostat in a multicentre, regulatory-compliant Phase III clinical trial in ambulatory boys with genetically confirmed DMD. A synopsis of the study protocol is provided below:

PROTOCOL SYNOPSIS

Study Title	Efficacy and safety of Vorinostat in ambulant patients With Duchenne Muscular Dystrophy
Clinical Phase	Phase III trial
Sponsor/Funding Source	Indian Council of Medical Research (ICMR)
Study Rationale	Duchenne Muscular Dystrophy (DMD) is a progressive, fatal neuromuscular disorder with limited treatment options. Epigenetic dysregulation contributes to inflammation, fibrosis, and impaired muscle regeneration in DMD. Vorinostat, a pan-HDAC inhibitor, has demonstrated preclinical efficacy in improving muscle histology and function suggesting it may slow disease progression. This Phase III open-label study aims to evaluate the efficacy and safety of Vorinostat in ambulant DMD patients, using functional outcomes and imaging markers, with the goal of establishing it as a potential disease-modifying therapy.
Study Objective(s)	1. To assess the efficacy of Vorinostat in preserving muscle function, measured by 6-minute walk test (6MWT). 2. North Star Ambulatory Assessment (NSAA), safety and tolerability, muscle biomarkers, and quality-of-life assessments.
Investigational products	Vorinostat
Indication	Oral suspension, weight-based dosing, administered twice daily. • Initial Dose (Regimen 1): _____(divided into two doses; max 400 mg/day). • Reduced Dose: _____ if AEs (e.g., thrombocytopenia, diarrhea) occur.
Study Design	Prospective, multicentre, single-arm, open-label
Subject Population key criteria for Inclusion and Exclusion:	**Ambulant boys with DMD** **Inclusion Criteria** • Male, aged ≥6 years, with genetically confirmed DMD (dystrophin gene mutation). • Ambulant, able to complete two four-stair climb assessments with mean ≤8 seconds (variance ≤1 second). • Time-to-rise from floor ≥3 seconds but <10 seconds. • Stable systemic corticosteroid use (deflazacort or prednisone) for ≥6 months, with no expected changes during the study. • Baseline VLFF measured by MRS.

	• Written informed consent from participant and parent/legal guardian. **Exclusion Criteria** • Recent surgery or medication changes (within 3 months) affecting muscle function. • Significant comorbidities (e.g., cardiac, hepatic, or renal dysfunction). • Known hypersensitivity to HDAC inhibitors. • Use of other investigational drugs within 30 days. • Platelet count <100,000/µL or other hematologic abnormalities at screening.
Number of patients	180 approximately
Study Duration	48 weeks of treatment, with 24-week follow-up post-treatment.
Study Phases	Screening: Confirm eligibility, obtain consent, perform baseline MRS, and collect medical history. Baseline (Day 1): Four-stair climb, NSAA, 6MWT, muscle strength, labs (hematology, chemistry), and PK sampling. Treatment Phase (Weeks 1-48): Visits every 12 weeks: Four-stair climb, NSAA, 6MWT, muscle strength, AE assessment, labs. Magnetic Resonance Spectroscopy (MRS) at weeks 24 and 48. PK sampling at weeks 4 and 24. Follow-Up (Week 72): Safety and functional assessments. Compliance: Assessed via participant diaries; compliance = [(expected doses - missed doses) / expected doses] × 100.
Endpoints	• Change in four-stair climb time (seconds) from baseline to 48 weeks. • Change in NSAA total score from baseline to 48 weeks. • Change in 6MWT distance (meters) from baseline to 48 weeks. • Incidence and severity of adverse events (AEs), serious adverse events (SAEs), and dose-limiting toxicities (DLTs).

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- Change in Vastus Lateralis Fat Fraction (VLFF) % from baseline to 48 weeks.
- PK parameters (Cmax, AUC, Tmax) at weeks 4 and 24.

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<tr><td>Exploratory endpoints (if any)</td><td>

- Change in time-to-rise from floor (seconds) and muscle strength (knee extension/elbow flexion via hand-held myometry).

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<tr><td>Data Collection & Statistical And Analytic Plan</td><td>

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<tr><td>Phase</td><td>Duration</td></tr>
<tr><td>Site Initiation</td><td>3 months</td></tr>
<tr><td>Recruitment</td><td>6 months</td></tr>
<tr><td>Treatment + Follow-up</td><td>12 months+ 6 months</td></tr>
<tr><td>Data Analysis & Reporting</td><td>3 months</td></tr>
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A. Data Collection Plan

1. Data Sources

- Data will be collected directly from participants, caregivers, and site assessments using standardized tools.
- Data will be entered into a secure, electronic data capture (EDC) system.
- Source documents will include clinic notes, lab reports, radiology images (MRI), ECG/ECHO reports, and patient diaries.

2. Schedule of Data Collection

- At Screening: Demographics, genetics, medical history, baseline labs, functional tests (6MWD, NSAA), MRI, ECG/ECHO, FVC, etc.
- During Treatment weeks 1 to 48): Functional scores, safety labs, AE reporting, ECG/ECHO, compliance, PK (subset), MRI at 24, 48 and 72 weeks.
- Follow-Up (weeks 48 to 72): Final safety, ambulation status, functional outcomes, and imaging if pending.
- Early Termination Visit: All final assessments as feasible.

3. Data Quality Assurance

- Source data verification (SDV) for all primary endpoint values
- Central monitoring of outliers and missing data
- Periodic audits by the sponsor or independent monitors

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Safety Evaluations	Adverse Events: AEs and SAEs graded per CTCAE v5.0, reported within 24 hours for SAEs. Dose-Limiting Toxicities: Thrombocytopenia (<50,000/μL), Grade 3/4 diarrhea, or other Grade 3/4 AEs deemed treatment-related. Monitoring: Weekly lab monitoring (first 8 weeks), then every 4 weeks. Independent Data Safety Monitoring Board (DSMB) reviews safety data quarterly. Stopping Rules: Study termination if >20% of participants experience DLTs or if futility criteria are met at interim analysis.
Data and Safety Monitoring Board	The DSMB will comprise of an independent panel of five experts in pediatric neurology, clinical pharmacology, biostatistics, and cardiology. The DSMB will periodically review unblinded safety and efficacy data to ensure participant safety and trial integrity. Meetings are scheduled at 25%, 50%, and 75% enrolment milestones, with additional ad hoc reviews as needed. Based on risk-benefit assessments, the DSMB will recommend whether the trial should continue as planned, be modified, paused, or terminated. All proceedings will remain confidential, and a detailed DSMB Charter will guide its operations.

Who can apply?

Institutes/Organizations registered as ICMR-INTENT trial centers can submit an expression of interest.

- The organization should have experience of conducting clinical trials in the treatment and management of inherited rare diseases.
- A Principal Investigator (PI) affiliated with the INTENT centre will be the lead applicant. A multi-disciplinary team of Co-Investigators comprising of a Neurologist (Pediatric/Adult), Clinical Pharmacologist, Biostatistician, and Geneticist/Molecular Biologist is to be involved; preferably, the number of Co-Investigators in the team should not be more than five. The PI and team should be endorsed by the Head of the Institute/College.

Review and selection process:

The applications will be reviewed by an independent committee of experts. The following criteria will be considered while shortlisting the centers for the clinical trial:

- Experience of the PI in the treatment and management of inherited rare diseases, specifically Duchenne muscular dystrophy

- The institute has access to potential trial participants, including both in-patient and out-patient.
- Publications of PI and team in journals with high impact factor on inherited rare diseases.
- The number of extramural grants received by the institute on inherited rare diseases in the last 5 years
- Presence of requisite infrastructure and space to conduct clinical trials.
- Institutional Ethics Committee (IEC) and CTRI registration available.

How to apply?

Interested institutes may submit the EoI via the Google form in the link given below: https://docs.google.com/forms/d/e/1FAIpQLSfGoG6x8k_s6J6Z-HgCX5qK6P0RXV0NYO-tSb1qNkEI2rLYpg/viewform?usp=header

Only ONLINE applications will be reviewed, and only the successful applicants will be informed via email.

Timelines

Activities	Date
Release of call for EOI	23rd July 2025
Last date of submission of EoI	10th August 2025
Review and shortlisting of centers	30th August 2025

For any queries related to this call, please reach out to the following:

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