PATIENT REGISTRY STUDY PROTOCOL

Prospective, long term, observational study (patient registry) of paediatric myotonic disorders from birth to less than six years of age who are treated with mexiletine (PEGASUS Study).

Protocol No	MEX-NM-401
Version	1.0
Date	May 31, 2024
Supersedes	Not applicable
Study drug:	Mexiletine
Development Phase:	N/A
EU PAS Registration No:	Study not yet registered
Current PIP decision number	P/0300/2023
Current approved PIP version	EMEA-002012-PIP01-16-M04
Sponsor:	Lupin Europe GmbH Address; Hanauer Landstraße 139-143 60314 Frankfurt am Main, Germany.

This study will be conducted according to the protocol and in compliance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

Sponsor Statement: This protocol was subject to critical review and has been approved by the following:

DocuSigned by Alla Zozulya-Weidenfeller
Alla Zozulya-Weidenfeller
I approve this document
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Signed: _____ Date: _____
2F5143935539497F9A00ADA42A358495

Alla Zozulya Weidenfeller, PhD
Study Medical Lead, Senior Director
Lupin Neuroscience, EMEA
Lupin Pharmaceuticals, Inc.

DocuSigned by Nikki Adetoro
Nikki Adetoro
I approve this document
5/31/2024 | 12:40:23 PM EDT
Signed: _____ Date: _____
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Nikki Adetoro
Vice-President Clinical Operations
Lupin Research Inc.
Lupin Pharmaceuticals, Inc.

STUDY SYNOPSIS

Title of Study: Prospective, long term, observational study (patient registry) of paediatric myotonic disorders in patients from birth to less than six years of age who are treated with mexiletine (PEGASUS Study).	
Protocol No.: **Version No. and Date**	**MEX-NM-401** Version: 1.0 May 31, 2024
Name of Sponsor/Company:	Lupin Europe GmbH
Name of finished product	Product is specified only by active substance (mexiletine)
Name of Active Ingredient:	Mexiletine HCl
Development Phase	N/A
Study Indication	Symptomatic treatment of paediatric myotonic disorders

Objectives:

Primary

The primary objective of this patient registry study is:

- To evaluate the safety and the efficacy (exploratory) of mexiletine for the treatment of myotonia in the paediatric population aged from birth to less than 6 years using real world data.

Secondary

The secondary objectives are:

- To assess the suitability of mexiletine administration using available formulations including, where appropriate, capsules or opening and sprinkling contents in food or drink according to the child´s age (from birth to less than 6 years) and ability to swallow.
- To understand how mexiletine is used by clinicians who have previously decided to use mexiletine for the treatment of myotonia in myotonic disorder patients, from birth to less than 6 years over a 2 year period in a prospective manner, to establish risk:benefit conclusions.

Overview of Study Design

This is a prospective, open-label, multi-centre, single arm, registry study to collect standard relevant clinical and epidemiological data during routine medical evaluation and treatment

in paediatric patients with myotonic disorders who are being treated with mexiletine therapy according to the physician.

Patients who meet the eligibility criteria will be enrolled in 2 cohorts by age groups although cohorts are not enrolled sequentially (cohort definition is to assure minimum requirements for meeting PIP agreements).

Cohort 1 – Infants and children aged between 6 months to less than 6 years.

Cohort 2 – Neonates and infants from birth to less than 6 months.

The overall treatment duration follow-up for each cohort will be at least 2 years.

Dosing and treatment administration in this registry study should be done as per the treating physician standard clinical practice.

Visits to the clinic are to occur according to routine site´s clinical practice, or when applicable according to the treating practice physician.

An initial visit (i.e., screening equivalent that will also serve as baseline) will take place to ensure the patient complies with all participation criteria. This visit will serve for the patient to enter the study.

End-of-treatment (EOT) visit: The end of treatment visit will be the first routine clinical practice visit after at least 2 years have elapsed since the patient entered the study (initial visit) or 2 weeks after the last mexiletine intake after 2 years of treatment (whichever occurs first).

The following data elements will be collected as permitted by the clinical site normal clinical practice for patients with myotonic disorders and/or the patient's age- using as example other registries (Lagrue *et al.*, 2019).

- Demographics
- Genetics: DM1, DM2 or NDM corresponding clinical forms
- Musculoskeletal manifestations (myotonia, Charcot-Marie-Tooth disability scale, facial hypotonia)
- Orthopaedic deformities (spine, feet or hands, orthoses, back brace, specialized follow-up, surgery)
- Cardiorespiratory signs (non-invasive ventilation, sleep disorders, ECG / left ventricular ejection fraction (LVEF), pacemaker/defibrillator)
- Ophthalmic and endocrinologic manifestations (cataract, diabetes, thyroid disorders)
- Psychomotor development disabilities
- Gastrointestinal disorders

Data will be entered at baseline upon patient enrolment and entered periodically thereafter for all routine clinical practice patient visits. For example, all laboratory values collected at routine clinical visits occurring between month 6 and month 12 of a patient's participation in the registry should be entered at the 12-month time point. All data will include the date each assessment was performed. Where available, additional retrospective data will be collected. Retrospective data will be focused primarily on patterns of mexiletine use and dose adjustments as well as any efficacy assessments. Retrospective safety data will also be recorded, especially in relation to any AEs that affect dosing, SAEs or AESIs, but there will be no requirement to report any retrospective AEs prior to signing the informed consent. In

cases where retrospective data are captured, this will be recorded from first mexiletine prescription up to the baseline visit or to the maximum age of eligibility for entering into the trial (that is, up to 6 years). For eligible patients who provide informed consent, data elements will be extracted from the information routinely recorded in the medical records and transcribed into the electronic Case Report Forms (eCRF). Safety, treatment administration and efficacy assessments will be collected during the visits.

AEs will be collected from the time informed consent is given to end of treatment.

No drug safety monitoring committee (DSMB) will be required. However, current DSMB members for related studies MEX-NM-301 (EudraCT number 2019-003757-28) and MEX-NM-303 (EudraCT number 2019-003758-97) will be kept informed and consulted if needed throughout the study.

Study sites

The study will be conducted at approximately two sites.

Study Population:

The study population will include male and female children from birth to less than 6 years of age with clinical symptoms or signs of myotonic disorders, normal electrocardiogram (ECG) exam and genetic confirmation of the diagnosis i.e., non-dystrophic myotonia (NDM), or myotonic dystrophy (DM) type 1 (DM1), or DM type 2 (DM2), and who comply with the inclusion / exclusion criteria.

Patients will be enrolled consecutively at each site in order to minimize selection bias

Numbers of Patients

A total of at least 10 paediatric evaluable patients in cohort 1 and 2. At least 4 patients from birth to less than 6 months (cohort 2) and at least 6 patients from 6 months to less than 6 years (cohort 1).

The number of patients, and type of study, was agreed with the paediatric committee (PDCO) during paediatric investigation plan (PIP) review.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Male or female patients from birth to less than 6 years
2. A genetically confirmed diagnosis of NDM or DM (DM1or DM2), as per the treating clinician.
3. Presence of clinical symptoms of myotonia (hand grip myotonia, myotonia in the leg muscles, any other myotonia symptoms) to be confirmed by the treating clinician.
4. Patients already receiving mexiletine treatment or who are clinically considered for mexiletine treatment as per the treating physician judgement.
5. No history of or significant cardiac abnormalities as determined by a cardiologist's assessment of the ECG and echocardiogram performed prior to enrolment in the study or as per the treating physician standard of care (NaMuscla SmPC, 2023)
6. No known history or signs and symptoms of any significant liver disorder as per treating physician.

7. No known clinically relevant abnormal laboratory investigations for haematology, biochemistry, and urinalysis values at screening (or based on values obtained within 3 months prior to screening in patient's medical record) that could affect the study objectives as judged by the treating physician.
8. Parent or legal guardian able to provide assent to study participation and to sign the written informed consent prior to study entry and perform any study-related activity.

Exclusion Criteria:

1. Any contraindication to mexiletine as listed in the Namuscla Summary of Product Characteristics (SmPC) (NaMuscla SmPC, 2023)
    a) Hypersensitivity to the active substance, or to any of the excipients
    b) Hypersensitivity to any local anaesthetic
    c) Ventricular tachyarrhythmia
    d) Complete heart block (i.e., third-degree atrioventricular block) or any heart block susceptible to evolve to complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 200 ms) and/or wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and trifascicular block),
    e) QT interval > 450ms
    f) Myocardial infarction (acute or past), or abnormal Q-waves
    g) Symptomatic coronary artery disease
    h) Heart failure with ejection fraction <50%
    i) Atrial tachyarrhythmia, fibrillation or flutter
    j) Sinus node dysfunction (including sinus rate < 50 bpm)
    k) Co-administration with medicinal products inducing torsades de pointes.
    l) Co-administration with medicinal products with narrow therapeutic index
2. Any other neurological or psychiatric condition that might affect the study assessments, as per the treating clinician.
3. Any clinically significant illness, laboratory findings, ECG, or other clinical symptoms, which in the opinion of the treating physician could affect the patient's optimal participation in the study
4. Receiving strong inducers or inhibitors of CYP2D6 or CYP1A2 or planned to receive them, during the subject participation (See section 4.1.5.1 Prohibited medications).
5. Any concurrent illness, or medications which could affect the muscle function, and confound the results according to the treating physician.
6. Seizure disorder, diabetes mellitus requiring treatment by insulin.

Study Duration and treatment period

Each patient will be followed up for a minimum period of at least 2 years (104 weeks) in connection to their routine clinical visits and safety assessment which are expected to be every 6 months.

Total duration of the study for each patient is approximately 104 weeks plus the period up to at least 2 weeks after their last 2-year mexiletine intake, or the last routine clinical visit (whatever happens first).

Study Drug Dose, Dosage Form, and Mode of Administration

Dosing recommendations for oral administration of mexiletine capsule are still being established and are currently estimated according to the child's body weight. Dosing in this registry study is at the discretion of the treating physician and the clinical response of the patient. No per protocol specific dosing instructions are provided to the treating physician. The Sponsor of this non-interventional registry study is trying to understand how the drug is currently being used in this disease and population and try to establish a benefit:risk assessment.

Administration will be via the oral route, using either capsules or opening and sprinkling contents on food/drink according to the child's age and ability.

Dose suitability with regard to sprinkling contents on food/drink will be assessed.

Study Endpoints and Outcome Variables:

As permitted by clinical practice and patient´s age, the following assessments are proposed:

- To assess the efficacy of mexiletine for the treatment of myotonic disorders as assessed by the clinician including as follows (where applicable).
  - Muscle strength measured using the modified Medical Research Council (MRC) scale to evaluate neck flexors, shoulder abductors, elbow flexors and extensors, wrist extensors, finger flexors, hip flexors, knee flexors and extensors, posterior foot flexors and plantar flexors.
  - Clinical Global Impression (CGI) Scores given to caregivers and assessed by the investigators
- To assess long-term safety
  - Number and frequency of adverse events (AEs), serious adverse events (SAEs) and AE leading to treatment discontinuation, throughout the study while on treatment with mexiletine
  - Incidence of adverse events of special interest (AESI), namely:
    - Severe Cutaneous Adverse Reactions (SCARs).
    - Cardiac arrhythmia.
    - Increased frequency of seizure episodes in patients with epilepsy.
- To assess the different routes of administration and formulations of mexiletine used according to clinician’s preferences
- To assess safety and efficacy of mexiletine dosing formulations used
- To assess dose and treatment compliance as well as acceptability and palatability of different modes of administration.

Statistical Methods

Sample Size

The number of patients in this study is not hypothesis driven; rather as agreed with PDCO, in that at least 10 evaluable subjects will be sufficient to assess efficacy and safety of mexiletine in this ultra-rare paediatric subpopulation for the age group of 0- 6 years old.

Statistical Analysis:

Summary descriptive statistics will be provided for all collected parameters. The categorical variables will be presented with frequency and percentages.

The analysis will be performed for all patients as well as by age cohort.

Overall data collected will be analysed to assess the safety and acceptability/palatability of different modes of mexiletine administration (i.e., capsule, sprinkled on food and/or gastric (enteral) tube where such formulations are used), and the factors that govern the route of administrations in paediatric patients.

If performed and available -as per the normal disease management of each participating site, and age-appropriate- the following will be analysed and presented:

- Change from baseline in time (in seconds) to relaxation of hand muscles and reduction in relaxation time from the first to the third/fifth contraction and time (in seconds) for Timed-up and go (TUG) test will be summarized.
- The actual Faces scores and the change from baseline in Faces score for muscle stiffness, pain, weakness and fatigue will be summarized.
- Quality of life data will be presented descriptively along with the change from baseline.
- The observed values of Clinical Global Impression (CGI) Scores and the change from baseline in CGI Scores assessed by the caregivers and investigators.
- The observed values of Myotonia Behaviour Scale (MBS) Scores and the change from baseline in MBS from baseline will be summarized.

The detailed statistical treatment of the data and any analysis methods will be specified in a

Statistical Analysis Plan (SAP)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Full form
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AP	Action potential
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
CBC	Complete blood count
CGI	Clinical Global Impression
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-reactive protein
CYP	Cytochrome P450
DAE	Discontinuation due to adverse events
DM1	Myotonic dystrophy type 1
DM2	Myotonic dystrophy type 2
DMPK	Dystrophia myotonica–protein kinase
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EF	Ejection fraction
EMG	Electromyograph
EOT	End-of-treatment
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HR	Heart rate
ICF	Informed Consent Form
IEC	Institutional Ethics Committee
IMP	Investigational medicinal product
ITT	Intention to treat
IUD	Intrauterine device

Abbreviation	Full form
LMP	Last menstrual period
LS	Least squares
MAA	Marketing Authorisation Application
Max	Maximum
MBS	Myotonia Behaviour Scale
MC	Myotonia congenital
NDM	Nondystrophic myotonia
PC	Paramyotonia congenital
PDCO	Paediatric Committee
PedsQL	Paediatric Quality of Life Questionnaire
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PP	Per protocol
PRO	Patient-reported outcomes
QD	Once daily
RBS	Random blood sugar
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SMP	Safety Management Plan
SmPC	Summary of Product Characteristics
SNEL	Severe neonatal episodic laryngospasm
SOC	System Organ Class
$t_{1/2}$	Apparent plasma terminal elimination halflife
TEAE	Treatment-emergent adverse event
TUG	Timed-up and go test
ULN	Upper limit of normal
UPT	Urine pregnancy test
US	Cardiac ultrasound
VAS	Visual analogue scale

1 INTRODUCTION

1.1 Background to myotonic disorders

Myotonic disorders (ICD-10 code G71.1; MedDRA low level term (LLT) 10028658) are a heterogeneous group of hereditary, rare disorders. A common and defining feature of myotonic disorders is myotonia which is a malfunction of muscular ion channels, usually chloride or sodium channels (Kurihara, 2005) with accompanying characteristic electromyographical (EMG) features. Myotonic disorders comprise *myotonic dystrophies* (DM) and *non-dystrophic myotonias* (NDM). Both groups of myotonic disorders can be further substantiated by genetic testing diagnosis of myotonic disorders can often be made based on the history and examination of the patient and family members in conjunction with confirmatory laboratory and genetic testing (Heatwole *et al.*, 2013) (Table 1).

Myotonia is caused by skeletal muscle fibre hyperexcitability (Pusch, 2002). Membrane excitability, which is critical for skeletal muscle function, is regulated by ion channels. In normal muscle, a high sarcolemmal chloride conductance sets the resting potential of the muscle fibre close to the chloride reversal potential. This allows for rapid repolarisation of the t-tubules following an action potential (AP). The skeletal muscle chloride channel also stabilises and regulates the electrical excitability of the muscle membrane. In turn, voltage-gated sodium channels are essential in the generation and propagation of APs in excitable tissues such as muscle, heart, and nerve (Simkin and Bendahhou, 2011). Consequently, the underlying cause of myotonic disorders are skeletal ion channelopathies mainly affecting sodium or chloride ion channels (Trip *et al.*, 2006). For example, mutations in the CLCN1 gene and α subunit of the SCN4A gene have been identified as causes of *non-dystrophic myotonic disorders* (Table 1). Electrophysiological studies on resting conductance of chloride, potassium, sodium, and calcium ions have revealed considerable insight into the pathophysiological mechanisms, which present with pathologically myotonic discharges of relaxed muscles in frequencies ranging from 20 to 80 Hz, and amplitudes ranging from 10 to 1000 μV (Heatwole *et al.*, 2013). Clinically, a delayed muscle relaxation after voluntary or evoked muscle contraction is observed in both channelopathies (Logigian *et al.*, 2005), while intermediary paralysis may also develop (in hyper- or hypokalaemic periodic paralysis).

The condition myotonic disorders, while not always life-threatening (Table 1), is chronically debilitating and incurable and may lead to impairment in daily functioning. The most common problems are stiffness and pain. Pain is a frequent symptom that may have been previously under-recognized and possibly undertreated in the non-dystrophic myotonias. In addition to pain and stiffness, permanent and debilitating muscle weakness and disability can develop (Trip *et al.*, 2009b).

Table 1 Myotonic disorders: affected gene, chromosome locus, affected ion channels, and mode of inheritance

Myotonic disorder	Gene	Locus	Channel	Trait	Comment
Myotonic dystrophies					
Myotonic dystrophy type 1	DMPK	19q13.3	chloride channel sodium channel?	dominant	CTG trinucleotide repeat expansion
Myotonic dystrophy type 2	Zinc finger protein 9	3q21	chloride channel sodium channel?	dominant	CCTG repeat expansion
Non-dystrophic myotonias					
Thomsen myotonia congenita	CLCN1	7q32-qter	chloride channel	dominant	
Becker myotonia congenita	CLCN1	7q32-qter	chloride channel	recessive	
Paramyotonia congenita	SCN4A	17q23	sodium channel	dominant	
Myotonia fluctuans	SCN4A?	17q23?	sodium channel?	dominant	likely
Myotonia permanens	SCN4A	17q23	sodium channel	dominant	can be life threatening
Acetazolamide-responsive myotonia	SCN4A	17q13	sodium-channel	dominant	
Hyperkalaemic periodic paralysis	SCN4A	17q23	sodium-channel	dominant	
Hypokalaemic periodic paralysis	SCN4A CACNA1S	17q23 1q31-32	sodium-channel calcium channel	? dominant	

1.1.1 Myotonic dystrophies type 1 and 2 (DM1 and DM2)

The two *myotonic dystrophies* (type 1 and 2; DM1 and DM2, respectively) are complex, multi-system disorders caused by an accumulation of expanded, non-coding RNAs, containing repetitive CUG and CCUG elements (Jurkat-Rott *et al.*, 2010; Heatwole *et al.*, 2013). DM1 is an autosomal dominant disorder caused by a CTG trinucleotide expansion in the untranslated region of the dystrophia myotonica–protein kinase (DMPK) gene on chromosome 19q13.3. There is increasing evidence that the transcribed DMPK pre-mRNA is directly toxic and results in abnormal splicing of other mRNA transcripts, including those of the muscle chloride ion channel. DM1 is further subdivided into five clinical subtypes: congenital, infantile/juvenile, adult-onset and late-onset forms. DM2 is an autosomal dominant disorder caused by a CCTG repeat expansion on intron 1 of the zinc finger protein 9 gene on chromosome 3q21. As well as the genetic definition, these disorders are also characterised by clinical differences and age of onset. Muscle weakness is generally distal and facial in DM1 and more proximal in DM2, whereas the presence of pain or muscle hypertrophy in DM2 and a family history of maternally

transmitted congenital disease are usually present in DM1, but not DM2. Both dystrophic types affect almost all human systems – not just skeletal muscles (Schoser and Timchenko, 2010). Frequently weakness, cataracts, conduction defects, insulin insensitivity, balding, hyperhidrosis, hypersomnia, and respiratory failure occur (Turner and Hilton-Jones, 2010).

In *dystrophic myotonia* type 1, the length of the CTG trinucleotide expansion in the untranslated region of the DMPK gene is correlated with onset of disease and severity of disease; this is not the case for type 2 (Turner and Hilton-Jones, 2010). DM1 is subdivided into several clinical categories: congenital, infantile/juvenile, adult-onset and late-onset forms (Kamsteeg *et al.*, 2012; Meola and Cardani, 2015a; De Antonio *et al.*, 2016; Hahn and Salajegheh, 2016)

Congenital DM1 shows a distinct clinical phenotype with distinct clinical features. These patients present at birth with marked generalised hypotonia and hyporeflexia and difficulties breathing and feeding which cause respiratory distress that needs assisted ventilation. Mortality in congenital DM1 during the neonatal period has been estimated at between 30% and 40% of patients. Some children who survive may die later from sudden infant death syndrome, or from respiratory failure (Hageman *et al.*, 1993). In severely affected patients surviving the neonatal period, as in less severely affected patients, the disease course is very much the same: the most constant feature is mental delay, preceded by speech and language delay, that exists in all cases and progressively worsens after several years of evolution. In these forms, signs of central nervous system dysfunction predominate, with mental deficiency and/or psychiatric disturbances. Motor development is delayed in most cases, the children becoming ambulant after the age of 2 years. But in terms of muscular weakness and the development of myotonic syndrome, disease progression is markedly variable from one patient to another (Echenne and Bassez, 2013).

DM2 is not normally diagnosed until adulthood with symptoms beginning in the second to sixth decade (median age 48 years) with variable manifestations including early-onset cataracts (younger than 50 years), varying grip myotonia, thigh muscle stiffness, and muscle pain, as well as weakness (Meola and Cardani, 2015b). Overall, it is considered that myotonia is less apparent in DM2 compared with DM1, being difficult to elicit by standard electromyography (EMG) testing except for proximal muscles such as the tensor fascia lata and vastus laterali. In cases of late-onset DM2, myotonia may only appear by EMG testing after examination of several muscles. In general, patients with myotonic dystrophy type 2 have clinical symptoms that are usually milder (Turner and Hilton-Jones, 2010).

1.1.2 Non-dystrophic myotonic disorders (NDM)

Non-dystrophic myotonic disorders (NDM) mainly affect skeletal muscles and can be classified into chloride channelopathies (Thomsen myotonia congenital (MC), Becker myotonia congenital) and sodium channelopathies (paramyotonia congenital (PC), myotonia fluctuans, myotonia permanens, acetazolamide-responsive myotonia, hyperkalaemic periodic paralysis, and hypokalaemic periodic paralysis).

In *non-dystrophic myotonias*, mutations in the chloride channel decrease the chloride current in the physiological range and destabilise the muscle membrane, predisposing it to the hyperexcitability created by the accumulation of potassium in the t-tubules. Though potassium is normally present in the t-tubular lumen after an action potential, repetitive depolarisation of

the sarcolemma (myotonia) only occurs when the chloride current cannot adequately buffer the cation load (Platt and Griggs, 2009). Non-dystrophic myotonia cases are diagnosed essentially from birth and depending on the specific mutation and subtype myotonia may be present from an early age.

Mutations in the sodium channel result in multiple defects in channel gating and produce different disease phenotypes depending on the location of the mutation in the ion channel. The voltage-gated sodium channel, Nav1.4 (SCN4A), generates the action potentials that initiate muscle contraction in response to nerve stimulation. Immediately after the action potential, the channels undergo fast inactivation to prevent repetitive discharge. Sodium channelopathies possess altered channel gating that causes slowed or incomplete inactivation, or sometimes enhanced activation. Furthermore, the worsening of myotonia in response to low temperatures may result from cold-induced disruption of sodium channel slow inactivation. The net effect of these disturbances is an increase in sodium entry into the cell, which prolongs the action potential duration and encourages persistent depolarisation of muscle fibres, causing myotonia. These mutations are known as gain-of-function due to their promotion of increased cell excitability (Platt and Griggs, 2009).

The major clinical manifestation of the *non-dystrophic myotonias* is muscle stiffness as a consequence of the myotonia. Severe muscles stiffness drastically reduces the patient's ability to perform daily activities (Lehmann-Horn *et al.*, 2004). Additional common symptoms include pain, weakness and fatigue. The intensity of symptoms range from mild (late onset) to life-threatening (Matthews *et al.*, 2010).

Particularly, sodium channelopathies can manifest in newborns as severe neonatal episodic laryngospasm (SNEL), characterised by muscle hypotonia and recurrent episodes of laryngospasm, followed by apnoea. SNEL exhibits a spontaneous decrease in frequency and duration; this clinical phase is usually followed by myotonia (i.e., myotonia permanens or paramyotonia congenita) (Matthews *et al.*, 2008).

Non-dystrophic myotonia cases are diagnosed essentially from birth and depending on the specific mutation and subtype, myotonia may be present from an early age.

1.2 Rationale

Mexiletine hydrochloride (CAS ID: 5370-01-4) is a class 1b anti-arrhythmic agent, based on the Vaughan Williams classification, with local anaesthetic properties, similar in structure and activity to lidocaine (lignocaine) and flecainide. As described in the Ph. Eur. Monograph (2008), mexiletine hydrochloride is a white or almost white, crystalline powder. It exhibits polymorphism. It is freely soluble in water and in methyl alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.0 to 5.5.

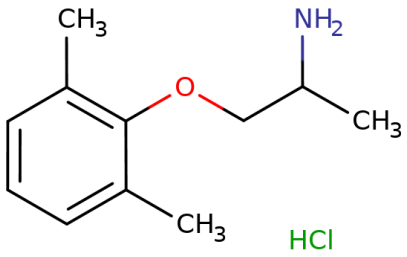

Figure 1 Chemical Structure of Mexiletine HCl (Source: ChemID Plus)

Mexiletine was initially developed as a treatment for ventricular arrhythmias with subsequent use in long QT syndrome (Heatwole *et al.*, 2013; Sarret *et al.*, 2024). However, after the marketing withdrawal of Boehringer Ingelheim's Mexitil® (indication: ventricular arrhythmias) in 2009, there was a significant shortage of supply of licensed mexiletine products in the EU. The originator product was withdrawn from the market because newer active substances superseded the use of mexiletine in the treatment of ventricular arrhythmias.

Despite the shortage, mexiletine gained acceptance as an effective anti-myotonia therapy in both dystrophic and non-dystrophic myotonia (that is, for both the chloride and sodium channelopathies) (Kwiecinski *et al.*, 1992; DGN, 2012; Heatwole *et al.*, 2013; Sarret *et al.*, 2024). Some availability of mexiletine for treatment of myotonic disorders was based on a named patient basis although often associated with supply issues. Therefore, based on the unmet need and the strong evidence for use of mexiletine for treatment of myotonic disorders, an application for marketing authorisation was submitted by the centralised procedure in June 2017 and approved for use throughout the EU in December 2018. Namuscla® containing mexiletine HCl as active substance is currently indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

The currently approved strength for Namuscla is 200 mg mexiletine HCl formulated as hard capsules for oral use containing 167 mg of mexiletine (NaMuscla SmPC, 2023). The recommended starting dose of mexiletine in adults is 167 mg daily (1 capsule per day). After at least 1 week of treatment, based on the clinical response, the daily dose can be increased to 333 mg daily (2 capsules per day). After at least 1 further week of treatment, based on clinical response, dose can be further increased to 500 mg daily (3 capsules per day). Maintenance treatment is between 167 mg – 500 mg daily (1 to 3 capsules per day), according to the intensity of symptoms and the clinical response, taken regularly throughout the day. The adult daily dose should not exceed 500 mg/day (NaMuscla SmPC, 2023).

As well as the approved 200 mg strength, new paediatric formulations of NaMuscla® were developed consisting of 75 mg and 100 mg strengths with identical qualitative composition to the 200 mg strength. These strengths are not yet authorized. The line extension application is expected to be submitted in April 2025.

Despite reported use and limited data from case studies in the paediatric population, the safety and efficacy of mexiletine in this paediatric population have not yet been established. A recent mini-review of the use of mexiletine in children concluded that special attention by health authorities was needed to maintain access to mexiletine in rare paediatric diseases and further paediatric research was required (Sarret *et al.*, 2024). They specifically mention that off-label

registries for the use of mexiletine in children, especially younger than 6 years, are also required in neuromuscular disorders. The authors admit that although the drug has no proven paediatric indication it has been used in various rare paediatric conditions since the 1970s including heart disorders, neuromuscular diseases, epileptic seizures and pain disorders. Mexiletine has long been reported to be useful in paediatric cardiology and paediatric neurology, with a usual dose ranging between 3 to 15 mg/kg/day (see also section 1.4 Regulatory background).

Observational or low interventional studies, aimed at collecting comprehensive data (Lagrue et al., 2019), even if limited to one single country and to DM1, provide valuable information on which data in children remains scant. In collaboration with the French Child Neurology Society this study included 314 paediatric patients who were recruited in 24 paediatric neuromuscular reference centres across France. The patients were classified as congenital (from birth to 1 year of age; N=155), infantile (between 1 and 10 years of age; N=88) and juvenile (aged 10 -18 years; N=38). The study collected epidemiologic, genetic and clinical data and lasted about 6 years to complete. The clinical data collected and tests performed were dependent on the patient's age group. Outcomes from such studies prove that there are still unmet medical needs with serious consequences in the paediatric myotonias field and that drugs that have proven safe and efficacious in adults to the point of clinical and regulatory approval (NaMuscla SmPC, 2023) deserve to be evaluated for risk-benefit assessment as well as in their use in paediatric populations.

1.3 Risk-Benefit Assessment

The major goal of mexiletine treatment is to alleviate muscle stiffness and thereby decrease associated pain and fatigue and increase movement and patient quality of life. In 2018 the CHMP gave a positive benefit-risk of mexiletine for the symptomatic treatment of myotonia in the adult NDM patient population. In particular, it was concluded that the efficacy and safety of mexiletine in NDM was demonstrated in the randomised, placebo-controlled MYOMEX study. The MYOMEX study included 25 patients with NDM (13 myotonia congenita (MC) and 12 paramyotonia congenita (PC); that is chloride and sodium channelopathies, respectively); with mexiletine dosing 200 mg/day for 3 days, 400 mg/day for 3 days and 600 mg/day for an additional 12-16 days; and total treatment duration of 19 days (mean 19 days, median 19 days, range 10-21 days). However, the CHMP considered that the submitted literature references and data did not firmly support the clinical relevance of the observed changes in muscle stiffness in DM type 1 patients. Additionally, while muscle stiffness is considered to be important disabling medical problem for patients with NDM, it is considered less disabling for patients with DM type 1. Despite this, the efficacy of mexiletine for the symptomatic treatment of myotonic disorders has also been described in several reports of off-label use and/or clinical studies in the DM target population such that mexiletine is usually considered the first line treatment for these conditions despite being off label.

In general, the safety profile of mexiletine is well known in adults through many years of use as an anti-arrhythmic agent (it was withdrawn from use in this indication for commercial and not for safety reasons).

In one of the registry studies (Wahbi *et al.*, 2017), DM1 patients had a cumulative 3.8 % incidence of sudden death due to arrhythmia and other cardiac causes over a median 10 years follow up. Mexiletine is known to be able to trigger arrhythmia or aggravate an existing arrhythmia and thus patients known to be at risk are excluded from the trial and contraindicated

in the product labelling. Similarly, the screening visit and safety assessments also closely monitor the risk of arrhythmia and cardiac safety, through ECG for example, and cardiac safety is an important consideration for paediatric dose titration. Mexiletine is contraindicated in case of heart failure with mid-range (40-49%) and reduced (<40%) ejection fraction because of the proarrhythmic effects. An increased mexiletine plasma concentration is a risk factor for patients with cardiac abnormalities or prone to such abnormalities, thus the SmPC recommends additional cardiac monitoring after any dose increase which has been applied in the study protocol to reduce risks.

Efficacy and safety data in special populations such as elderly and paediatric subjects have not yet been clearly demonstrated, although several reports describing use have been published (See section 1.3) (Lagrue *et al.*, 2019; Sarret *et al.*, 2024). Lupin has also conducted an open-label, non-comparative study to evaluate the steady-state pharmacokinetics, safety, and efficacy of mexiletine in adolescents and children with myotonic disorders (MEX-NM-301). To date, MEX-NM-301 has collected evaluable data for PK, efficacy and safety from 7 subjects aged 12 less than 18 years, and 3 subjects aged 6 to less than12 years (10 subjects in total). This study is still ongoing. In addition, Lupin is also conducting MEX-NM-303, an open-label extension study to evaluate the long-term safety and efficacy of mexiletine in paediatric patients with myotonic disorders who have completed the MEX-NM-301 study. This study is also ongoing.

The objective of this registry in paediatric patients aged from birth to 6 years is to assess safety, tolerability and efficacy (exploratory) data in the paediatric population under routine regular clinical practice. However, given the rareness of the condition, there is no specific hypothesis testing or statistical assumptions and data will be collected and analysed descriptively.

Overall, it can be concluded that:

- Myotonic disorders refer to conditions (DM1, DM2 and NDM) that are rare (orphan) diseases with no known cure and only symptomatic treatment, therefore there is a great unmet need for this patient population.
- Mexiletine is the only approved product for symptomatic treatment of NDM in adults although there is evidence to suggest that it also can have benefits to symptomatic DM patients. Therefore, patients enrolled in the study are expected to have some benefit in their myotonic symptoms from the treatment.
- Safety of mexiletine has been determined in adults when used in antiarrhythmic indications as well as in some studies of patients with myotonic disorders. Risk minimisation measures have been proposed in the study design to address the known safety concerns.
- As there is very limited safety data in the paediatric population, it is considered essential to generate relevant data to inform dosing and labelling requirements.
- Registries or non-interventional studies like this one allows to establish standard of care and assess the value and the safety of medications like mexiletine in the paediatric population.

Therefore, the risk-benefit balance of the study is considered positive and supports the conduct of this registry and the continued clinical development of mexiletine.

1.4 Regulatory background

On 7 July 2016 an application for a paediatric investigation plan (PIP) and deferral was submitted by the applicant Lupin (Europe) Ltd. And on 2 June 2017 the EMA granted a positive decision (P/0155/2017).

The applicant submitted on 26 June 2017 a Marketing Authorisation Application (MAA) for Namuscla through the centralised procedure. Subsequently, the PDCO was requested by the Agency to initiate a partial compliance procedure (EMEA-C1-002012-PIP01-16) which started on 18 July 2017 with a positive outcome on 15 August 2017.

On 18 October 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Namuscla, intended for the treatment of myotonia in adults with certain hereditary muscle disorders (EMA/CHMP/650838/2018). The date of issue of the marketing authorisation valid throughout the European Union was 18th December 2018.

Several modifications to the initial PIP have been submitted and agreed and the current decision is P/0300/2023 for EMEA-002012-PIP01-16-M04. An additional modification (M05) was submitted in February 2024 and is ongoing. The changes in former modification M03 introduced the requirement for the current registry study, referred to as a prospective, long-term observational study (registry) of paediatric myotonic disorder patients from birth to less than 6 years of age who are treated with mexiletine. The study population was to include patients with myotonic disorders (DM1, DM2, and NDM) with a total of at least 10 paediatric subjects evaluable for the primary analysis with at least 4 patients in the birth to less than 6 months and 6 in the in the 6 months to less than 6 years. Each participant must be followed for at least 2 years.
Based on epidemiological data, approximately 2 in 10,000 people are affected with myotonic disorders (which comprise the two main entities, myotonic dystrophies and non-dystrophic myotonias) in the EU. Consequently, mexiletine was granted orphan designation for "treatment of myotonic disorders" EU/3/14/1353 (EMA/OD/074/14). Namuscla was subsequently designated as an approved orphan medicinal product in the indication treatment of myotonic disorders after granting of the CHMP positive opinion. No protocol assistance procedure has ever been performed.

This trial will be conducted in compliance with the protocol, Declaration of Helsinki, Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

There is a 2021 EMA guideline on registry-based studies (EMA/426390/2021, 2021) defined as an investigation of a research question using the data collection infrastructure or patient population of one or more patient registries. However, there is no equivalent guidance for a prospective patient registry for the currently proposed protocol. Which is an organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure. Guidance exists on real world evidence as used to support regulatory filings, but only FDA has published clear guidance on this (FDA Center for Drug Evaluation and Research (CDER), 2023), whereas an ICH Concept Paper has also been recently published (EMA/CHMP/ICH/295401/2023, 2023).

The trial is considered as a non-intervention study:

- Assignment of patients is already decided in advance of the clinical trial protocol by the treating physician as part of normal clinical practice.
- The decision to prescribe a particular medicinal product is made prior to inclusion of the patient in the study.
- All diagnostic and monitoring procedures applied to the patients included in the study are applied as part of normal clinical practice.
- Mexiletine is currently authorised albeit not for paediatric patients. Nonetheless, use of mexiletine in this population is evidence-based and supported by published scientific evidence.

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 The Primary objectives

The objectives of this patient registry study are:

- To evaluate the safety and the efficacy (exploratory) of mexiletine for the treatment of myotonia in the paediatric population aged from birth to less than 6 years using real world data.

2.1.2 Secondary objectives

- To assess the suitability of mexiletine administration using available formulations including, where appropriate, capsules or opening and sprinkling contents in food or drink according to the child´s age (from birth to less than 6 years) and ability to swallow.

- To understand how mexiletine is used by clinicians who have previously decided to use mexiletine for the treatment of myotonia in myotonic disorder patients, from birth to less than 6 years over a at least 2 years period, to establish risk:benefit conclusions.

3 STUDY DESIGN

3.1 Overall Study Design

This is an open-label, multi-centre, single arm, registry study to collect standard relevant clinical and epidemiological data during routine medical evaluation and treatment in paediatric patients with myotonic disorders who are being treated with mexiletine therapy according to the physician.

This study will be performed under routinary typical conditions without imposing any clinical practice or restrictions to the treating physician who prescribe and use mexiletine, or to the participants or caregivers and also without influencing in the usual clinical practice of patients with myotonias. With the exception of taking extra safety measures or performing tests, scales or questionnaires used as tools to protect the patient or to measure the outcomes of this study. Patients will not undergo any intervention whether for diagnostic, treatment or follow up purposes that are not usual in the clinical practice of their disease.

The participating centres will be selected based on their neurological specialisation and the treating physicians' expertise in the treatment of patients with myotonias.

3.2 Discussion of Study Design

Study inclusion screening time will be approximately 2 weeks.

Patients who meet the eligibility criteria will be enrolled in two cohorts by age groups although cohorts are not planned to necessarily enrol sequentially (cohort definition is to assure minimum requirements for meeting PIP agreements).

- Cohort 1 – Infants and children aged between 6 months to less than 6 years.
- Cohort 2 – Neonates and infants from birth to less than 6 months.

The overall treatment duration follow-up for each cohort will be at least 2 years.

Dosing and treatment administration in this registry study should be done as per the treating physician clinical practice.

Visits to the clinic are to occur according to routine site´s clinical practice, or when applicable according to the treating practice physician.

An initial visit (i.e., screening equivalent that will also serve as baseline) will take place to ensure the patient currently complies with all participation. This visit will serve for the patient to enter the study.

The end of treatment (EOT) visit will be the first routine clinical practice visit after at least 2 years have been completed since the patient entered the study (baseline visit) or 2 weeks after the last mexiletine intake after 2 years of treatment (whichever occurs first).

After 24 months, no study specific visits and data collection are required and patients will be treated and followed up as per the investigator's site protocol.

The following data elements will be collected during this registry, as permitted by the clinical site normal clinical practice for patients with myotonic disorders and according to the patient's age, using as the example other myotonia registries (Lagrue *et al.*, 2019).

- Demographics
- Genetics: DM1, DM2 or NDM corresponding clinical forms
- Musculoskeletal manifestations (myotonia, facial hypotonia)
- Orthopaedic deformities (spine, feet or hands, orthoses, back brace, specialized follow-up, surgery)
- Cardiorespiratory signs (non-invasive ventilation, sleep disorders, ECG / left ventricular ejection fraction (LVEF), pacemaker/defibrillator)
- Ophthalmic and endocrinologic manifestations (cataract, diabetes, thyroid disorders)
- Psychomotor development disabilities
- Gastrointestinal (GI) disorders
- Patterns of mexiletine use including dose/ frequency.

Data will be entered at baseline upon patient enrolment and entered periodically thereafter for all routine clinical practice patient visits. For example, all laboratory values collected at routine clinical visits occurring between month 6 and month 12 of a patient's participation in the registry should be entered at the 12-month time point. All data will include the date each assessment was performed. Where available, additional retrospective data will be collected. Retrospective data will be focussed primarily on patterns of mexiletine use and dose adjustments as well as any efficacy assessments. Retrospective safety data will also be recorded, especially in relation to any AEs that affect dosing, SAEs or AESIs, but there will be no requirement to report any retrospective AEs prior to signing the informed consent. In cases where retrospective data are captured, this will be recorded from first mexiletine prescription up to the baseline visit or to the maximum age of eligibility for entering into the trial (that is, up to 6 years). For eligible patients who provide informed consent, data elements will be extracted from the information routinely recorded in the medical records and transcribed in to the electronic Case Report Forms (eCRF). Safety, treatment administration and efficacy assessments will be collected during the visits. AEs will be collected from the time informed consent is given to end of treatment.

No drug safety monitoring committee (DSMB) will be created.

3.2.1 Appropriateness of Measurements

The efficacy endpoints chosen for the study are based on those that have been commonly used during routine clinical practice in adults (Logigian *et al.*, 2010; Statland *et al.*, 2012a; Statland *et al.*, 2012b), but they have been adapted according to the patient's age and ability to participate in the efficacy evaluation. The Sponsor has also received feedback from KOLs regarding what measures are considered appropriate for different ages. Moreover, the approach to and the scope of efficacy endpoints was accepted by the Regulatory Authorities (in particular the Paediatric Committee; PDCO) during the evaluation and discussion on the paediatric investigation plan (PIP) that this protocol is specifically designed to support.

Similarly, the safety parameters proposed are also in line with the conventional endpoints to evaluate safety and are suitable for use in the paediatric population.

3.2.2 Control Group

Not applicable as it is a single arm, non-comparative study.

3.2.3 Duration of Study

The overall treatment duration follow-up for each patient will be 2 years.

3.3 Selection of Study Population

3.3.1 Inclusion Criteria

1. Male or female patients from birth to less than 6 years
2. A genetically confirmed diagnosis of NDM or DM (DM1or DM2), as per the treating clinician.
3. Presence of clinical symptoms of myotonia (hand grip myotonia, myotonia in the leg muscles, any other myotonia symptoms) to be confirmed by the treating clinician.
4. Patients already receiving mexiletine treatment or who are clinically considered for mexiletine treatment as per the treating physician judgement.
5. No history of or significant cardiac abnormalities as determined by a cardiologist's assessment of the ECG and echocardiogram performed prior to enrolment in the study or as per the treating physician standard of care (NaMuscla SmPC, 2023)
6. No known history or signs and symptoms of any significant liver disorder as per treating physician.
7. No known clinically relevant abnormal laboratory investigations for haematology, biochemistry, and urinalysis values at screening (or based on values obtained within 3 months prior to screening in patient's medical record) that could affect the study objectives as judged by the treating physician.
8. Parent or legal guardian able to provide assent to study participation and to sign the written informed consent prior to study entry and perform any study-related activity.

3.3.2 Exclusion Criteria

1. Any contraindication to mexiletine as listed in the Namuscla Summary of Product Characteristics (SmPC) (NaMuscla SmPC, 2023)
    a) Hypersensitivity to the active substance, or to any of the excipients
    b) Hypersensitivity to any local anaesthetic
    c) Ventricular tachyarrhythmia
    d) Complete heart block (i.e., third-degree atrioventricular block) or any heart block susceptible to evolve to complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 200 ms) and/or wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and trifascicular block),
    e) QT interval > 450ms
    f) Myocardial infarction (acute or past), or abnormal Q-waves
    g) Symptomatic coronary artery disease

h) Heart failure with ejection fraction <50%
i) Atrial tachyarrhythmia, fibrillation or flutter
j) Sinus node dysfunction (including sinus rate < 50 bpm)
k) Co-administration with medicinal products inducing torsades de pointes.
l) Co-administration with medicinal products with narrow therapeutic index

2. Any other neurological or psychiatric condition that might affect the study assessments, as per the treating clinician.
3. Any clinically significant illness, laboratory findings, ECG, or other clinical symptoms, which in the opinion of the treating physician could affect the patient's optimal participation in the study
4. Receiving strong inducers or inhibitors of CYP2D6 or CYP1A2 or planned to receive them, during the subject participation (See section 4.1.5.1 Prohibited medications)
5. Any concurrent illness, or medications which could affect the muscle function, and confound the results according to the treating physician.
6. Seizure disorder, diabetes mellitus requiring treatment by insulin.

3.3.3 Withdrawal of Patients

In accordance with the Declaration of Helsinki and the informed consent form, patients may discontinue the study at any time without any penalty or loss of benefits to which the patient is otherwise entitled. For all patients withdrawn from the study, efforts will be made to ascertain the reason for withdrawal.

A withdrawn patient is one who meets any of the following withdrawal criteria stated below and whose study participation is discontinued. The reasons for patient withdrawal will be recorded in the case report form, signed, and dated at the last assessment visit.

Criteria for Withdrawal from Study

A patient may be withdrawn from the study due to any of the following withdrawal criteria:

- A patient's desire/ or guardian decision to withdraw for any reason (withdraws consent)
- Lost to follow-up (every effort must be made to contact the patient; the effort to contact must be documented in the Investigator's file)
- Inability of patient to comply with the Protocol for any reason
- The patient needs emergency treatment or is unable to continue participation in the trial due to the exacerbation of symptoms.
- If in the Investigator's opinion that continuing the patient in the trial is not appropriate, the Investigator may withdraw a patient at any time if it is considered to be in the patient's best interest.
- Withdrawn patients will be replaced to comply with the agreed minimum number of patients with PDCO.

Criteria for Treatment Discontinuation

- An adverse event, which in the opinion of the Investigator and/or Sponsor, necessitates discontinuation of treatment.

3.3.4 Rescreening of Patients

Not applicable.

3.3.5 Early Termination of Study/ Site

This study may be terminated at any time by Lupin if any safety concerns arise, or inability to achieve recruitment. In this event, Lupin will inform about the decision along with reason to the study Investigators, Institutions, ECs and all applicable regulatory authorities. The study may be terminated by the sponsor if new scientific knowledge becomes available that makes the objectives of the study no longer feasible or scientifically and ethically invalid.

In such cases, patients will be continued on/shifted to appropriate alternate therapy by the Investigator.

4 TREATMENT OF PATIENTS AND INVESTIGATIONAL PRODUCT MANAGEMENT

4.1 Treatment of Patients

4.1.1 Dosage and Treatment Regimen

Mexiletine will be used at the discretion of the treating physician without protocol mandated instructions or limitations.

Patients should take the study medication as prescribed by the investigator, preferably with food and at the same time daily.

For patients who are not able to swallow capsules, capsule contents to be opened and sprinkled on food or mixed with milk/juice. Details on dosing, formulation, route and mode of administration will be collected by the caregiver in the electronic data capture (EDC).

Each patient/caregiver will be provided with sufficient prescriptions until next clinically indicated study visit.

4.1.1.1 Dose Escalation

Any dose escalation -or reduction- will be at the discretion of the treating physician and will be duly collected in the CRF.

4.1.1.2 Stopping rules

Treatment will be permanently discontinued immediately if one of the following criteria is met:

- Ventricular tachyarrhythmia
- Complete heart block (i.e. third-degree atrioventricular block) or any heart block susceptible to evolve to complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 200 ms) and/or wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and trifascicular block),
- QT Interval ≥ 450 ms
- Myocardial infarction (acute or past), or abnormal Q-waves
- Symptomatic coronary artery disease
- Heart failure with ejection fraction <50%
- Atrial tachyarrhythmia, fibrillation or flutter
- Sinus node dysfunction (including sinus rate < 50 bpm)

In case of permanent discontinuation of the study medication, details of reason for discontinuation must be documented in the CRF and every attempt should be made to complete the EOT assessments.

Medical monitor will perform a comprehensive review and evaluation of the events and will make a decision as to the continuation of recruitment, dosing as well as in the trial.

4.1.2 Randomization of Study Treatment

Not applicable.

4.1.3 Blinding of Study Treatment

This is an open-label study; therefore, blinding is not applicable.

4.1.4 Patient Compliance

Compliance will be assessed by drug intake history. The number of capsules or amount of powder (and way it is subsequently administered, such as yoghurt, juice etc.) as well as the dose (strength) of study drug taken daily and weekly will be captured and this data will be later transcribed into the CRF.

Patients/caregivers judged to be non-compliant will be counselled on the importance of daily intake of study medication, as prescribed. A compliance between 80% - 125% will be desired for the adequate assessment of the study outcomes. Patients who are repeatedly non-compliant or have a compliance of less than outside 80-125% may be discontinued, at investigator's discretion after discussion with the medical monitor. Replacement of subjects will be at sponsor's discretion.

4.1.5 Concomitant Therapy

The Investigator must record in the eCRF any concomitant medication (including indication for the same) taken by the patient during the course of the study. The investigator will use the data from the EDC with information collected by caregivers in between visits.

4.1.5.1 Prohibited Medications

Medicinal products which induce torsades de pointes e.g. class Ia, Ic, III antiarrhythmics are prohibited. Other antiarrhythmics (class Ib, II, IV antiarrhythmics) should not be used, unless exceptionally, because of increased risk of adverse cardiac reactions.

CYP1A2 and CYP2D6 inhibitors (CYP1A2 inhibitor: ciprofloxacin, fluvoxamine, propafenone; CYP2D6 inhibitor: propafenone, quinidine) - significantly increases mexiletine exposure and thus the associated risk of adverse reactions to mexiletine.

CYP1A2 and CYP2D6 inducers (CYP1A2 inducer: omeprazole; CYP2D6 inducer: phenytoin, rifampicin) – Decrease the plasma concentration and half-life of mexiletine.

CYP1A2 Substrate such as theophylline, caffeine, lidocaine or tizanidine: Mexiletine is a potent inhibitor of CYP1A2; therefore, co-administration with mexiletine may be associated with elevations in plasma concentrations of the concomitant medicine that could increase or prolong the therapeutic efficacy and/or the adverse reactions of these medications.

The organic cation transporter 2 (OCT2) substrates (such as metformin and dofetilide): If mexiletine and other OCT2 substrates are to be used concurrently, the OCT2 substrate blood levels should be monitored, particularly when the mexiletine dose is changed. An appropriate adjustment in the dose of the OCT2 substrate should be considered.

Drugs with narrow therapeutic window narrow therapeutic window such as digoxin, lithium, phenytoin, theophylline or warfarin.

Any other medications for the treatment of myotonia.

4.2 Investigational Medicinal Product (IMP)

4.2.1 IMP Dosage Form and Strength

Mexiletine is typically formulated as hard gelatine capsules with the most frequent presentation being 200 mg mexiletine HCl (which corresponds to 167 mg mexiletine strength).

4.2.2 IMP Packaging and Labelling

Not applicable.

Mexiletine will be obtained from the marketplace by the caregiver and/or the treating physician via typical drug prescription process.

Patients/caregivers will be provided with mexiletine prescriptions by the treating physician to last until the next clinically planned visit.

4.2.3 Storage

Mexiletine must be stored at a temperature not exceeding 30°C and away from moisture.

4.3 Mexiletine Supply, and Accountability

The investigator or designee is responsible for ensuring adequate accountability of the study drug. All study drug prescribed to subjects/caregivers must be accurately recorded on an appropriate drug accountability record maintained by the Investigator or designee. Mexiletine should not be used for purposes other than those intended by the treating physician for the treatment of myotonias.

5 STUDY PROCEDURES

All patients/ caregivers / parents or legal representatives must provide their written informed consent and assent before any assessments or evaluations required by the study are performed. All screening assessments must be completed within 2 weeks of informed consent.

The evaluations and assessments during the study will be performed according to routine clinical practice or as necessary for each individual patient according to the treating physician. Consulted clinical experts have recommended that according to standards of care visits are usually performed with a frequency no longer than every 6 months.

There will be a screening visit to ensure the patient complies with all the participation criteria.

5.1 Screening Visit – V0 (Maximum 2 weeks)

The screening procedures will include recording the following parameters which typically have already been collected in the patient's medical history:

1. Obtaining written informed consent/ assent as per regulatory requirement
2. Patient demographics and anthropometric measurements (age, gender, ethnicity, height, weight)
3. Vital signs, including blood pressure (BP), heart (pulse) rate (HR)
4. Current medical condition: Type of myotonic disorder (genetic diagnosis), age of symptom onset, family history of myotonic disorders.
5. Signs and symptoms of myotonia as documented in medical history.
6. Clinical myotonia evaluation appropriate to patient's age and treating physicians standard clinical practice including proposed efficacy assessments and quality of life evaluations, where performed.
7. Review of inclusion/exclusion criteria
8. Medical history of:
   - Neurological disorders (Seizure, Epilepsy, Vertigo, Headache, Paraesthesia, Dysgeusia, Ataxia)
   - Gastrointestinal disorders (Abdominal pain, Nausea, Vomiting, Diarrhoea, Constipation, Intestinal ulcer, GI bleeding, Dysphagia, Oesophageal ulceration)
   - Renal or hepatic disorders
9. Any other significant medical history
10. History of unprovoked falling and stumbling, fractures
11. History of swallowing difficulties and/or laryngospasm (particularly below 6 months of age) / history of aspirations/ aspirational pneumonia (myotonia of mastication muscles)
12. History of hospitalisation due to muscle condition
13. History of any cardiac, rhythm disorders.
14. Cardiac status at baseline (ECG and echocardiogram (cardiac ultrasound; US), done up to 3 months prior to screening is acceptable. If not done earlier, ECG and echocardiogram to be performed at screening visit)
15. Surgical history
16. For patients previously prescribed mexiletine, any modification in mexiletine dose/ frequency in addition to the current dose/frequency as prescribed by the treating physician

17. History of previous anti-myotonia treatment other than / mexiletine
18. Concomitant medications in use (along with dose and frequency)
19. Washout for any current/ ongoing medications required/not required
20. Collection of known laboratory investigations if performed according to the treating physician regular practice including basic haematology, biochemistry and urinalysis.

Prescription for mexiletine doses for the use until next visit will be dispensed at this visit if the patients/caregivers did not have enough already.

5.2 Pharmacokinetic Assessments

Not applicable.

6 ENDPOINTS AND VARIABLES

6.1 Primary Variables

The endpoints to assess efficacy (exploratory) will be adapted to the patient's age and the corresponding tests they are able to perform. When feasible the following will apply in accordance with standard clinical practice:

- Muscle strength measured using the modified Medical Research Council (MRC) scale to evaluate neck flexors, shoulder abductors, elbow flexors and extensors, wrist extensors, finger flexors, hip flexors, knee flexors and extensors, posterior foot flexors and plantar flexors.
- Clinical Global Impression (CGI) Scores given to caregivers and assessed by the investigators
- Number and frequency of adverse events (AEs), serious adverse events (SAEs) and AE leading to treatment discontinuation, throughout the study while on treatment with mexiletine
- Incidence of adverse events of special interest (AESI)
- Description over time of efficacy outcomes obtained from clinically indicated tests as per the treating physician typical clinical practice and according to patient's age and cohort.
- Any changes in frequency, treatment interruptions of mexiletine.

6.2 Secondary Variables

- Description over time of outcomes of mexiletine use including dosing, formulation used, method of administration, acceptability and palatability as per the data collected by the treating physician according to age and cohort.
- The treating physician with elaborate a brief text with risk-benefit conclusions using the information from both the primary and secondary variables.

ASSESSMENT OF EFFICACY

Data Interpretation of Instruments/Scales

The efficacy endpoints chosen for the study are based on those that have been commonly used during routine clinical practice in adults (Logigian *et al.*, 2010; Statland *et al.*, 2012a; Statland *et al.*, 2012b), but they have been adapted according to the patient's age and ability to participate in the efficacy evaluation. Moreover, the approach to and the scope of efficacy endpoints has been accepted by the Regulatory Authorities (in particular the Paediatric Committee; PDCO) during the evaluation and discussion on the paediatric investigation plan (PIP) that this protocol is specifically designed to support. However, in this observational study the performance of these tests is not mandated by protocol or pre-scheduled. They will only be performed during the study according to routine clinical practice for the treatment of patients with myotonias at the discretion of the treating clinician.

I. Faces scale

A Faces (or other symbol) self-reported scale for children aged 6 years will be used to score muscle stiffness (myotonia severity) as by the patient. This type of scale has been validated and is considered suitable for use in at least a subset of the age group proposed (Tsze *et al.*, 2013). Muscle stiffness is commonly used as either a primary or secondary measure of efficacy in myotonic disorders clinical trials.

Similarly, the Faces scale will be used to assess pain, weakness and tiredness in study participants as secondary endpoints. As above, the Faces for severity score of pain, weakness and tiredness as self-reported will be constructed the same as for the stiffness score with a 10 cm straight horizontal line having the endpoints "no [symptom] at all" and "[symptom] as worst possible

II. *Hand Grip Myotonia Test*

The score of handgrip myotonia as quantitatively measured using a commercially available grip dynamometer and computerised capture system. In standardised conditions (i.e. in a room at controlled temperature, after a definite period of rest), maximum voluntary contractions following forced right hand grip will be recorded and the time to relax from 90% to 5% of maximal force will be determined using automated analysis software (Moxley *et al.*, 2007; Logigian *et al.*, 2010; Statland *et al.*, 2012b).

III. Action myotonia in eyelid muscles and right hand flexor muscles (Grip myotonia)

Subjects will be asked to squeeze their eyes closed for 5 seconds then rapidly open them; and make a tight fist for 5 seconds then rapidly open. Five trials of each manoeuvre will be performed in sequence at each visit and the time measured on a stopwatch (Statland *et al.*, 2012b).

IV. Timed-up and Go (TUG) Test

The Timed "Up and Go" Test (Podsiadlo and Richardson, 1991; Trip *et al.*, 2009a) measures, in seconds, the time taken by an individual to stand up from a standard arm chair (approximate seat height of 46 cm, arm height 65 cm), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down. This clinical test, developed in a medical setting, asks subjects to wear their regular footwear and use their customary walking aid (none, cane, walker). No physical assistance is given. They start with their back against the chair, their arms resting on the armrests, and their walking aid at hand. They are instructed that, on the word "go" they are to get up and walk at a comfortable and safe pace to a line on the floor 3 meters away, turn, return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a stopwatch or a wristwatch with a second hand can be used to time the trial. This test is only appropriate for children ≥3 years of age.

V. Medical Research Council (MRC) scale

The modified Medical Research Council (MRC) scale can be used to evaluate neck flexors, shoulder abductors, elbow flexors and extensors, wrist extensors, finger flexors, hip flexors, knee flexors and extensors, posterior foot flexors and plantar flexors (MRC, 1975; Verreydt *et al.*, 2022). The MRC scale of muscle strength uses a score of 0 to 5 to grade the power of a particular muscle group in relation to the movement of a single joint (score 0 corresponds to no contraction, 3 active movement against gravity and 5 equates to normal power).

VI. Paediatric Quality of Life Questionnaire (PedsQL)

Changes in health-related quality-of-life as measured by the PedsQL™ Quality of Life (version 4.0) and Neuromuscular modules (version 3.0). These multidimensional scales assess the frequency of health problems using generic and disease-specific approaches, respectively. Subjects and/or parent or proxies report a score of 0 to 4 (never to almost always) and questionnaires are tailored to age groups. The Quality of Life module consists of 23 questions that are further divided into physical, emotional, social and school functioning subsets. The 25-question PedsQL™ Neuromuscular module was created as a more specific tool to measure health-related quality of life for musculoskeletal diseases such as Duchenne's muscular dystrophy and Spinal Muscular Atrophy (Iannaccone *et al.*, 2009; Davis *et al.*, 2010). It is subdivided into symptom/function, communication and family resource dimensions. Greater scores indicate morbidity and illness burden compared to healthy controls, the latter scoring no less than 80 in all scales (Varni *et al.*, 2002).

VII. Clinical Global Impression (CGI) scores

This will be evaluated by a caregiver and by the investigator. Efficacy will be evaluated on a 4-point scale as very efficient, good, fair or poor.

VIII Acceptability of mexiletine administration

Acceptability of different modes of mexiletine administration (i.e., capsule, sprinkled on food and/or gastric (enteral) tube where such formulations are used), and the factors that govern the route of administrations in paediatric patients will be assessed by reviewing the patient records, interviewing patients and their caregivers. Any difficulty in swallowing or compliance will be noted and if capsules were opened and content was taken, details should be recorded accordingly.

IX Palatability

Palatability of alternative administration (capsule content with milk/juice or sprinkled on food)will be recorded . Any complaint of bad taste or numbness will be inquired and recorded in the EDC or CRF accordingly.

X. FLACC (face, legs, activity, crying, and consolability) scale.

Pain is assessed by the investigator using the FLACC (face, legs, activity, crying, and consolability) scale (Drendel *et al.*, 2011), as a secondary endpoint, for Cohort 1 (≥6 months and <6 years). Each behaviour is scored from 0 to 2, with the highest possible cumulative score being 10 (most pain).

XI. PIPP (Premature Infant Pain Profile) scale.

Pain is assessed by the investigator using the PIPP (Premature Infant Pain Profile) scale (Stevens *et al.*, 2010), as a secondary endpoint for infants and toddlers < 6 months.

7 ASSESSMENT OF PHARMACOKINETICS

Not applicable.

8 ASSESSMENT OF SAFETY

The assessment of safety will be performed according to the collection of AEs during routine clinical practice visits by the treating physician, and medical monitor.

8.1 Adverse Events

Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that staff involved in the study is familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

8.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign, symptom or disease (including intercurrent illness), deterioration of a pre-existing illness, accident, any suspected drug reaction, or a clinically relevant change of laboratory values temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigational) product and/ or study treatment.

A treatment emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

8.1.2 Serious Adverse Event (SAE)

A SAE is defined as, any untoward medical occurrence that at any dose:

1. Results in death.
2. Is life-threatening (defined as a participant at immediate risk of death at the time of the event). It does not include an event that, had it occurred in a more severe form, might have caused death.
3. Requires in-patient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/ incapacity.
5. Is a congenital anomaly/ birth defect.
6. Consists of any other medically important condition.

8.1.3 Recording and Collection of Adverse Events

It is the responsibility of the investigator to collect all AEs (both serious and non-serious) derived from spontaneous, unsolicited reports of patients, by observation and by routine open questions.

AE reporting will extend from date of informed consent until completion of the final visit (EOT). Any ongoing AE at end of study visit should be followed until the outcome is evident and resolved, clinically stabilized or a plausible explanation has been found.

Pre-existing diseases (before participating in the study) are not considered to be AEs, unless the disease worsens during the study period. Concomitant diseases prior to enrolment will be recorded in the eCRF.

Signs and symptoms clearly associated with the disease under study (including symptoms of disease progression) should be reported as AEs if they are newly emergent (i.e., findings not previously observed in the patients), or are determined by the investigator as severe or a worsening, or if the investigator considers deterioration of disease-related signs and symptoms to be caused directly by the study drug.

Abnormal laboratory values/ ECGs/ vital signs/ ophthalmic/ physical and systemic examination should be reported as AEs *only* if the Investigator considers the abnormality as clinically relevant or significant or believes that the abnormality should be reported as an AE.

Any dose (and associated symptoms) given to the patient that exceeds the dose prescribed to the patient has, at a minimum, to be recorded as a non-serious AE in the patient file and CRF/ eCRF. Any case of overdose leading to an AE or SAE should be reported to Medical Monitor according to reporting requirements. In case of an accidental overdose, the patient should be monitored by the Investigator for any adverse clinical events, as deemed necessary by the Investigator.

After completion of all visit assessments, the Investigator must document any AEs arising from these assessments. In case of an SAE, the Investigator must also complete an SAE report form and report it to safety contact, as described in Section 8.1.4.2 Relationship to the Study Drug.

All AEs will be recorded in case report form (eCRF) regardless of the causal relationship to the study drug.

All AE records should contain AE term/ AE diagnosis, date of onset, severity, relationship to the study drug, outcome, date of recovery or outcome, action taken with the study drug, action taken with AE, AE leading to discontinuation of patient from study and whether the event is classified as serious.

The investigator must continue to follow-up the patient with all AEs regardless of the causal relationship to the study drug until the AE has resolved or until the condition stabilizes to an acceptable level or is determined to pose no issue, or until follow-up is no longer feasible.

8.1.4 Evaluation of Adverse Events

Each adverse event is evaluated depending on the following categories by the investigator.

8.1.4.1 Definition of severity of an AE

Wherever possible, all observed AEs will be graded using the CTCAE ver. 5.0. The severity of the AE shall be classified using the following grading.

- *Grade 1*: Mild; asymptomatic or mild symptoms, or clinical or diagnostic observations only, or intervention not indicated
- *Grade 2*: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money etc.).
- *Grade 3*: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care (bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden).
- *Grade 4*: Life-threatening consequences; urgent intervention indicated.
- *Grade 5*: Death related to an AE.

8.1.4.2 Relationship to the Study Drug

The assessment of the relationship of an adverse event to the administration of study drug is based on the presence or absence of a "reasonable possibility" that investigational drug has caused the AE. An AE is considered to be "related" to the study medication if a causal relationship between the IMP and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out). An AE related to the study drug is referred to as an adverse drug reaction (ADR).

The causal relationship between an adverse event and the study drug will be defined as below:

- *Not Related*: When the adverse event is definitely caused by the subject's clinical state, or the study procedure/ conditions or other concomitant drugs
- *Unlikely Related*: When the temporal association between the adverse event and the drug is such that the drug is not likely to have any reasonable association with the adverse event
- *Possibly Related*: When the adverse event follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/ conditions
- *Related*: When the adverse event follows a reasonable temporal sequence from the time of drug administration, abates upon discontinuation of the drug and reappears when the drug is reintroduced.

Reporting of Serious Adverse Events

All SAEs occurring after the time of informed consent until the final visit must be reported.

All AEs (non-serious) and SAEs should be reported by the investigator to the Medical Monitor and Safety Monitor via Email or telephone as soon as possible after the investigators become aware of its occurrence but no later than 24 hours regardless of the causal relationship with the study drug (following knowledge of the SAE). After receiving reports of the SAEs, the Safety Contact should communicate with the investigator to get additional information for evaluation

of SAEs. If the AE is fatal or life-threatening, the EU-QPPV/Lupin Safety Monitor must be notified immediately (as mentioned in the Safety Monitoring Plan), irrespective of the extent of information about the event available.

All AEs/SAEs shall be reported by investigator/ Sponsor/ sponsor designee as per applicable regulatory requirements.

The Details of Medical Monitor and Safety Monitor

Medical Monitor	**Safety Monitor:**
Siyu Liu, MD, PhD Director, Clinical Development, Inhalation Lupin Research Inc. 4006 NW 124th Ave, Coral Springs, FL 33065 +1 (443) 853-7065 (Office) +1 (443) 240-7434 (Mobile) Email: SiyuLiu@lupin.com	Clinical Safety, DSRM. 3rd Floor, Kalpataru Inspire Off. Western Expressway, Highway, Santacruz East, Mumbai, Maharashtra 400055 Mobile Number: +91-7045584407 Email: mailto:**clinicalsafety@lupin.com**

8.1.4.3 Follow – Up of Serious Adverse Events (SAEs)

The investigator must continue to follow the patient until the SAE has resolved or until the condition stabilizes to an acceptable level or is determined to pose no issue, or until follow-up is no longer feasible. Any ongoing SAE at end of study visit should be followed until the outcome is evident and resolved, clinically stabilized or a plausible explanation has been found.

8.1.4.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

An SAE that is also an unexpected adverse drug reaction is called a Suspected Unexpected Serious Adverse Drug Reaction (SUSAR). Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product or the Summary of Product Characteristics for an authorized medicinal product or available literature).

SUSARs will be reported in compliance with regulatory reporting requirements of participating countries by Lupin's pharmacovigilance group. The details of reporting of SAE, significant AEs and SUSARs will be captured in the Safety Management Plan (SMPs).

8.2 Adverse Events of Special Interest (AESI)

Adverse events, which are considered by the investigator to be a neurological disorder or gastrointestinal in nature, will be recorded as an adverse event of special interest.

All subjects should be carefully monitored for the diagnosis of listed AEs of special interest. All AEs of special interests should be evaluated properly and their relationship with the study drug should be recorded

Severe Cutaneous Adverse Reactions (SCARs)

Mexiletine is contraindicated in patients with known hypersensitivity to mexiletine, or to any of the excipients or to any local anaesthetic, as there is possibility of occurrence of potentially lethal severe cutaneous adverse reactions, usually severe cutaneous eruption along with fever, lymphadenopathy, hypereosinophilia, lymphocytosis or organ damage (notably liver and kidney).

Cardiac Arrhythmia

Mexiletine is a class I b antiarrhythmic drug according to the Vaughan Williams classification, and as such, it may induce an arrhythmia or accentuate a pre-existing arrhythmia, either diagnosed or undiagnosed. Mexiletine should be administered with caution in patients with pre-existing cardiac conduction anomalies. The advent (under mexiletine therapy) of an atrioventricular block, a permanent complete heart block, or a sinoatrial block necessitates the interruption of the mexiletine treatment.

Increased Frequency of Seizure Episodes in Patients with Epilepsy

Common elements of pathogenesis create a basis for the assumption that antiarrhythmic drugs may affect seizure phenomena and interact with antiepileptic drugs.

8.3 Physical and Systemic Examination

A physical examination will be performed at the time of screening to ensure patients comply with participation criteria. Other physical and or systemic examinations will be performed according to regular clinical practice or at the discretion of the treating physician.

8.4 Vital Signs

Vital signs, including blood pressure (BP), heart (pulse) rate (HR) will be measured according to regular clinical practice or at the discretion of the treating physician.

8.5 Electrocardiogram Assessments (ECGs)

A 12-lead ECG will be performed at screening and after screening according to regular clinical practice or at the discretion of the treating physician. Any abnormal findings will be evaluated for clinical significance.

8.6 Clinical Laboratory Examinations

Haematology tests, biochemistry, and urine analysis tests for safety assessment will be performed at screening and according to regular clinical practice or at the discretion of the treating physician.

Collection of Laboratory Samples

Sample collection and handling for laboratory tests will be performed according to regular clinical practice or at the discretion of the treating physician.

Any clinical test results outside the reference value range will be evaluated for clinical significance. After dosing, laboratory abnormalities considered by the investigator to have worsened compared to that prior to dosing will be recorded as AEs.

8.7 Pregnancy

Not applicable.

8.8 Sample Size

The number of patients, and type of study, was agreed with the paediatric committee (PDCO) during paediatric investigation plan (PIP) review. A total of at least 10 paediatric evaluable patients in cohorts 1 and 2. At least 4 patients from birth to less than 6 months (cohort 2) and at least 6 patients from 6 months to less than 6 years (cohort 1).

8.9 Statistical Methods

Summary descriptive statistics will be provided for all collected parameters. The categorical variables will be presented with frequency and percentages.

8.10 Handling of Missing Data

Missing data will be treated as missing, and no imputation will be done.

8.11 Patient Disposition

An overall summary of subject disposition will be presented using number and percentage (wherever applicable) for subjects screened, number enrolled, subjects who completed study

and subjects who discontinued, along with the reason of discontinuation. Disposition information will also be listed for each subject. Summary of screen failures will be presented. Number of subjects in each analysis population will be summarized.

8.12 Analysis Population

Safety Population: Safety population will comprise of the subjects who received at least one dose of mexiletine after the ICF was signed by their parents or legal guardians.

Intent to Treat (ITT) Population: ITT population will comprise of the subjects who have taken at least one dose of the study treatment and have at least one post-enrolment assessment done.

8.13 Efficacy Analysis

When possible and according to age, the actual Faces scores and the change from baseline in Faces score for muscle stiffness, pain weakness and fatigue will be summarised over time.

Change from baseline in time (in seconds) to relaxation of hand muscles and reduction in relaxation time from the first to the third/fifth contraction and time (in seconds) for Timed-up and go (TUG) test will be summarised over time from screening to week 104.

Quality of life data will be presented descriptively by visit along with the change from baseline.

The observed values of Clinical Global Impression Scores and the change from baseline in Clinical Global Impression Score from baseline to Week 104 will be summarised.

The observed values of Myotonia Behaviour Scale Scores and the change from baseline in Myotonia Behaviour Scale Score from baseline to Week 104 will be summarised.

When performed, changes in clinical laboratory values from Screening to Week 104 will be summarised.

A separate Statistical Analysis Plan will be prepared.

8.14 Safety Analysis

All summaries of adverse events will use only treatment emergent adverse event (TEAE) records.

In general, events will be described by counts and percentages.

Following information will be summarized for TEAEs.

- Overall Summary of TEAEs
- TEAEs by preferred term and System Organ Class (SOC)
- Treatment Related TEAEs by preferred term and SOC
- TEAEs by preferred term and SOC, Maximum Severity and Relationship
- Serious TEAEs by preferred term and SOC

- TEAEs leading to discontinuation of study drug by preferred term and SOC

Also, listing of all adverse events will be provided. The listing will include Adverse event number, description, preferred term, SOC, Start and End Date, Seriousness, Frequency of Occurrence, Severity, Action taken regarding study treatment, outcome, relationship to study treatment.

When collected laboratory and vital signs parameters will be summarised descriptively. Laboratory tests done at screening will be considered baseline.

9 DATA MANAGEMENT

9.1 Data Handling

This is a non-interventional observational study performed according to the routine regular practice at the discretion of the treating physician following recognised treatment practices for patients with myotonias. Within these constraints, and when collected, data will be recorded at the site in source documents and transcribed on to the eCRFs. The investigator shall verify the accuracy of data in the eCRF.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient's parents or legal guardians (a signed copy is given to the patient's parents or legal guardians).

Lupin monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific Registry Monitoring Plan. No information in source documents about the identity of the patients/subjects will be disclosed.

Data from external sources (such as laboratory data) will be appropriately handled into the database. Medical information will be coded using MedDRA and WHO DD.

Data Collection

Designated investigator staff will enter the data into the CRFs using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock or when a site is closed, the investigator will receive copies of the patient data for archiving at the investigational site.

The Principal Investigator is responsible for assuring that the data entered by the site personnel into CRF is complete, accurate, and that entry and updates are performed in a timely manner.

10 CLINICAL STUDY MANAGEMENT

10.1 Conduct of the Study

Lupin Europe GmbH will conduct the study according to written standard operating procedures to ensure that the study is conducted and data are generated, documented and reported in compliance GCP, applicable regulatory requirements and with the site clinical practice, and when feasible given the nature of an observational study also according to ICH.

10.2 Direct Access to Source Data

During the course of the study, the monitor will visit study sites to review protocol compliance, compare eCRFs and individual patient medical records, assess drug accountability records and ensure that the study is being conducted according to applicable regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

A review of the eCRFs for completeness, accuracy, legibility, timeliness and clarity, as well as with source documents will be required to monitor the progress of the study. Moreover, the applicable regulatory authorities, Institutional Ethics Committees (IECs) and/ or the sponsor designated Clinical Quality Assurance team may perform source data checks and/ or on-site audits/ inspections to confirm the validity of the trial conduct and the integrity of data collected. Direct access to the source data will be required for these inspections and audits; these will be carried out giving due consideration to data protection and medical confidentiality. The investigator must ensure provision of the necessary support to the sponsor/ sponsor's representative, regulatory or the IEC at all times.

10.3 Amendments to the Protocol

Important changes to the protocol and study design require a mutual agreement between the investigator and sponsor and will be effective following approval of the IEC and regulatory authorities (as necessary). These changes are to be described in the revised protocol and a list of changes detailing the pre-change and post-change versions will be prepared.

10.4 Guidance and Supervision of Sub-Investigators

The principal investigator shall maintain the list of appropriately qualified sub-investigators and study support staff (e.g., pharmacists, nurses and other staff) to whom significant trial-related duties have been delegated.

The principal investigator shall ensure that all sub-investigators and study support staff participating in the trial are adequately trained on the protocol, the study medication and their trial-related duties and functions and they are timely informed of any new information pertaining to the study.

10.5 Archiving Study Records

The essential study documents should be retained and archived for at least 15 years after completion or discontinuation of the trial. However, these documents should be retained for a longer period, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/ institution as to when these documents no longer need to be retained.

10.6 Data and Safety Monitoring Board (DSMB)

No drug safety monitoring committee (DSMB) will be required.

11 QUALITY ASSURANCE AND QUALITY CONTROL

The Sponsor will implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP, applicable regulatory requirements and institutional research policies and procedures. Auditing procedures developed by CRO will be followed to comply with GCP guidelines and to ensure accuracy, completeness and authenticity of the data generated, recorded, reported and acceptability of the study data for international registration purposes. The study may be audited at the discretion of the Sponsor by any of its representative.

11.1 Monitoring

Due to the nature of this registry, remote site management and centralized monitoring will be the main strategies employed. This risk-based monitoring approach will be detailed in the Registry Monitoring Plan. The Sponsor-assigned monitors may conduct site visits as needed to the clinical facilities for monitoring various aspects of the registry. The Investigator must agree to Sponsor authorized personnel having direct access to the clinical (or associated) files for all patients considered for registry entry for verifying entries made in the registry and assist with their activities, if requested. The Investigator should make adequate time and space for monitoring. The site must complete the eCRFs in a timely manner and on an ongoing basis to allow review per the Registry Monitoring Plan.

The investigator must cooperate with the sponsor to ensure that the conduct of the clinical trial is GCP compliant.

11.2 Agreement and Compliance with the Protocol

Prior to trial initiation, the protocol/ other related documents must be approved by the IEC/regulatory authority in compliance with applicable regulatory requirements. Before the first patient is allowed to participate in the clinical trial, the sponsor must ensure that all the ethical and legal requirements are met.

The investigator should not deviate from the protocol approved by the IEC, except when the changes are necessary to eliminate a risk to the patients. This trial must accurately comply with the protocol. If changes to the protocol are required, the changes must be made in writing and notified or submitted for approval by the IEC/regulatory authorities (as necessary).

11.3 Audits and Inspections

An auditor from the sponsor, the regulatory authorities, or the IEC may conduct an audit or inspect the clinical sites.

The purpose of audits and inspections is to systematically and independently verify that study-related activities are performed, data in clinical studies are accurately recorded, analysed and reported and that the study has been conducted in accordance with protocol, ICH- GCP guidelines and the applicable regulatory requirements.

Regulatory authorities will communicate the purpose of the audit to the investigator and the investigator should notify the sponsor of the audit. The sponsor may provide support to the investigator so that the site is inspection ready.

12 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

This study will be conducted in compliance with the protocol and with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the World Medical Association Declaration of Helsinki (2013) and in compliance to the specific local regulatory requirements wherever applicable and required.

The study is conducted according to Good Clinical Practice (GCP) principles as required by Directive 2001/20/EC, as amended.

Subject Confidentiality requirements as stated in the Data Protection legislation.

This study is also performed to satisfy the requirements of the Paediatric Regulation 1901/2006/EC, as amended.

12.1 IEC Approval

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol, informed consent document and other applicable study documents have been reviewed and approved by an EC. The IEC will be appropriately constituted and perform its functions in accordance with ICH GCP and local requirements as applicable.

12.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each patient (or their legally responsible guardian). Before each patient is enrolled into the study, informed consent will be obtained from the patient (or his/ her legally authorized representative) according to the most current applicable regulatory and legal requirements. The consent will be obtained on the IEC approved and most recent version of consent form in language best comprehended by the patient. The consent documents to be used for the study will include all the elements of informed consent as outlined in the applicable regulatory guideline and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki and be reviewed and approved by the appropriate EC prior to use at each site. In addition, paediatric assent will be obtained as appropriate according to the subject's age and institutional requirements.

The patients /caregivers should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The patients will be re-consented as required.

12.3 Confidentiality

All study findings and documents will be regarded as confidential. The investigator and members of his/ her research team must not disclose such information without the prior written approval from the sponsor. The anonymity of the participating patients must be maintained. Patients will be identified on the CRF/ eCRF and other documents submitted to the CRO or the independent data management centre by unique coded patient identification/ registration number but not by name. The confidentiality of records that could identify patients (e.g., the signed informed consent) should be protected, respecting the privacy and confidentiality rules

in accordance with the applicable regulatory requirement(s) and should only be disclosed to the authorized study personnel/ sponsor representative/ IEC/ Regulatory authorities if required.

12.4 Liability and Insurance

The sponsor will obtain a reasonable third-party liability insurance coverage in accordance with all local legal regulatory requirements.

The sponsor will provide for insurance coverage with respect to liability caused by trial-related injuries caused by IPs being tested or by study-related procedures/ medical steps taken in the course of the study in accordance with the applicable regulatory requirement(s). The terms and conditions will apply as specified in the insurance policy document.

12.5 Publication Policy

Lupin shall retain the sole and exclusive ownership of any and all Data arising (whether directly or indirectly) out of the conduct of clinical trials in relation to the study ("Data"). Upon completion of the Study, Lupin may, at its sole discretion, arrange the analysis and tabulation of the Data. Lupin shall be entitled to utilize the Data and CSR in any manner whatsoever including using the same for publication, presentation at scientific meetings or for submission with regulatory authorities in the manner it deems fit. Investigator hereby agrees and acknowledges that it shall not use and/or publish the Data and/or any reports, presentation, information arising out of or in relation to the clinical trial without prior written approval of Lupin.

Since such studies are published with data of all patients pooled and analysed together, isolated and independent publications at study centre/country level may provide inaccurate representation of safety, efficacy or immunogenicity of the investigational product. Hence, if the Investigators would like to publish/present any paper/poster, the Investigators should provide Lupin the draft material to review for approval any such proposed publication/presentation or other type of disclosure before it is submitted or disclosed in order to ensure against any inadvertent disclosure of confidential information or unprotected invention. For approval by Lupin, the Investigator shall send such reports, presentation, information and/or Data for Lupin review and approval at least 90 (ninety) days prior. It is hereby agreed that all proposed publications based on the study shall be subject to Lupin written approval with a possibility of denial for any reason including the reasons given above. If approved with comments from Lupin, the Investigator shall incorporate all such comments suggested by Lupin in the publication. By signing this Protocol, the Investigator agrees to unequivocally release the Data from the study to the Lupin without conditions and acknowledges this publication policy.

13 APPENDICES

13.1 Appendix 1: Investigators signature page

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: Prospective, long term, observational study (patient registry) of paediatric myotonic disorders from birth to less than six years of age who are treated with mexiletine (PEGASUS Study).

PROTOCOL NUMBER: MEX-NM-401

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients. I agree to conduct this study in full accordance with the protocol, all applicable regulations and Good Clinical Practice (GCP) guidelines.

Principal Investigator Name and Job Title:_____

_____

Institution/Clinic: _____

Address: _____

Signature: _____

Date (day/month/year)

13.2 Appendix 2: Summary of Changes

The revisions listed below have been made to the protocol and synopsis as appropriate and are considered substantial. Redline versions of the documents are available. Where appropriate revised or new text is presented below in bold italics and deletions are struck through. Minor formatting errors were corrected throughout the protocol and may not be indicated in the table.

Section	Modification	Reason
Version 01 – Valid from 30th May 2024		
N/A	First version	N/A

14 REFERENCE LIST

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