Non-Interventional Study Protocol

Study Title	An Observational Study to Describe the Long-term Safety and Effectiveness of Namuscla in the Symptomatic Management of Myotonia in Adult Patients with Non-dystrophic Myotonic Disorders
Type of Study	Non-interventional Prospective Post Authorisation Safety Study (PASS)
EU PAS Registration No	Study not yet registered
Protocol Number	LUP/MEX/2018/001
Protocol Version Number	1.6
Protocol Date	25 November 2019
Active Substance	Mexiletine hydrochloride
Medicinal Product	Namuscla ™ (167 mg mexiletine hard capsules)
Countries of Study	UK, France, and Germany.
Marketing Authorisation Holder (Name and address)	Lupin Europe GmbH Address; Hanauer Landstraße 139-143 60314 Frankfurt, Germany
Joint PASS	No
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This study will be conducted in compliance with this protocol and all applicable regulatory guidelines.

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2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CDM	Clinical Data Management
CI	Confidence Interval
CRO	Contract Research Organisation
DAE	Discontinuation due to Adverse Event
DM	Dystrophic Myotonia
DMP	Data Management Plan
DRESS	Drug Reactions with Eosinophilia and Systemic Symptoms
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End-of-Study
EU	European Union
EOS	End-of-Study
GVP	Good Pharmacovigilance Practices
INQoL	Individualised Neuromuscular Quality of Life
MBS	Myotonia Behaviour Scale
NDM	Non-dystrophic Myotonia
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient-reported Outcomes
PT	Preferred Term
RMP	Risk Management Plan
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SCAR	Severe Cutaneous Adverse Reactions
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class

Abbreviation	Definition
SRSD	Single Reference Safety Document
TEAE	Treatment-emergent adverse events
UK	United Kingdom
VAS	Visual Analogue Scale

3.0 RESPONSIBLE PARTIES

This study will be conducted by qualified Investigators under the Sponsorship of Lupin Europe GmbH. Lupin and contracted CROs will manage the conduct of the study.

4.0 ABSTRACT

Title of Study: An Observational Study to Describe the Long-term Safety and Effectiveness of Namuscla in the Symptomatic Management of Myotonia in Adult Patients with Non-dystrophic Myotonic Disorders	
Protocol Number	LUP/MEX/2018/001
Protocol Version Number	1.6
Protocol Date	25 November 2019
Author	Brajesh Pandey, MBBS, MD Associate Director, Clinical Development, Lupin Research Inc. 325 Sentry Parkway, 5 Bldg West, Suite 300, Blue Bell, PA 19422, USA Phone: +1 (443) 853-6900
Medicinal Product	Namuscla (167 mg mexiletine hard capsules)
Study Duration: 3 years	**Type of Study**: Non-interventional, Prospective Post Authorisation Safety Study (PASS)

Rationale and Background:

Rationale for the Study

Namuscla™ is approved in European Union (EU) for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. Active ingredient of Namuscla is 167 mg mexiletine, a class Ib antiarrhythmic. To date, randomised studies conducted for mexiletine have assessed only short-term efficacy and safety with little supporting data for long-term use from observational research.

This non-interventional study will collect data on the long-term (12 months to 3 years) safety of Namuscla in a real-world setting for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders over a period of up to 3 years.

This study is being conducted as part of the agreed European Risk Management Plan (RMP).

Research Question: To describe the long-term safety and tolerability of Namuscla in the management of myotonia symptoms in adult patients with NDM in a real-world setting.
Study Objectives: **Primary Objective:** To describe the long-term safety and tolerability of Namuscla for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. **Secondary Objectives:** 1. To evaluate the safety of Namuscla in NDM patients 2. To evaluate the safety of Namuscla in special populations: – patients with hepatic impairment – patients with severe renal impairment – elderly patients (aged 65 years and above), – patients with seizure disorders, 3. To assess the occurrence of severe cutaneous adverse reactions (SCARS), cardiac arrhythmia, and seizures on treatment with Namuscla 4. To evaluate the clinical effectiveness of Namuscla in NDM patients in terms of clinical evaluation, and based on patient-reported outcomes (PRO).
Study Design and Conduct This is a non-interventional, prospective, observational, multicentre study to evaluate the long-term safety and effectiveness of Namuscla in adult patients with NDM. Namuscla should be prescribed as per the approved Summary of Product Characteristics (SmPC). Adult patients with non-dystrophic myotonic disorders who have been prescribed Namuscla by the treating physician, and who meet the eligibility criteria will be enrolled in this study. This includes: • Patients newly initiated on Namuscla for the treatment of NDM (newly exposed) • Patients already on Namuscla/ mexiletine at enrolment - For patients receiving mexiletine other than Namuscla, only those who switch to Namuscla will be included in the study.

Patients already being treated with Namuscla/ mexiletine at the time of enrolment will be considered for enrolment provided they meet the eligibility criteria. The study will be initiated at specialized centres for the treatment of myotonic disorders ("reference centres") in the United Kingdom (UK), France, and Germany, depending on availability of Namuscla in the specific country. Depending on the enrolment and marketing status (availability) of Namuscla in other countries in the EU, inclusion of additional sites in other countries will be considered. The study population will comprise patients who are diagnosed with non-dystrophic myotonic disorders and considered suitable candidates for the treatment by Namuscla by the investigators according to the approved SmPC. Patients will be enrolled over an approximate 2-year enrolment period and will be followed-up on-treatment for up to 3 years. Each enrolled patient will be observed for 3 years or until discontinuation (if discontinued early). For all enrolled patients, the baseline would be the latest data available at the enrolment visit. For the patients already on Namuscla, cumulative data (data related previous exposure as well as current data) will be collected for adverse events (AEs) on Namuscla treatment. No drug will be supplied for this study; patients will receive medicines through local standard practices. All evaluations and investigations during the study will be performed according to the routine clinical practices and discretion of the treating physician.
Number of Patients (Planned): The study will target the enrolment of 50 patients who are treated with Namuscla.
Number of Centres (Planned): Approximately 6 specialized centres for myotonic disorders in the UK, Germany, and France.
Inclusion Criteria: 1. Adult, male or female patients with non-dystrophic myotonic disorders planned to be started on Namuscla according to the approved SmPC 2. Patients already receiving Namuscla/mexiletine for the treatment of NDM; (for patients on mexiletine other than Namuscla, only those who switch to Namuscla will be enrolled). 3. Patients who understand and are willing to provide informed consent. **Exclusion Criteria:**

1. Patients who are enrolled or participating in any other clinical trial for an investigational product.
2. Hypersensitivity to mexiletine, or to any of the excipients of Namuscla, or hypersensitivity to any local anaesthetic
3. Ventricular tachyarrhythmia
4. Atrial tachyarrhythmia, fibrillation or flutter
5. Complete heart block (ie, third-degree atrioventricular block) or any heart block susceptible to evolve to complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 240 ms) and/or wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and trifascicular block),
6. Myocardial infarction (acute or past), or abnormal Q-waves
7. Symptomatic coronary artery disease
8. Heart failure with reduced ejection fraction <50%
9. Sinus node dysfunction (including sinus rate < 50 bpm)
10. Patients receiving drugs that can induce torsades de pointes
11. Patients receiving medicinal products with narrow therapeutic index (ie, theophylline, tizanidine, digoxin, lithium, phenytoin or warfarin)
12. Patients who are pregnant or lactating.

Patients meeting all the above inclusion criteria and none of the above exclusion criteria will be eligible for enrolment in the study.

Data Collection

As it is a non-interventional study, the frequency of visits and the actual assessments performed will be in line with the routine clinical practice and any local treatment protocols. Data elements will be collected from information routinely recorded in the medical record. No study visits or examinations, laboratory tests or procedures are mandated by the study.

Patients who fulfil the eligibility criteria and complete the informed consent process will be enrolled.

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 (eCRFs). Follow-up data will be collected annually (every 12 months) from all routine care visits.

No study visits or examinations, laboratory tests or procedures are mandated as part of this study. Additional data collection via phone calls would serve as a source to capture safety data.

In this prospective, observational study, the baseline for all patients (patients newly initiated on Namuscla and those already on Namuscla) will be the latest data available at the enrolment visit.

Data for the following parameters will be collected as per availability from all enrolled patients:

Baseline (Enrolment) assessments captured for all enrolled patients (newly exposed as well as patients already on Namuscla/ mexiletine)

1. Visit date
2. Patient demographics (gender, ethnicity, age, smoking status, occupation status)
3. Myotonia history: Type of myotonic disorder (diagnosis), age of symptom onset, family history of myotonic disorders.
4. Signs and symptoms of myotonia as documented in medical history.

Relevant medical history at baseline

5. History of hepatic impairment – (Hepatic impairment is defined as elevated Liver function test grade-3 and above as per NCI CTCAE v. 5.0; specifically Total Bilirubin and AST/ALT or Child-Pugh categories B and C at baseline - if available in medical records)
6. History of renal impairment - (Renal impairment is defined as decreased eGFR, grade-3 and above as per NCI CTCAE v. 5.0 ie, eGFR <30 ml/min/1.73 m^2 - if available in medical records)
7. Cardiac abnormalities (eg, arrhythmia, heart failure, cardiovascular disease) (along with any relevant investigations, if available)
8. History of seizure disorders
9. Autoimmune diseases
10. Skin diseases and cutaneous drug reactions
11. Any medical history associated with impaired muscle function: fractures, respiratory disorders, swallowing difficulties / history of aspirations/ aspirational pneumonia, myotonia of mastication muscles
12. Obstetric history
13. Surgical history/ hospitalisation due to muscle condition

14. Previous anti-myotonia treatment other than Namuscla/ mexiletine (including any experimental therapies).
15. Concomitant medications in use
16. Baseline vitals and anthropometric measurements (pulse rate, blood pressure, weight) (latest documented value)
17. Latest documented 12-lead electrocardiogram (ECG), cardiac evaluation including 2-D echocardiogram, Holter monitoring if available as per routine standard of care
18. Laboratory investigations (haematology, biochemistry and urinalysis) as available

Efficacy variables to be assessed at baseline

19. Clinical myotonia evaluation - hand and eyes (Time in seconds to make a tight fist and hold for 5 seconds, then rapidly open it again; Time in seconds to open the eyes after squeezing the eyes closed for 5 seconds, and then rapidly open them)
20. Baseline Visual Analogue Scale (VAS) scores - Patient self-assessment of myotonia symptoms stiffness, and fatigue on VAS (VAS, 0-100);
21. Baseline Myotonia Behaviour Scale (MBS) score
22. Individualised Neuromuscular Quality of Life (INQoL)
23. Dose/frequency of Namuscla prescribed by the treating physician

For patients already on Namuscla

For patients already on Namuscla, in addition to all the above data elements, the following will be captured:

24. Dosage/ duration of previous Namuscla/ mexiletine use
25. Any previous AEs associated with the use of Namuscla/mexiletine.

Follow-up (on-treatment follow-up) data collection will be at 12, 24, and 36 months from enrolment – for newly exposed patients as well as patients already on Namuscla

Following data will be collected as per availability for all enrolled patients:

1. Visit date
2. Current pulse rate, blood pressure, weight
3. Current dose/frequency of Namuscla prescribed by the treating physician.

4. Any changes since the previous record for all data points captured at baseline or any new events since enrolment.

Follow-up phone calls (at Months 6, 18, and 30):

Site staff will make a telephonic follow-up at approximately 6, 18, and 30 months after enrolment. Following information will be recorded, as available:

1. Date of phone call
2. Current dosage of Namuscla
3. Any changes in frequency, treatment interruptions of Namuscla
4. Overall wellbeing, status of any ongoing AEs, changes in medical history events and new AEs
5. Start and stop of any new concomitant medications and reason to take concomitant medications
6. Any change in myotonia symptoms (better/ worse/ no change).

Study discontinuation

Following data will be recorded, where available, for all enrolled patients at the time of discontinuing the study:

1. Date of discontinuation
2. Reason for discontinuation

Outcome Variables

Primary:

1. Proportion of patients with treatment-emergent AEs ([TEAEs], including SAEs) from study enrolment to 6, 12, 24 and 36 months on Namuscla
2. Proportion of patients requiring dose reduction or treatment discontinuation due to AEs (including SAEs).

Secondary:

Safety:

1. Proportion of patients with AEs /SAEs/ Adverse Event of Special Interest (AESI) from study enrolment to 6, 12, 24, and 36 months

2. Proportion of AEs in patients with abnormal hepatic function (abnormal hepatic function defined as: elevated Liver function test grade-3 and above as per NCI CTCAE v. 5.0 (specifically Total Bilirubin and AST/ALT) or Child-Pugh categories B and C at baseline) during the study
3. Number of AEs in patients with abnormal renal function during the study (abnormal renal function defined as: decreased eGFR, grade-3 and above as per NCI CTCAE v. 5.0 i.e eGFR <30 ml/min/1.73 m^2) during the study
4. Number of AEs in geriatric patients (patients aged 65 years and above)
5. Number of patients presenting with cardiac arrhythmia, severe cutaneous adverse reactions (SCAR), Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS), or seizures

Efficacy:

6. Change in VAS scores for pain, stiffness and fatigue from baseline
7. Clinical myotonia evaluation – change over time
   - Relaxation of hand grip after sustained closure – (Mean time in seconds)
   - Eye opening after eye closure – (Mean time in seconds)
8. Change in Individualized Neuromuscular Quality of Life (INQoL) Questionnaire scores from baseline
9. Change in Myotonia Behaviour Scale (MBS) scores from baseline.

Data Management and Quality Assurance:

All study data will be entered directly into the electronic data capture (EDC) system. Participating sites will only have access to those data entered by their own institution. All sites will be fully trained on using the online data capture system, including electronic Case Report Form (eCRF) completion guidelines and help files. The eCRFs will include programmable edits to deliver immediate feedback if data are missing, out of range, illogical or potentially erroneous.

Safety:

All AEs, SAEs, and both serious and non-serious AESI will be recorded in the eCRF, from the patient's first dose of Namuscla (from date of enrolment) until End-of-Study (EOS). End-of-study is defined as

permanent discontinuation of Namuscla treatment or completion of 3 years on treatment after enrolment.

Statistical Considerations:

This is a non-interventional, observational study. The study is not powered for efficacy or safety testing. Data will be presented by myotonic disorder, by age group (18 - 64 years, inclusive, and ≥65 years), other subgroups of interest, and by Namuscla use (newly exposed and patients already on Namuscla).

Summary statistics will be provided for all collected parameters, including mean, standard deviation (SD), minimum, maximum, and 95% confidence interval (CI) of mean for continuous variables. The categorical variables will be presented with frequency and percentages.

The details of statistical analyses and the methods will be given in the Statistical Analysis Plan (SAP).

Milestones:

Milestone	**Planned Date**
Start of data collection	July 2020
End of data collection	July 2025
Study progress report	To be included in Periodic Benefit-Risk Evaluation Report (PBRER) (PBRER for the period 18 Jun 20 to 17 Dec 20)
Interim Analysis 1	July 2021
Interim Analysis 2	July 2023
Final Study Report	December 2025

5.0 AMENDMENTS AND UPDATES

The original protocol (Version 1.0) dated 04 August 2017 was submitted as an Annexure (Annex 3) to Risk Management Plan (RMP) version 0.2 of Mexiletine.

Revisions to the protocol - Version 1.1 – 1.6 include:

- Changes based on the comments received from PRAC,
- To align with the updates to RMP
- Administrative changes.

Current version of the Protocol: Version 1.6.

Version History:

Version Number	Version Date	Key Amendment or Update to the Previous Version	Section of the Protocol Updated
Version 1.0 (Original Protocol)	04 August 2017	NA	NA
Version 1.1	September 2018	• Updated text to include the use of myotonia reference centres instead of Registries to enrol patients. • Efficacy evaluations modified.	Relevant sections of the protocol synopsis.
Version 1.2	October 2018	• Objectives and endpoints updated to align with the updates to RMP • Administrative changes	Relevant sections of the protocol synopsis.
Version 1.3	October 2018	• Objectives and endpoints updated to align with the updates to RMP • Administrative changes	Relevant sections of the protocol synopsis.
Version 1.4	11 February 2019	• Study title updated (mention of registries deleted from title) • Objectives and endpoints updated • Study design updated to reflect change in setting from registry to reference centres and as per PASS protocol template • Changes applied to all relevant sections	Relevant sections of the Abstract and main body of the protocol.
Version 1.5	19 July 2019	The following updates were made:	Relevant sections of the Abstract

Version Number	Version Date	Key Amendment or Update to the Previous Version	Section of the Protocol Updated
		• Study Title updated to ensure the study population is consistent with the approved indication (specific for adults with NDM) • Objectives updated • Background and Rationale updated • Study design updated (reworded) to align with the observational design • Outcome variables listed • Added data management details • Sample size justification added and Statistical section updated • Assessment methods described • Milestones updated • AESI .listed Administrative changes: • Contact details of QPPV and Protocol author updated.	and the main body of the Protocol
Version 1.6	22 November 2019	The following changes were made: • Objectives - objectives related to pregnant and nursing mothers, and co-administration of Namuscla with CYP1A2 substrates deleted. • A statement to the effect that inclusion of additional sites in other EU countries will be considered has been added. • Exclusion criteria - In line with the SmPC, patients receiving medicinal products with narrow therapeutic index excluded. • Variables corresponding to deleted objectives - have been removed. • The period of PBRER that will include study progress report updated. • Version history updated	Relevant sections of the Abstract and the main body of the Protocol.

Version Number	Version Date	Key Amendment or Update to the Previous Version	Section of the Protocol Updated
		• Limitations- Statements in Limitations Section reworded. • AE/SAE reporting timelines and contact details updated • Minor grammar and formatting changes.	

6.0 STUDY MILESTONES

Milestone	Planned Date	Comments, if any
Start of data collection	July 2020	
End of data collection	July 2025	
Study progress report	To be included in Periodic Benefit-Risk Evaluation Report (PBRER) (PBRER for the period of 18 Jun 20 to 17 Dec 20)	
Interim Analysis 1	July 2021	
Interim Analysis 2	July 2023	
Final Study Report	December 2025	

7.0 RATIONALE AND BACKGROUND

Myotonic disorders are hereditary, rare-to-ultra-rare, heterogeneous diseases characterised by the malfunctioning of skeletal sodium or chloride ion channels. All these disorders share a common clinical symptom - myotonia (Pusch, 2002; Trip *et al.*, 2006; Hahn and Salajegheh, 2016), which is clinically defined as the inability to relax muscles after voluntary contraction or after percussion. Symptomatic myotonia is present in almost all patients with non-dystrophic myotonia (NDM) and is usually the first symptom, with the age of onset typically being in the first decade (Trip *et al.*, 2006; Matthews *et al.*, 2010; Trivedi *et al.*, 2013). Patients with NDM suffer lifelong from stiffness and locked muscles, which can be accompanied by pain and transient muscle weakness. It can affect all lumbar sites with patients individually reporting about problems in the hands, legs, and facial muscles, including tongue (Matthews et al, 2010). In NDM, myotonia substantially affects the patient's quality of life and ability to do routine activities, which could, subsequently lead to unemployment (Trip *et al.*, 2006; Trivedi *et al.*, 2013; Sansone, 2016).

The prevalence of myotonic disorders as a group ranges from 19.8 to 25.1 per 100,000 person-years with approximately 2 in 10,000 people being affected in the EU. The global prevalence of NDM is estimated to be 1/100,000 (Deenen *et al.*, 2015). The most frequent form of NDM is the autosomal recessive congenital (Becker) myotonia, the prevalence of which has been reported to be 1/25,000 (Lehman-horn, Jurkat-Rott and Rudel, 2008) . All other forms are more rare with the estimated prevalence data ranging from 1/400,000 for autosomal dominant congenital (Thomsen) myotonia (Lehman-horn, Jurkat-Rott and Rudel, 2008) and approximately 1/200,000 for some forms of dominant dyskalaemic episodic paralyses (limited data available) (Charles *et al.*, 2013).

7.1 Non-dystrophic Myotonia

Non-dystrophic myotonias - also often described as channelopathies - are caused by mutations in the skeletal muscle chloride and sodium ion channel genes causing hyperexcitability of muscle fibres (Matthews et al, 2010).

Chloride ion channelopathies can be autosomal dominant (Thomsen myotonia) or autosomal recessive (Becker myotonia). They arise from missense or nonsense mutations or deletions in the CLCN1 gene on chromosome 7q35 encoding the major muscle chloride channel, ClC-1 which leads to faulty or missing chloride ion channels in the fibre membrane. The activity of the chloride ion channels at the resting potential of the muscle fibres is therefore impaired, decreasing muscular chloride conductance (Lehman-horn, Jurkat-Rott and Rudel, 2008; Matthews *et al.*, 2010). Normal chloride conductance is critical to maintain muscle activity during potassium ion leakage, which occurs during repeated muscle contractions. If the resting potential is decreased in case of impaired chloride ion channel function the excitability of the membrane is increased, triggering the opening of sodium channels, further leading to myotonia (Heatwole, Statland and Logigian, 2013).

Sodium ion channelopathies are a group of autosomal dominantly inherited myotonic disorders including paramyotonia congenita, potassium aggravated myotonia with myotonia fluctuans, myotonia permaneans and acetazolamide-responsive myotonia and hyperkalemic periodic paralysis (Lehmann-Horn and Jurkat-Rott, 1999). They arise from point mutations in the SCN4A gene on chromosome 17q23 that encodes the sodium channel Nav1.4 of skeletal muscles, which lead to altered sodium ion channel gating. Impaired gating causes slower or incomplete inactivation of activation potentials and results in repetitive firing and hyperexcitable muscle fibres, thereby triggering myotonia (Lehmann-Horn, Jurkat-Rott and Rüdel, 2008; Matthews *et al.*, 2010; Heatwole, Statland and Logigian, 2013).

7.2 About Namuscla (Mexiletine)

Active ingredient of Namuscla is mexiletine.

Namuscla received approval for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders by the European Commission on 18 December 2018.

Mexiletine blocks sodium channels with a stronger potency in situations of excessive burst of action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block), as occurring in diseased tissues, rather than on physiological excitability (resting or tonic block). Mexiletine is, therefore, mostly active on muscle fibres subject to repeated discharges (such

as skeletal muscles). It improves myotonic symptoms by decreasing muscle stiffness through reduction in delay of muscle relaxation.

Namuscla is available as oral capsules; each capsule contains 166.62 mg of mexiletine corresponding to 200 mg of mexiletine hydrochloride. The recommended starting dose of mexiletine 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, the 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 dose should not exceed 500 mg/day. Before starting mexiletine treatment, detailed and careful cardiac evaluation should be carried out. Throughout the treatment with mexiletine, cardiac monitoring needs to be continued and adapted as a function of the cardiac condition of the patient. For initiation of Namuscla, please see Namuscla Summary of Product Characteristics (SmPC).

Scientific Rationale

Myotonia is a chronic symptom with no definitive cure currently and needs periodic evaluation.

To date, randomised studies conducted for mexiletine have assessed only short-term efficacy and safety with little supporting data for long-term use from observational research.

There is limited data on the long-term use of Namuscla in adult patients with NDM. .

This study will collect data on long-term safety of Namuscla in adult patients with non-dystrophic myotonic disorders in a real-world setting. The primary objective of this PASS is to collect long-term safety information during routine clinical use of Namuscla.

8.0 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

To describe the long-term safety and tolerability of Namuscla in the management of myotonia symptoms in adult patients with NDM in a real-world setting.

This study is being conducted as part of the agreed European Risk Management Plan (RMP).

8.2 Primary Objective

To describe the long-term safety and tolerability of Namuscla for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

8.3 Secondary Objectives

1. To evaluate the safety of Namuscla in NDM patients
2. To evaluate the safety of Namuscla in treatment of myotonia in special populations:
   - patients with hepatic impairment
   - patients with severe renal impairment
   - elderly patients (aged 65 years and above),
   - patients with seizure disorders,
3. To assess the occurrence of severe cutaneous adverse reactions (SCARS), cardiac arrhythmia, and seizures on treatment with Namuscla
4. To evaluate the clinical effectiveness of Namuscla in NDM patients in terms of clinical evaluation, and based on patient-reported outcomes (PRO)

9.0 RESEARCH METHODS

9.1 Study Design

This is a non-interventional, prospective, observational, multicentre study.

Patients with NDM who have been prescribed Namuscla by the treating physician will be enrolled in this study.

Patients will be enrolled over an approximate 2-year enrolment period and will be followed-up on-treatment for up to 3 years. The total study duration including enrolment period and data collection would be 5 years. For eligible patients who provide informed consent, data elements will be extracted from the information routinely recorded in medical records.

For all enrolled patients, the baseline will be the latest data available at the enrolment visit. Follow-up data will be collected annually (every 12 months) for all visits occurring as per routine care.

No study visits or examinations, laboratory tests or procedures are mandated as part of this study. Data collection via phone calls every 3 months will serve as a source to capture safety data.

Namuscla will be prescribed as per the approved label (Namuscla SmPC) at the clinical discretion of the treating physician. As this is an observational study, patients will receive care based on standard treatment practices for myotonic disorders per the judgement of the treating physician. Patients who are already on Namuscla treatment will continue to receive Namuscla at the prescribed dose. The dosage and duration of previous Namuscla use will be recorded for these patients.

For patients who are already on Namuscla, cumulative data (data related to previous exposure as well as current data) will be collected for the AEs that occurred on treatment with Namuscla.

No drug will be supplied for this study; patients will receive medication as per local practice. All evaluations and investigations during the study will be as per the clinical discretion of the treating physician.

Patients will be given paper diaries (Appendix I) to capture the following: daily Namuscla dose, changes in Namuscla dose/frequency (if any), any new symptoms/ aggravation of symptoms, AEs

(if any), and concomitant medications (along with dose and frequency. Diary data will be collected at routine clinic visits.

9.2 Setting

The study will be conducted at specialized centres for the treatment of myotonic disorders that see at least 20-30 patients annually ("reference centres"). By July 2020 Namuscla will be available in Germany, France and UK, hence study will be initiated in all countries with plan to have 6 sites initiated till December 2020.

It is currently estimated that approximately 40-50% of patients which are seen annually at reference centre will receive Namuscla. With 50 % willing to participate in this study, it is currently estimated that 24 to 45 patients are enrolled first year with 6 sites initiated. The enrolment period is a total of 2 years, additional sites will be assessed and opened after 9 months if the actual enrolment is less than 80% of the expected target during that period.

Depending on the enrolment and marketing status (availability) of Namuscla in other countries in the EU, inclusion of additional sites in other countries will be considered.

9.3 Study Population

The study population will comprise patients who are diagnosed with non-dystrophic myotonic disorders and considered suitable candidates for the treatment by Namuscla by the investigators according to the approved SmPC and who meet the eligibility criteria.

This includes:

1. Patients newly initiated on Namuscla for the treatment of NDM (newly exposed)
2. Patients already on Namuscla/ mexiletine at enrolment - For patients receiving mexiletine other than Namuscla, only those who switch to Namuscla will be included in the study.

Patients already being treated with Namuscla/ mexiletine at the time of enrolment will be considered for enrolment provided they meet the eligibility criteria.

9.3.1 Inclusion Criteria

1. Adult, male or female patients with NDM planned to be started on Namuscla according to the approved SmPC
2. Patients already receiving Namuscla/mexiletine for the treatment of NDM disorders; (for patients on mexiletine other than Namuscla, only those who switch to Namuscla will be enrolled)
3. Patients who understand and are willing to provide the informed consent.

9.3.2 Exclusion Criteria

1. Patients who are enrolled or participating in any other clinical trial for an investigational product.
2. Hypersensitivity to mexiletine, or to any of the excipients of Namuscla, or hypersensitivity to any local anaesthetic
3. Ventricular tachyarrhythmia
4. Atrial tachyarrhythmia, fibrillation or flutter
5. Complete heart block (ie, third-degree atrioventricular block) or any heart block susceptible to evolve to complete heart block (first-degree atrioventricular block with markedly prolonged PR interval (≥ 240 ms) and/or wide QRS complex (≥ 120 ms), second-degree atrioventricular block, bundle branch block, bifascicular and trifascicular block),
6. Myocardial infarction (acute or past), or abnormal Q-waves
7. Symptomatic coronary artery disease
8. Heart failure with reduced ejection fraction <50%
9. Sinus node dysfunction (including sinus rate < 50 bpm)
10. Patients receiving drugs that can induce torsades de pointes
11. Patients receiving medicinal products with narrow therapeutic index (ie, theophylline, tizanidine, digoxin, lithium, phenytoin or warfarin).
12. Patients who are pregnant or lactating.

Patients meeting all the above inclusion criteria and none of the above exclusion criteria will be eligible for enrolment in the study.

9.3.3 Study Enrolment

Patients who present to the clinic for routine clinic visits will be invited to participate in this study. Informed consent for this study will be obtained by the treating physician prior to enrolment of patients. Data of all patients who provide consent will be assessed for eligibility according to the defined selection criteria during the enrolment period, and those who meet the eligibility criteria will be enrolled.

9.3.4 Patient Withdrawal

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study follow-up period, any known reason for withdrawal should be documented in the database. All the information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

9.4 Exposure Definition and Measures

This is an observational study of real-world treatment practices in NDM patients. This protocol does not recommend the use of any specific treatments. No study medication is provided as part of study participation.

Patients will be enrolled after the patient agrees to participate and signs the informed consent form. All exposure to Namuscla (including any exposure prior to enrolment) will be collected.

As an observational study to understand safety in patients treated in the post-marketing setting, no restrictions on concomitant treatments are associated with the study. All concomitant treatments (and any subsequent treatments for NDM during follow-up) will be carefully recorded in order to evaluate their potential influence on the outcomes of interest.

9.5 Data Collection

As it is a non-interventional study, the frequency of visits and the actual assessments performed will be in line with the routine clinical practice and any local treatment protocols. No study visits or examinations, laboratory tests or procedures are mandated by the study.

For eligible patients who provide informed consent, data elements will be extracted from the information routinely recorded in medical records and transcribed in to the electronic Case Report Forms (eCRFs). Follow-up data for all routine care visits will be collected annually (every 12 months). Additional data collection via phone calls every 3 months would serve as a source to capture safety data.

9.5.1 Schedule of Recommended Recording of Essential Data

Essential data for the study are presented in the Schedule of Recommended Recording Essential Data provided in **Table 1**.

Table 1 Schedule for Data Collection

Data Elements for capture	Baseline Data (Enrolment)	Follow-up Telephone Calls at 6, 18, and 30 months	Follow-up Data collection at 12, 24 and 36 months from enrolment.
Patient eligibility	X	-	-
Informed consent	X	-	-
Visit Date/ Date of Telephonic follow-up	X	X	X
Demographics (gender, ethnicity, age, smoking status, occupation status[#])	X	X[#]	X[#]
Myotonia history: Type of myotonic disorder (diagnosis), age of symptom onset, family history of myotonic disorders	X		
Signs and symptoms of myotonia	X		X[a]
History of renal impairment (clinical/ laboratory investigations, if any)	X		X[a]
History of hepatic impairment (clinical/ laboratory investigations)	X		X[a]
Cardiac abnormalities (eg. arrhythmia, heart failure, cardiovascular disease)	X		X[a]
Seizure disorders	X		X[a]

Data Elements for capture	Baseline Data (Enrolment)	Follow-up Telephone Calls at 6, 18, and 30 months	Follow-up Data collection at 12, 24 and 36 months from enrolment.
Autoimmune disease	X		
Skin diseases and cutaneous drug reactions	X		X[a]
Obstetric history	X		
Medical history associated with impaired muscle function (fractures, respiratory disorders, swallowing difficulties / history of aspirations/ aspirational pneumonia, myotonia of mastication muscles)	X		X[a]
Surgery/hospitalisation due to muscle condition	X		
Previous antimyotonia treatment other than Namuscla/ mexiletine (All patients)	X		
Previous Namuscla/ mexiletine use and duration (prior exposure patients)	X[d]		
Any previous AE due to Namuscla/ mexiletine use	X[d]		
Concurrent (ongoing) conditions	X	X	X
Concomitant medications	X	X	X
Vitals and anthropometric measurements (Pulse rate, blood pressure, weight)	X		X
Baseline laboratory investigations[b] (haematology, biochemistry and urinalysis)	X[b]		X[b]
ECG	X		X
24-hour Holter monitoring, or other cardiac investigations - only if required (at the discretion of treating physician)[b]	X[b]	-	X[b]
Change in existing treatment of myotonia (drug or dosage) or treatment discontinuation or dosage modification, if any along with reasons for change	-	X	X
Clinical myotonia of hand and eye	X		X[c]
VAS (Stiffness, Pain, and Fatigue) score	X		X[c]
MBS score	X		X[c]
INQoL	X		X[c]
Details of other antimyotonia treatment (if any) treatment		X	X

Data Elements for capture	Baseline Data (Enrolment)	Follow-up Telephone Calls at 6, 18, and 30 months	Follow-up Data collection at 12, 24 and 36 months from enrolment.
Details of all AEs (serious and non-serious), DAEs	X[d]	X [a]	X [a]

[#] Any change in occupation/working status due to myotonia will be recorded.

[a] Measurements will be captured as changes since previous visit/phone call (if available)
[b] Investigations will be performed as per standard of care and if considered necessary by the treating physician.
[c] Will be captured at routine clinic visits – as available in the medical records
[d] These details will be captured at baseline for patients with prior exposure to Namuscla/mexiletine)
AE = Adverse event; BMI = Body mass index; DAE= Discontinuation due to adverse event; ECG= Electrocardiogram; EOS = End-of-study; INQoL= Individualised Neuromuscular Quality of Life; MBS= Myotonia behaviour scale; VAS = Visual Analogue Scale.

9.5.2 Baseline /Enrolment Data

In this prospective, observational study, baseline for all patients (patients newly initiated on Namuscla and those already on Namuscla) will be the enrolment visit. Data for the following parameters will be collected as per availability from all enrolled patients:

1. Visit date
2. Patient demographics (gender, ethnicity, age, smoking status, occupation status)
3. Myotonia history: Type of myotonic disorder (diagnosis), age of symptom onset, family history of myotonic disorders.
4. Signs and symptoms of myotonia as documented in medical history

<u>Relevant medical history at baseline</u>

5. History of hepatic impairment – (Hepatic impairment is defined as elevated Liver function test grade-3 and above as per NCI CTCAE v. 5.0; specifically Total Bilirubin and AST/ALT or Child-Pugh categories B and C at baseline – if available in medical records)
6. History of renal impairment – (Renal impairment is defined as decreased eGFR, grade-3 and above as per NCI CTCAE v. 5.0 ie, eGFR <30 ml/min/1.73 m^2 – if available in medical records)

7. Cardiac abnormalities (eg, arrhythmia, heart failure, cardiovascular disease) (along with any relevant investigations, if available)
8. History of seizure disorders
9. Autoimmune diseases
10. Skin diseases and cutaneous drug reactions
11. Medical history associated with impaired muscle function: fractures, respiratory disorders, swallowing difficulties / history of aspirations/ aspirational pneumonia, myotonia of mastication muscles
12. Obstetric history
13. Surgery/ hospitalisation due to muscle condition
14. Previous anti-myotonia treatment other than Namuscla/ mexiletine (including any experimental therapies).
15. Concomitant medications in use
16. Baseline vitals and anthropometric measurements (pulse rate, blood pressure, weight) (latest documented value)
17. Latest documented 12-lead electrocardiogram (ECG), cardiac evaluation including 2-D echocardiogram, Holter monitoring if available as per routine standard of care
18. Laboratory investigations (haematology, biochemistry and urinalysis) as available

<u>Efficacy variables to be assessed at baseline</u>

19. Clinical myotonia evaluation - hand and eyes (Time in seconds to make a tight fist for hold for 5 seconds, then rapidly open it again; Time to open the eyes after squeezing the eyes closed for 5 seconds, the rapidly open them)
20. Baseline Visual Analog Scale (VAS) - Patient self-assessment of myotonia symptoms: pain, stiffness, and fatigue on VAS (VAS, 0-100)
21. Baseline Myotonia Behaviour Scale (MBS) score
22. Individualised Neuromuscular Quality of Life (INQoL)
23. Dose/frequency of Namuscla prescribed by the treating physician

For patients already on Namuscla:

For patients already on Namuscla, in addition to all the above data elements, the following will be captured:

24. Dosage/ duration of previous Namuscla/ mexiletine use
25. Any previous adverse events (AEs) associated with the use of Namuscla/mexiletine.

9.5.3 On-Treatment Follow-up (12, 24, 36 months from enrolment)

Follow-up data collection will be at 12, 24, 36 months from enrolment) – for newly exposed patients as well as patients already on Namuscla.

The following data will be collected as per availability for all enrolled patients:

1. Visit date
2. Current pulse rate, blood pressure (BP), weight
3. Current dose/frequency of Namuscla prescribed by the treating physician.
4. Any modification in Namuscla dose/ frequency
5. Any changes since previous record for all data points captured at baseline or new events since enrolment.

9.5.4 Telephone Calls for Data Collection (at 6, 18 And 30 months)

Site staff will make a telephonic follow-up at approximately 6, 18, and 30 months after enrolment. Following information will be recorded, as available:

1. Date of phone call
2. Current dosage of Namuscla
3. Any changes in frequency, treatment interruptions of Namuscla
4. Overall wellbeing, status of any ongoing AEs, changes in medical history events and new AEs
5. Start and stop of any new concomitant medications and reason to take concomitant medications
6. Any change in myotonia symptoms (better/ worse/ no change).

9.5.5 Study Discontinuation

Following data will be recorded, where available, for all enrolled patients at the time of discontinuing the study:

1. Date of discontinuation
2. Reason for discontinuation

9.6 Outcome Variables

Assessments will be completed during visits undertaken by the subject as per routine care. The frequency of visits and actual assessments undertaken at each visit will be determined by clinical practice. In cases where assessments are undertaken by investigator site staff the following will be captured in the database during the study:

9.6.1 Primary Variables

1. Proportion of patients with treatment-emergent AEs ([TEAEs], including SAEs) from study enrolment to 6, 12, 24 and 36 months on Namuscla
2. Proportion of patients requiring dose reduction or treatment discontinuation due to AEs (including SAEs).

9.6.2 Secondary Variables

Safety

1. .Proportion of patients with AEs /SAEs/ Adverse Event of Special Interest (AESI) from study enrolment to 6, 12, 24 and 36 months)
2. Proportion of AEs in patients with abnormal hepatic function (abnormal hepatic function defined as: elevated Liver function test grade-3 and above as per NCI CTCAE v. 5.0 (specifically Total Bilirubin and AST/ALT) or Child-Pugh categories B and C at baseline) during the study
3. Proportion of AEs in patients with abnormal renal function during the study (abnormal renal function defined as: decreased eGFR, grade-3 and above as per NCI CTCAE v. 5.0 ie, eGFR <30 ml/min/1.73 m^2) during the study
4. Number of AEs in geriatric patients (patients aged 65 years and above)

5. Number of patients presenting with cardiac arrhythmia, severe cutaneous adverse reactions (SCAR), Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS), or seizures.

Efficacy

6. Change in VAS scores for pain, stiffness and fatigue from baseline
7. Clinical myotonia evaluation – change over time
   - Relaxation of hand grip after sustained closure – (Mean time in seconds)
   - Eye opening after eye closure – (Mean time in seconds)
8. Change in Individualized Neuromuscular Quality of Life Questionnaire (INQoL) scale scores from baseline
9. Change in Myotonia Behaviour Scale (MBS) scores from baseline.

9.6.3 Data Interpretation of Instruments/Scales

Table 2 Summary of Scales Used in the Study

Parameter	Scale	Administration Method	Possible Scores
Muscle stiffness Pain Fatigue	10cm VAS (0 – 100 points)	Self	VAS will be measured with a straight, horizontal, 10 cm line having the endpoints 'No stiffness at all' and 'Stiffness as worst possible'. The subject responses will be scored on the line to the nearest millimetre (a 100-point scale).
Myotonia	Eye closure and opening	Investigator	The time to open the eye after squeezing the eyes closed for 5 seconds, then rapidly open them - determined in seconds using a stopwatch
Myotonia	Hand grip	Investigator	The time taken to make a tight fist and hold for 5 seconds, then rapidly open - determined using a stopwatch (in seconds)
Quality of life	INQoL	Investigator	The final score for each of 10 sections and total INQoL score will be presented as a percentage of the maximum detrimental impact; a higher percentage indicates greater symptom impact or worse quality of life
Myotonia	MBS	Self	The patient chooses one out of six framed sentences, which most closely describe the impact of the stiffness on everyday life

INQoL, Individualized Neuromuscular Quality of Life Questionnaire; MBS Myotonia Behaviour Scale; VAS: visual analogue scale

9.7 Data Sources

Data elements will be collected from the information routinely recorded in the medical record. No study visits or examinations, laboratory tests or procedures are mandated by the study.

Data elements will be extracted from the information routinely recorded in the medical record and transcribed in to the electronic Case Report Forms (eCRFs).

Data will be collected at the baseline visit and will be updated at each visit. Data will be captured in the eCRFs, through physician assessment (Clinical assessments – handgrip, eyelid myotonia), patient self-assessment tools (VAS and MBS scales), INQoL questionnaire, and patient diaries. Prescriptions as per medical records and patient diary data will be used to calculate adherence and

persistence to treatment. Adverse events will be collected from medical records, information collected via phone calls, and patient diary.

Targeted Questionnaire for Cardiac Arrhythmia:

In case of reported cardiac arrhythmia, this structured questionnaire will be administered to capture information regarding the event.

Note: Any abnormality on resting a resting ECG will be noted.

- Mild ECG abnormalities: PR interval ≥200 ms and QRS duration ≥100 ms
- Severe ECG abnormalities: PR interval ≥240 ms, QRS duration ≥120 ms, second or third degree AV block and a rhythm other than sinus.

On 24-hour Holter monitoring, the following variables will be considered: average heart rate, longest RR interval, any degree of AV block, number of supraventricular and ventricular ectopic beats and runs of supraventricular or ventricular tachycardia.

9.8 Sample Size

Approximately 50 patients will be enrolled in the study.

The main objective of the study is to evaluate the long-term safety. This will be evaluated in terms of TEAEs.

The sample size was calculated based on the following formula:

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2 p(1-p)}{d^2}$$

Here, α = level of significance (considered as 5%).

Z = standard normal variate.

p = expected proportion of AEs in population (based on previous studies)

d = absolute error allowed

The absolute error was considered as 5%.

The expected proportion of AEs in the population (p) was considered as 3% on the basis of six previously published studies (Statland *et al.*, 2012; Logigian *et al.*, 2010; Kwiecinski *et al.*, 1992; Suetterlin *et al.*, 2015; Lo Monaco *et al.*, 2015; Contardi *et al.*, 2012). The percentage of subjects who discontinued study or treatment due to an AE was 3%.

Based on this, the sample size for this study was determined to be forty-five. Assuming a dropout rate of 10%, the plan is to enrol 50 subjects.

Table 3 lists the precision allowed by this sample size for the occurrence of events, at different rates.

Table 3 The Precision for Occurrence of Events Based on the Sample Size

N	Event rate	95% lower limit	95% upper limit	Width
50	10.0%	3.3%	21.8%	18.5%
50	20.0%	10.0%	33.7%	23.7%
50	30.0%	17.9%	44.6%	26.7%
50	40.0%	26.4%	54.8%	28.4%
50	50.0%	35.5%	64.5%	28.9%

9.9 Data Management

Data will be generated at clinical sites in defined source documents which will be maintained by individual sites throughout the study period. Data will be transcribed from the source documents to the eCRFs by the respective site coordinators by using their login credentials as per the eCRF completion guidelines. The Investigator shall maintain all source documents, such as laboratory reports, ECGs, consultation reports, and complete medical history and physical examination, etc. at the site as per the investigator site file. All data captured in the eCRF will be electronically signed by respective investigators using their log-in credentials. Source data will be identified using unique subject IDs. All data will be routinely backed up and can be recovered whenever required as per IT policy. All measures will be taken to ensure data integrity and confidentiality is maintained.

The eCRF will be design as per the database design specification considering all data collections requirements of the protocol **(As per the section 9.3 of the protocol).** Through user acceptance testing will be done on the eCRF before realising the database in production. All data transections made in the eCRF will be audit trailed in the database. All users will undergo proper training on the eCRF before providing the study specific the eCRF access.

Data cleaning will be performed using automated system checks as well as manual checks, system checks will be implemented for blank fields, conditional checks, logical checks and range checks. Auto queries will be flagged by the system upon deviating from the mentioned checks. Manual checks will be executed by the respective data manager at scheduled intervals, and queries will be generated. It will be ensured that the data of all applicable visits are entered and cleaned, there are no open queries, medical coding is completed and reviewed for all reported terms, all reconciliations are done, and observations are addressed, and comments from all reviewers are appropriately addressed, audit trail reports are derived before making database lock. More specific details on CDM process will be provided in study specific Data Management Plan (DMP).

Medical Coding of all captured AEs, medical history and prior/concomitant medications will be done using the latest dictionary versions of MedDRA and WHO Drug Global available during the database set-up.

Diary Cards

Diary cards for the study will be created in the form of booklets. Patients will be instructed to enter their data. **(As per the Table 1, Schedule of data collection).** The study staff will provide patient diary with precise instructions on how to use it and advise patients to bring the completed diary at each visit.

The patients have to present their diaries to the investigator at every routine clinic visit. The investigator will review the diary at every visit, furthermore, the investigator has to check the usage of concomitant medication as entered in the diary. After the review of the entries for plausibility

and completeness, the investigator will collect the first (original) pages of the visit sets for data management.

Diary data will be entered into an eCRF. The investigator is responsible for the correct identification of the collected pages, with patient number, date and initials (no names, to safeguard data protection). Correct and complete data entry into the diaries by the patients will allow calculation of adherence and persistence to treatment.

Quality Assurance

Auditing procedures developed by the 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.

9.10 Data Analysis

This is a non-interventional, observational study. The study is not powered for efficacy or safety testing. Data will be presented by myotonic disorder, by age group (18 to 64 years, inclusive, and ≥65 years), other subgroups of interest, and by Namuscla use (newly exposed and prior mexiletine exposure).

Summary statistics will be provided for all collected parameters, including mean, standard deviation (SD), minimum, maximum, and 95% confidence interval (CI) of the mean for continuous variables. The categorical variables will be presented with frequency and percentages.

Adverse events with the start date and time before initiating on the study medication will be considered as non-treatment emergent events. Such events will only be displayed in the individual subject data listing. All summaries of adverse events will use only treatment-emergent adverse event 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 (PT) and System Organ Class (SOC)
- Treatment-related TEAEs by PT and SOC
- TEAEs by PT and SOC, maximum severity and relationship
- Serious TEAEs by PT and SOC
- TEAEs leading to discontinuation of study drug by PT and SOC

Also, listing of all adverse events will be provided. The listing will include AE number, description, PT, SOC, start and end date, seriousness, frequency of occurrence, severity, action taken regarding study treatment, outcome, relationship to study treatment.

Similar representation of data will be given for interim analyses.

The details of statistical analyses and the methods will be included in the statistical analysis plan (SAP).

9.11 Quality Control

Lupin maintains a robust Quality Management System that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, reporting of results, documentation of actions, and escalation of issues identified during the review of quality metrics, incidents, audits and inspections. The conduct of the study may be audited either by the Sponsor or the Competent Authorities where the study is performed. Auditors should have access to any study records (CRFs, site files, trial master file etc.) and sources patients' medical documentation. Investigators accept the possibility to be audited and agree to dedicate the necessary time to the proper conduct of the audit at their sites. It will enable to check that the study is being run in conformity to the protocol and to current rules and regulations.

9.12 Limitations of the Research Methods

Data for this non-interventional study protocol will be collected from adult patients with NDM who have been prescribed Namuscla for myotonia as a part of routine clinic practice. As with all observational studies, selection bias could be a concern. In order to minimise this source of bias,

inclusion and exclusion criteria have been applied and it is expected that most, if not all, patients indicated for treatment according to the product labelling (Namuscla SmPC) will be eligible for enrolment in the study.

In addition, the sites will be instructed to invite consecutive eligible patients initially being prescribed who are planned to start or have already started treatment with Namuscla as part of routine clinical care. Sites will be expected to complete a screening log which will collect limited amount of data (eg, age range, disease type, reason for not participating) for non-enrolled patients newly prescribed Namuscla in order to understand through descriptive analysis the representativeness of the enrolled population. The potential for confounding by previous exposure will be inherently limited by the review and recording of the data available regarding medical history, and previous/concomitant medications.

Due to differences in clinical practices and being a non-interventional study, lack of control group will be a limitation of the study. The outcomes of the study will be discussed in context of available safety data of MYOMEX study as the latter represents the only source of appropriate patient population as per current Namuscla label.

The ability to meaningfully assess the subgroups of interest could be limited by the actual use in routine clinical care.

Owing to differing clinical practice between countries who will recruit subjects into the study, the study protocol is flexible to allow for differing assessments conducted at each visit. It is anticipated that for some subjects there will be fewer data points than others.

10.0 PROTECTION OF HUMAN SUBJECTS

10.1 Ethical Conduct of the Study

The study will follow the Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies (Rev 3), and the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH 2004) referring to the nature of non-interventional observational studies.

10.2 Patient Information and Consent

The informed consent process and Informed Consent Form (ICF) will be in compliance with the local regulatory requirements. The investigator will retain the original copy of signed ICF for each patient.

10.3 Patient Withdrawal

Patients may withdraw from the study at any time at their own request or may be withdrawn by the investigator at any time at the discretion of the investigator.

If the patient withdraws from the study, and withdraws consent for disclosure of future information, no further data will be collected for the patient. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4 Institutional Review Board/ Independent Ethics Committee

Consistent with local regulations and prior to enrolment of the patients at a given site, the study protocol will be submitted together with its associated documents to the responsible IEC for its review. Patient enrolment will not start at any site before the Sponsor has obtained written confirmation of a favourable opinion/approval from the relevant central or local IEC. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with the local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with the local regulations and requirements. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms,

and other relevant documents, if applicable, from their local IEC and provide documentation of approval to Sponsor/CRO.

11.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

Safety assessments will be recorded from the point at which the Informed Consent is signed. These will include recording and monitoring of all AEs (serious and non-serious) and special situations (including, reports of overdose, abuse, misuse, medication error or occupational exposure, lack of therapeutic efficacy, off-label, misuse, abuse and medication error), observed or reported, regardless of the causal relationship to Namuscla.

The obligations and responsibilities with regards to the collection, distribution, and onward reporting of AEs to the appropriate regulatory authorities will be carried out in accordance with the current European and local regulations and standard operating procedures for collection of adverse events for non-interventional studies.

All AEs (non-serious AEs, serious AEs), special situations must be reported to Lupin regardless of whether the event is determined by the investigator to be related to the drug under study. Specifically, 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.

Timelines of reporting AEs by the Investigator to Lupin:

- All serious AEs need to be reported by the investigators to Lupin within 24 hours of awareness at the EU-PV@lupin.com
- All other non-serious AEs should be entered in the eCRF as soon as investigator becomes aware of but no later than 7 calendar days of awareness

The timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports.

11.1 Adverse Events

An AE is any untoward or unfavourable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical examination or laboratory finding), symptom or

disease, temporarily associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

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

AEs will be documented as serious or non-serious related or unrelated and expected or unexpected; as applicable to the study drug.

An SAE is defined as an AE meeting one of the following outcomes:

- Death during the period of protocol-defined surveillance
- Life-threatening event (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.
- Inpatient hospitalisation or prolongation of existing hospitalisation during the period of protocol-defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Medical judgement should be exercised in deciding whether other situations should be considered serious. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered serious.

All AEs that do not meet any of the criteria for **serious AEs** should be regarded as **non-serious AEs**.

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an AE only if the frequency, intensity or the character of the condition worsens during the study period.

If relevant to the study, a clinical laboratory abnormality should be documented as an AE if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management, eg. change of dose, discontinuation of the drug, more frequent follow-up assessments, and further diagnostic investigation.
- The laboratory value lies out of the normal range and satisfies the CTCAE criteria for severity

If relevant to the study, any AE that results in hospitalisation or prolonged hospitalisation should be documented and reported as a serious AE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

The condition, hospitalisation, prolonged hospitalisation, or surgery is not reported as an AE in the following circumstances:

- Hospitalisation or prolonged hospitalisation for diagnostic or elective surgical procedures for a pre-existing condition. Surgery should **not** be reported as an AE if the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalisation or prolonged hospitalisation required to allow efficacy measurement for the study.
- Hospitalisation or prolonged hospitalisation for treatment of the target disease of the study, unless there is worsening of symptoms or increase in frequency of hospital admissions as judged by the clinical investigator.

11.2 Adverse Events of Special Interest

As per the secondary objective mentioned in Section 8.3 (point no. 4) of the protocol the following AESI will be assessed for their occurrence while on treatment with Namuscla.

11.2.1 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).

11.2.2 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.

11.2.3 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.

11.3 Special Situations

Special situations are considered as reports of overdose, abuse, misuse, medication error or occupational exposure, lack of therapeutic efficacy, off-label. Those should be collected in a manner similar to AEs. All pregnancy related reports will be collected, processed and reviewed as per the Safety Monitoring Plan (SMP).

11.4 Recording of Adverse Events

At each contact with the patient, the investigator will seek information on AEs by spontaneous reporting, specific questioning and, as appropriate, by examination. Information on all AEs (serious or non-serious) should be immediately recorded in the source document. All clearly related signs, symptoms and abnormal diagnostic procedures results should be recorded in the source document.

Additionally, targeted follow-up questionnaire (Appendix II) will be used for detailed investigation of the reported AEs related to cardiac arrhythmia to monitor and further characterise the risk (incidence and severity in a wider population) of cardiac arrhythmia especially in patients with no previous history of cardiac arrhythmia.

11.5 Evaluation of Adverse Events

Each AE is evaluated depending on the following categories by the investigator.

11.5.1 Definition of Severity of an Adverse Event

Wherever possible, all observed AEs will be graded using the CTCAE version 5.0. The severity of the AE shall be classified using the following grading (Semicolon (;) indicates "or").

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; 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, not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to an AE.

Record the maximum intensity for AE occurring frequently than once a day. If the intensity category changes over several days, then those changes should be recorded as a new AE with the onset date of the new intensity category.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 11.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE

11.5.2 Relationship to the Study Drug

The assessment of the relationship of an AE to the administration of the study drug is based on the presence or absence of a "reasonable possibility" that the study drug has caused the AE. An AE is "related" to the study medication if a causal relationship between the study drug 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.

The expression "reasonable causal relationship" is meant to convey that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline) based on relationship between the time of onset and drug administration, temporary withdrawal, not attributable to any other drug or condition, dechallenge and rechallenge information as available.

11.6 Notification of Adverse Events

All AEs will be reported to European Medicines Agency in line with Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2).

11.7 Single Reference Safety Document

The product label (Namuscla SmPC) will serve as the single reference safety document (SRSD) during the course of the study, which will be used by Lupin safety to assess any safety events reported to Lupin by the investigator.

The SRSD should be used by the investigator for prescribing purposes and guidance.

12.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Data generated from this study will be compiled in a final study report. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Research information will be published or presented in a way that it does not identify any individual patient.

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14.0 LIST OF APPENDICES

Appendix No	Description
Appendix I	Sample Paper Diary
Appendix II	Targeted follow up questionnaire for patients experiencing cardiac arrhythmia.