26 March 2026
EMADOC-1700519818-2457059
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Namuscla

International non-proprietary name: Mexiletine

Procedure No. EMA/X/0000258210

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
AESIs	Adverse Events of Special Interest
ANOVA	Analysis of Variance
AP	Action potential
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
$AUC_{0\text{-}tau}$	Area under the concentration time curve for one dosing interval at steady-state
AUC_{last}	Area under the curve from the time of dosing to the time of the last measurable (positive) concentration
BCS	Biopharmaceutical classification system
BID	Twice daily
BLQ	Below limit of quantitation
BMI	Body Mass Index
CAS	Chemical Abstracts Service
C_{avSS}	Average plasma concentration at steady-state
CGI	Clinical Global Impression
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLCN1	Chloride Voltage-Gated Channel 1
CNS	Central nervous system
C_{max}	Peak plasma concentrations
C_{maxSS}	Peak concentrations during the dosing interval at steady-state
CQA	Critical quality attribute
$C_{trough\text{-}ss}$	Concentration at the end of a dosing interval
DM	Myotonic dystrophy
DM1	Myotonic dystrophy type 1
DM2	Myotonic dystrophy type 2
DMA	Dimethylacetamide
DMF	Dimethylformamide or Drug master file
DSMB	Data Safety Monitoring Board
EC	European Commission
ECG	Electrocardiogram

eCRF	electronic Case report form
EF	Ejection fraction
eGFR	estimated Glomerular filtration rate
EMA	European Medicines Agency
EMG	Electromyogram
EOS	End of Study
EU	European Union
Eur.Ph./Ph.Eur.	European Pharmacopeia
FAS	FACES scores, Family Adaptability and Cohesion Evaluation Scales
FOCE-LB	First Order Conditional Estimation – Lindstrom Bates
Fpen	Population penetration factor
FT-IR	Fourier Transform Infrared spectroscopy
GC	Gas chromatography
GCP	Good Clinical Practice
GI	Gastrointestinal
GLDH	Glutamate Dehydrogenase
GLP	Good laboratory practice
GM	Geometric mean
GMP	Good manufacturing practice
HCl	Hydrochloride
HPLC	High-performance liquid chromatography
ICH	International council for harmonisation
ID	Identification
IP	Investigational product
IPC	In-process control(s)
IR	Infrared
ITT	Intent to Treat
IUD	Intrauterine device
LOD	Loss on drying
Log Kow	Logarithm of the n-octanol/water partition coefficient
LUC	Large unstained cells
MA	Marketing authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder

MBS	Myotonia Behaviour Scale
MC	Myotonia congenital
MedDRA	Medical Dictionary for Regulatory Activities
MIA	Manufacturing and import authorization
MO	Major objection
MRA	Mutual recognition agreement
NDM	Non-dystrophic myotonias
NDMA	N-nitroso dialkylamine
NMT	Not more than
NOAEL	No Observed Adverse Effect Level
OC	Other concern
OCT2	Organic cation transporter 2
OD	Orphan designation
OECD	Organization for Economic Co-operation and Development
OFV	Objective function values
PBT/vPvB	Persistence, bioaccumulation and toxicity
PC	Paramyotonia congenital
PD	Pharmacodynamics
PDCO	Paediatric Committee
PECsw	Predicted Environmental Concentration in Surface Water
PedsQL	Paediatric Quality of Life Questionnaire
PI	Product information
PiL	Package leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PND	Postnatal day
PP	Per-Protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
PVC	Polyvinyl chloride
PVDC	Polyvinylidene dichloride
QD	Once-a-day
QP	Qualified person
QTPP	Quality Target Product Profile

RMP	Risk management plan
RSE	Relative standard error
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
SOC	System Organ Class
TAMC	Total aerobic microbial count
TEAEs	Treatment emergent adverse events
TID	Three Times a Day
TK	Toxicokinetics
T_{max}	Time of the maximum observed plasma concentration
T_{maxSS}	Time until C_{maxSS} is reached
TUG	Timed-up and Go
TYMC	Total yeasts and moulds count
UATR	Universal attenuated total reflectance
UV	Ultraviolet
VAS	Visual analogue scale
VPC	Visual predictive check
WBC	White blood cells

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 04 March 2025, Lupin Europe GmbH submitted an extension of the marketing authorisation and the following variation(s)

Variation(s) requested		Type	Annexes affected
C I 6 A	Extension of indication to include the symptomatic treatment of myotonia in children and adolescents (from 6 to 18 years of age) with non-dystrophic myotonic disorders	II	I, IIIA, IIIB
A.7.	Delete a site responsible for secondary packaging of the finished product	IA	
A.7.	Delete a site responsible for batch release.	IA	II, IIIB

Extension application to add new strengths of 62 mg and 83 mg grouped with an Extension of indication to include the symptomatic treatment of myotonia in children and adolescents (from 6 to 18 years of age) with non-dystrophic myotonic disorders for NAMUSCLA, based on final results from study MEX-NM-301 as well as population pharmacokinetic analysis of mexiletine in healthy volunteers and myotonic patients; MEX-NM-301 is an open-label, multi-centre, single arm, interventional study to describe the steady-state PK, safety, and efficacy of mexiletine in pediatric patients (6 to <18 years of age) with myotonic disorders.
Line and Paediatric extension Application for Namuscla 62 mg and 83 mg hard capsules was grouped with Type II grouped variations to add a Paediatric indication, delete a Secondary packaging and batch release site for Namuscla 167 mg hard capsules.

As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet.

A.7. - Type IA - To delete a site responsible for secondary packaging of the finished product.

A.7. - Type IA - To delete Lupin Healthcare (UK) Limited, 2nd Floor, The Urban Building, 3-9 Albert Street, Slough, Berkshire SL1 2BE, United Kingdom as a site responsible for batch release.

1.2 Legal basis and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (1) - Extensions of marketing authorisations.

Type of application:

Article 3(1) - Indent 4 - Orphan designated medicinal product of Regulation (EC) No 726/2004

Known active substance (Article 8(3) of Directive No 2001/83/EC)

Namuscla was designated as an orphan medicinal product EU/3/14/1353 on 19.11.2014. in the following condition: treatment of myotonic disorders

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Following the CHMP positive opinion on this line extension, the Committee for Orphan Medicinal Products was of the view that the scope of this procedure does not raise justified and serious doubts in respect to the fulfilment of the orphan designation criteria.

1.3 Scientific advice and protocol assistance

Not applicable.

1.4 Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0227/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002012-PIP01-16-M05 (P/0227/2024) was not yet completed as some measures were deferred.

A partial compliance check was conducted in December 2024 (EMA/PE/0000233491). The PDCO discussed the completed studies, i.e., Study 1 (quality – age-appropriate capsules), Study 3 (juvenile rat toxicity study), Study 4 (PK, safety and efficacy study in 6<18-year-ods) and Study 8 (modelling and simulation study) and considered that these are compliant with the latest Agency's Decision (P/0227/2024) of 19/07/2024.

1.5 Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Fátima Ventura

The application was received by the EMA on	04 March 2025
The procedure started on	22 May 2025
The CHMP Rapporteur's first Assessment Report was received on	07 August 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	19 August 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 September 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	18 September 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	28 November 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	05 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 January 2026
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	29 January 2026
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 February 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 March 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Namuscla on	26 March 2026

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4 of this report.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0227/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Relevant paediatric statement in section 5.1 of the SmPC if the EMA has deferred a paediatric development have also been included.

1.7.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.5. of this report.

Following the CHMP positive opinion on this line extension, the Committee for Orphan Medicinal Products (COMP) was of the view that the scope of this procedure does not raise justified and serious doubts in respect to the fulfilment of the orphan designation criteria.

1.7.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of 62 mg hard capsules, 83 mg hard capsules and 167 mg hard capsules of Namuscla is favourable in the following indication(s):

Namuscla is indicated for the symptomatic treatment of myotonia in children aged 6 to 11 years weighing at least 20 kg, adolescents aged 12 to 17 years and adult patients ≥18 years with non-dystrophic myotonic disorders.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Namuscla, subject to the conditions described in the following sections.

In addition, the CHMP does recommend the variation to the terms of the marketing authorisation concerning the following changes:

Variation(s) requested		Type	Annexes affected
C I 6 A	Extension of indication to include the symptomatic treatment of myotonia in children and adolescents (from 6 to 18 years of age) with non-dystrophic myotonic disorders	II	I, IIIA, IIIB
A.7.	Delete a site responsible for secondary packaging of the finished product	IA	
A.7.	Delete a site responsible for batch release.	IA	II, IIIB

Extension application to add new hard capsules strengths of 62 mg and 83 mg for Namuscla, grouped with an Extension of indication to include the symptomatic treatment of myotonia in children and adolescents (from 6 to 18 years of age) with non-dystrophic myotonic disorders, based on final results from study MEX-NM-301 as well as population pharmacokinetic analysis of mexiletine in healthy volunteers and myotonic patients; MEX-NM-301 is an open-label, multi-centre, single arm, interventional study to describe the steady-state PK, safety, and efficacy of mexiletine in pediatric patients (6 to <18 years of age) with myotonic disorders. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.8, 5.1, 5.2, 5.3, 6.1, 6.5 and 8 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet. Additional changes include: Type IA - To delete as a site responsible for secondary packaging of the finished product. Type IA - To delete Lupin Healthcare (UK) Limited, 2nd Floor, The Urban Building, 3-9 Albert Street, Slough, Berkshire SL1 2BE, United Kingdom as a site responsible for batch release.

1.7.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.7.5. Other conditions and requirements of the marketing authorisation

1.7.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.7.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.7.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.7.6.2. Additional risk minimisation measures

Prior to launch of Namuscla in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

In order to prevent and / or minimise the important identified risks of Cardiac Arrhythmia in patients with Dystrophic Myotonia (off-label use) and Decreased Namuscla clearance, thus the risk of adverse reactions in patients with hepatic impairment, the MAH shall ensure that in each MS where Namuscla is marketed, all healthcare professionals (HCPs) and patients are provided, respectively, with:

- Educational guide for HCPs;
- Patient alert card

The Educational guide for HCPs, which should always be read in conjunction with the Summary of Product Characteristics (SmPC) before prescribing Namuscla, should contain the following key elements:

- Information about the risk of cardiac arrhythmias in patients using Namuscla;
- Guidance to identify (and exclude) patients at a greater risk of developing arrhythmias due to Namuscla treatment;
- Contraindications with Namuscla which may increase the susceptibility to arrhythmias;
- Before starting treatment, HCPs should perform a detailed and careful cardiac evaluation in all patients, in order to determine the cardiac tolerability of Namuscla. A cardiac evaluation is also recommended shortly after starting Namuscla (e.g. within 48 hours).
- Throughout treatment with Namuscla:

- In patients without cardiac abnormalities, an electrocardiogram (ECG) monitoring should be performed periodically (every 2 years or more frequently, if considered necessary);

- In patients with cardiac abnormalities, and in patients prone to such abnormalities, a detailed cardiac evaluation, including ECG should be carried out before and after any dose increase. During maintenance treatment, detailed cardiac evaluation including ECG, 24-48 hour Holter-monitoring and echocardiography, is recommended at least annually, or more frequently if considered necessary as part of routine cardiac assessment.

- Namuscla should be stopped immediately if the patient develops cardiac abnormalities, is not responding or experiencing benefit within Namuscla long-term treatment;

- Highlight the risk of decreased Namuscla clearance in patients with hepatic impairment and provide guidance on how to treat those patients in order to prevent it, ensuring Namuscla cautious titration in patients with mild or moderate hepatic impairment (increasing the dose after at least 2 weeks of treatment). Namuscla should not be used in patients with severe hepatic impairment;

- HCPs should counsel patients on:

  - The risk of cardiac arrhythmias (informing about symptoms of arrhythmias, advising patients to contact immediately their HCP, or emergency centres, if they experience any of these symptoms);

  - The risk of decreased Namuscla clearance in patients with hepatic impairment (advising patients to inform their HCP if they have any underlying hepatic disorder);

- Reporting of adverse reactions in patients using Namuscla.

The patient alert card (wallet size), to be handed by prescribing specialist and to be read in conjunction with the patient leaflet, should contain the following key messages:

- Patients should carry the card at all times, and show it at all medical visits to HCPs other than the prescriber (e.g. emergency HCPs);

- Prompts to enter the contact details of the patient, the treating physician, and Namuscla treatment starting date;

- Inform patients that, before starting and throughout treatment with Namuscla, HCPs should perform a detailed and careful cardiac evaluation;

- Patients should inform the HCP about any ongoing medications or before starting any new medication, while on treatment with Namuscla;

- Information about symptoms of cardiac arrhythmias, which can be life-threatening, and when patients should seek HCP attention;

- Patients should not take more than 3 capsules of Namuscla per day or a double dose to make up for a forgotten dose;

1.7.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.7.8. Proposed list of recommendations

***Table 1*: Proposed list of recommendations**

Description of Recommendation(s)
To investigate alternative administration methods for children unable to swallow capsules whole, including administration of the capsule contents with food or drinks and the suitability of administration of the capsule contents via enteral feeding tubes by Q2 2028. The SmPC and PL will be updated accordingly.

2. Introduction

Therapeutic Context

Myotonic disorders are a heterogeneous group of hereditary rare (orphan) diseases with no known cure and only symptomatic treatment. A common and defining feature of myotonic disorders is myotonia which is a malfunction of muscular ion channels, usually chloride or sodium channels 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 which can often be made based on the history and examination of the patient and family members in conjunction with confirmatory laboratory and genetic testing.

Myotonia is caused by skeletal muscle fibre hyperexcitability. 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. Consequently, the underlying cause of myotonic disorders are skeletal ion channelopathies mainly affecting sodium or chloride ion channels. Electrophysiological studies on resting conductance of chloride, potassium, sodium, and calcium ions have revealed considerable insight into the pathophysiological mechanisms.

The two myotonic dystrophies (type 1 and 2; DM1 and DM2, respectively) are autosomal dominant and multi-systemic disorders caused by an accumulation of expanded, non-coding RNAs, containing repetitive CUG and CCUG elements. 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. Frequently weakness, cataracts, conduction defects, insulin insensitivity, balding, hyperhidrosis, hypersomnia, and respiratory failure occur. DM2 is not normally diagnosed until adulthood and, in general, has clinical symptoms that are usually milder than DM1.

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). 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. 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. The intensity of symptoms ranges from mild (late onset) to life-threatening.

Mexiletine is the only approved product for the symptomatic treatment of NDM in adults. The MAH sought to extend the approved adult indication to children and adolescents (6 to up to 18 years).

2.1. Aspects of development

Mexiletine hydrochloride 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. Mexiletine hydrochloride is a white or almost white, crystalline powder. It is freely soluble in water and in methyl alcohol; sparingly soluble in dichloromethane. Mexiletine was initially developed as a treatment for ventricular arrhythmias with subsequent use in long QT syndrome. The first MA for mexiletine (MEXITIL 200 mg) was granted in 1975 (international birth date, IBD) to Boehringer Ingelheim (BI) in France. However, after the marketing withdrawal of BI's MEXITIL (indication: prevention of recurrence of life-threatening ventricular tachycardia) 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 has been reported for more than 30 years in Europe and gained acceptance as an effective anti-myotonia therapy in both dystrophic and non-dystrophic myotonia (that is, for both the chloride and sodium channelopathies). When production of MEXITIL ceased because the drug was no longer considered useful in the previously authorized indication, myotonic patients were left without effective alternative therapeutics. Therefore, the marketing authorisation holder (MAH) (BI France) was requested by the French Health Authority (Afssaps at that time) to continue to provide the product in France. On 12 October 2010, the MA ownership in France was transferred from BI to AP-HP (Assistance Publique Hôpitaux de Paris, Paris, France). The name of the medicinal product was changed from MEXITIL to MEXILETINE AP-HP. It has been available on the French market under this name since 01 November 2010. The Afssaps asked AP-HP to conduct a post-authorisation clinical study (Study MYOMEX) to investigate the efficacy and safety of mexiletine in NDM.

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 is 200 mg mexiletine HCl formulated as hard capsules for oral use containing 167 mg of mexiletine. 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. EMA granted Namuscla® a Marketing Authorisation with Orphan Drug Designation to Lupin Europe

GmbH on 18 December 2018 for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

As well as the approved 200 mg strength, new paediatric formulations were developed consisting of 75 mg and 100 mg mexiletine HCL strengths, hard capsules for oral use. The MAH requested to add these new strengths (corresponding to 62.48 mg and 83.31 mg of mexiletine, respectively) for paediatric population and to extend the current indication for adults for the symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders to children and adolescents from 6 to up to 18 years of age.

2.2. Description of the product

Mexiletine hydrochloride (mexiletine) 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. It is a sodium channel blocker intended for myotonic disorders (ATC class M09AX, officially classified in ATC class C01BB due to historical MA as antiarrhythmic).

Mexiletine hydrochloride active substance is a white or almost white, crystalline powder. It is freely soluble in water, in methanol and in ethanol 95°C; sparingly soluble dichloromethane; slightly soluble in acetonitrile; and practically insoluble in diethyl ether. The finished product is presented as hard capsules. The 62.48 mg capsules contain 75 mg of mexiletine hydrochloride, the 83.31 mg capsules contain 100 mg of mexiletine hydrochloride and the 167 mg capsules contain 200 mg of mexiletine hydrochloride.

Name of the active substance:	Mexiletine hydrochloride
Proposed name of the medicinal product:	Namuscla
Dosage form and strength:	Hard capsule 62 mg and 83 mg
Route(s) of administration:	Oral use
Therapeutic class:	ATC C01BB02 - Cardiac therapy, antiarrhythmics, class Ib
Indication	Namuscla **83 mg** hard capsules and Namuscla **62 mg** hard capsules: Children and adolescents (from 6 to 18 years of age): Namuscla is indicated for the symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders. Namuscla **167 mg** hard capsules: Adults (over 18 years of age), children and adolescents (from 6 to 18 years of age): Namuscla is indicated for the symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders.
Proposed dosage range:	The recommended starting dose depends on the age and body weight of the person. The daily dose can be increased, based on clinical response, up to 500 mg.

This application concerns a line extension to add two new strengths 62.48mg and 83.31mg for paediatric population and to extend the current indication for adults for the symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders to children and adolescents from 6-18 years of age.

The present line extension is a consequence of a modification of the initially approved PIP (P/0155/2017 - 2 June 2017). This latest PIP modification decision (P/0227/2024 – 19 July 2024) from EMA under procedure EMEA-002012-PIP01-16-M05 for mexiletine (hydrochloride) (Namuscla) corresponds to the planned submission of an application for a line extension to include new strengths (75 mg and 100 mg for mexiletine hydrochloride equivalent to 62 mg and 83 mg of mexiletine), and a paediatric indication in the labelling. The paediatric indication will enable children from 6 years and less than 18 years of age to receive Mexiletine hydrochloride based on data from PIP clinical study 4 and supportive studies 1 - Completion date was deferred), 3 (11-week toxicity study in juvenile rats with a 4-week recovery period - Completed by 15 May 2018) and 8 (Modelling and simulation study for dose selection in all paediatric clinical studies - Completed by 10 October 2024) which have been completed. In addition, the MAH intends to submit a further line extension application to expand the paediatric indication from birth to 5 years of age upon completion of clinical study 5 in the PIP.

The MAH manufactured in April 2017 batches of mexiletine hydrochloride capsules of 200 mg, 100 mg and 75 mg strength The measures according to a. and b. above are therefore considered fulfilled. The

MAH will continue the formulation work related to this measure as is outlined in the paediatric investigational plan.

In paediatric patients (children and adolescents) from 6 to less than 18 years of age, the recommended dose is dependent on body weight:

Body weight (kg)	Approximate age group	Mexiletine dose			
		Once daily dosing (morning)	Twice daily dosing (morning and evening)	Thrice daily dosing (morning, afternoon and evening)	Maintenance / Maximum total daily dose
20-30 kg	6 to 9 years	62.48 mg (as 1 x 62.48 mg capsule)	124.96 mg (as 2 x 62.48 mg capsules)	187.44 mg (as 3 x 62.48 mg capsules)	187 mg
30-40 kg	10 to 11 years	83.31 mg (as 1 x 83.31 mg capsule)	166.62 mg (as 2 x 83.31 mg capsules)	249.92 mg (as 3 x 83.31 mg or 4 x 62.48 mg capsules)	250mg
40-60 kg	12 to 15 years	124.96 mg (as 2 x 62.48 mg capsules)	249.92 mg (as 4 x 62.48 mg capsules)	374.88 mg (as 6 x 62.48 mg capsules)	375 mg
≥ 60 kg	16 to 17 years	166.62 mg (as 1 x 166.62 mg or 2 x 83.31 mg capsules)	333.24 mg (as 2 x 166.62 mg or 4 x 83.31 mg capsules)	499.86 mg (as 3 x 166.62 mg or 6 x 83.31 mg capsules)	500 mg

The PK population study has been completed to support dosing recommendations in children as presented in the dose recommendation table.

2.3. Inspection issues

2.3.1. GMP inspection(s)

No inspection required.

2.3.2. GLP inspection(s)

No inspection required.

2.3.3. GCP inspection(s)

No inspection required.

3. Quality aspects

Introduction

This application concerns a line extension to add two new strengths 62 mg and 83 mg for paediatric population to extend the current indication for adults for the symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders to children and adolescents from 6 to up to 18 years of age. The applicant also grouped two Type IA variations (A.7.) to delete an alternative batch release site, and a secondary packaging site.

The finished product is presented as hard capsules containing 62 and 83 mg of mexiletine hydrochloride corresponding to 62.48 mg and 83.31 mg of mexiletine respectively as active substance.

Other ingredients are:

Capsule content: maize starch, colloidal anhydrous silica, and magnesium stearate

Capsule shell (62 mg): titanium dioxide (E 171) and gelatine.

Capsule shell (83 mg): iron (III) oxide hydrated, titanium dioxide (E 171), and gelatine.

The product is available in in Aluminium/PVC/PVDC blisters as described in section 6.5 of the SmPC.

3.1. Active substance

The active substance used in these two new strengths is the same as that used in the already marketed formulation. There is a monograph in the European Pharmacopeia for mexiletine hydrochloride, and therefore a CEP is used (CEP 2017-107 – Rev 02).

3.2. Finished medicinal product

30.1.1. Description of the product and Pharmaceutical development

The finished product is presented as white hard shell capsules (15 mm) hard capsules filled with white powder for the 62 mg strength, and Swedish orange (cap) and white (body) hard shell capsules (20 mm) filled with white powder for the 83 mg strength.

The proposed strengths were developed as dose proportional formulations to the already approved strength (167 mg). The MAH provided information concerning the pharmaceutical development of the already approved strength, stating that the manufacturing process of the new formulations is identical to the point of encapsulation. Additional data were provided where appropriate. Since, at the time of the original formulation development (1970's) development studies were not required, the information concerning the proposed commercial process and its controls is minimal.

The active substance mexiletine hydrochloride is described in current Ph. Eur. (No. 1029) and a certificate of suitability (R0-CEP 2017-107-Rev02) was provided in the initial application. It is a BCS class I active substance.

All excipients used are well known and long used in solid dosage forms and described in the Ph. Eur., meeting the requirements defined there in: maize starch, colloidal silica anhydrous, magnesium stearate, purified water and ethanol 96%. Hard gelatin capsule shells are not compendial and are controlled against an in-house specification. Information is provided on the functionality related

characteristics of maize starch, silica, colloidal anhydrous, and magnesium stearate. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The use of an alternative colourant in the capsule shells was addressed in the PIP. The MAH has informed that administration in younger patients (6 years of age) is restricted to the 62 mg capsule strength, which does not contain iron oxide (E172). Consequently, no excipient-related safety or toxicological concerns are anticipated.

The finished product concerns two new strengths. All formulation development is based on that already approved. No Quality Target Product Profile (QTPP) of the product has been defined as recommended by the guideline ICH Q8. However, there is extensive stability data available for the formulation, with a long commercial history.

As stated above, the marketed formulation for mexiletine 167 mg hard capsules is the same as the clinical formulation tested in the pivotal clinical study, apart from the colourant for the hard capsules.

Since the original development, launched in 1979, the manufacturing process has been only slightly modified to account for new manufacturing sites with different equipment types and capacities. The same process, wet granulation, as is proposed in the current application dossier was used to manufacture the batch used in the clinical trial.

As the proposed formulations are intended for paediatric patients (6 to 18 years old), it is confirmed that the available capsule sizes are appropriate for use in the studied paediatric population, with no clinically relevant issues related to swallowability or acceptability. However, the CHMP considered that swallowing difficulties occur more frequently in the younger paediatric population, therefore recommended to investigate alternative administration methods for children unable to swallow capsules whole, including administration of the capsule contents with food or drinks and the suitability of administration of the capsule contents via enteral feeding tubes by Q2 2028. The SmPC and PL will be updated accordingly (REC).

The studies for selection of a dissolution method were performed using one batch (167 mg capsules, according to the validation data) and not 62 mg or 83 mg capsules, which is acceptable since lower doses of the same formulations are not expected to dissolve slower.

The discriminatory power of the dissolution method was addressed. Mexiletine HCl is a BCS class I substance. The dissolution of the active substance is governed primarily from capsule disintegration time. Once disintegrated the active substance is quickly dissolved. In vivo absorption for a BCS class I substance such as mexiletine HCl is expected to be limited by factors such as gastric emptying and not by the solubility of the active substance. To explore the discriminatory properties of the dissolution method, the MAH has explored the impact of minor formulation or process changes which could occur during manufacturing on the dissolution properties: moisture content of final blend on dissolution; particle size of final blend on dissolution; amount of disintegrant on dissolution. Particle size of the active substance is not expected to meaningfully affect dissolution, as mexiletine hydrochloride is a BCS Class I compound with high solubility and permeability. The tested formulation or process changes did not produce altered dissolution profiles. However, as the active substance is rapidly soluble at all pH levels, developing a dissolution method that shows suitable discriminatory power is challenging; this is accepted. In conclusion, it is considered that the discriminatory power of the dissolution method has been sufficiently addressed.

No overages are included in the formulation. The physicochemical and biological properties described and studies in this line extension are limited to the dissolution profiles of the proposed formulations and based on data obtained with the approved dose (167 mg capsules). This is relevant to the performance of the finished product. The final comparison between dissolution profiles of 62 mg and 167 mg capsules is acceptable and can be applied to the intermediate dose of 83 mg capsules.

The manufacturing is essentially the same that is approved for the marketed formulation. The process has been well characterized throughout the years and proven to be robust. However, all development is based on that already approved formulation and no CQAs or design space have been defined as recommended by the guideline ICH Q8. The manufacturing process has been well characterized throughout the years and proven to be robust.

The primary packaging is Aluminium/PVC/PVDC blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

30.1.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process consists of 7 main steps: blending, wet granulation, fluid bed drying, sieving, blending/lubrication, encapsulation and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Critical steps have been identified and the proposed in-process controls are adequate for this type of manufacturing process.

30.1.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC / UV spectrum), identification chloride (Ph. Eur.), identification titanium dioxide (Ph. Eur.), disintegration (Ph. Eur.), loss on drying (Ph. Eur.), uniformity of dosage units (Ph. Eur.), assay (HPLC), dissolution (HPLC), related substances (HPLC), residual solvents (GC), and microbiological purity (Ph. Eur.)

The specifications are based on pharmacopeial requirements for the dosage form, the physiochemical properties of the active substance as well as ICH recommendations.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

At the time of evaluation, a risk assessment concerning the potential presence of nitrosamines impurities in the finished product was performed, however, the CHMP considered that the information provided on nitrosamines was brief and requested as major objection (MO) that the risk assessment should be updated. Considering this line extension is associated also with an extension of indication to paediatric population an update of the risk evaluation should be presented including all potential risk factors of nitrosamine impurities currently listed in the Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant conducted an updated

nitrosamine risk assessment for the finished product and identified no risk. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary, and the MO is considered resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

30.1.4. Stability of the product

Stability data from 3 commercial scale batches of the finished product (62 mg strength and 167 mg strength) stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for disintegration, loss of drying, assay and related substances and dissolution. The analytical procedures used are stability indicating.

All batches of mexiletine 62 mg that were placed on stability remained within the specifications throughout the stability studies at accelerated and long-term conditions. Similarly, all batches of mexiletine 167 mg that were placed on stability remained within the specifications throughout the stability studies at accelerated and long-term conditions.

An additional stability study has been started in 2019 with the highest strength 167 mg capsules (bulk and in blisters) stored for up to 36 months under long term conditions (25 ºC / 60% RH) and under intermediate conditions (30 ºC / 65% RH) for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. All batches of mexiletine 167 mg that were placed on stability remained within the specifications throughout the stability studies at accelerated, intermediate and long-term conditions.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Data revealed no deviations from the finished product specifications; therefore, the finished product is photostable.

Based on available stability data, the proposed shelf-life of 3 years and the storage condition do not store above 30 °C, as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

30.1.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

3.3. Discussion on chemical, and pharmaceutical aspects

This application concerns a line extension to add two new strengths 62 mg and 83 mg for paediatric population. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

One MO was raised during the procedure relating to the risk assessment for potential presence of nitrosamine impurities. As a response an updated nitrosamine risk assessment for the finished product was conducted and identified no risk. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to investigate alternative administration methods for children unable to swallow capsules whole, including administration of the capsule contents with food or drinks and the suitability of administration of the capsule contents via enteral feeding tubes by Q2 2028. The SmPC and PIL will be updated accordingly. This point is put forward and agreed as recommendations for future quality development.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

3.5. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To investigate alternative administration methods for children unable to swallow capsules whole, including administration of the capsule contents with food or drinks and the suitability of administration of the capsule contents via enteral feeding tubes by Q2 2028. The SmPC and PL will be updated accordingly.

4. Non-clinical aspects

The MAH submitted a non-clinical juvenile toxicity study in Sprague-Dawley rats, conducted following GLP and relevant guidelines, in support of addressing the current benefit-risk profile on the basis of safety/toxicity data generated and evaluated in the animal study. It is intended to support line extension application for Namuscla® capsules to add paediatric indication to the currently approved EMA license for Namuscla® (mexiletine). The study aimed to characterise the potential effects of mexiletine on growth, development, and functional maturation during juvenile stages, including neurobehavioral and reproductive parameters, following repeated oral administration.

No other new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

Introduction

The MAH conducted a GLP-compliant juvenile toxicity study with mexiletine hydrochloride (HCl) to support a line extension application for the inclusion of a paediatric indication for Namuscla® capsules.

According to the signed GLP compliance statement, the nonclinical study supporting the line extension submission grouped with the paediatric indication for Namuscla, Mexiletine complies with all necessary nonclinical requirements, safety pharmacology and toxicology studies were carried out in conformance of Good Laboratory Practice (GLP) standards. Also, all GLP studies were conducted in OECD member countries and in compliance with OECD1 guidelines.

4.1. Pharmacology

No new non-clinical pharmacodynamic data were submitted, which is acceptable.

4.2. Toxicology

4.2.1. Toxicokinetics and exposure margins

In treated groups, plasma concentrations of Mexiletine were variable, warranting cautious interpretation of the data. Systemic exposure to Mexiletine was confirmed in most animals at 30 and 90 mg/kg/day, except on Day 1 (PND 7) and Day 15 (PND 21), where late sampling ($\geqslant$6 h or $\geqslant$10 h post-dose) likely contributed to non-quantifiable levels. At 10 mg/kg/day, exposure was demonstrated in approximately half the animals. Due to limited quantifiable data, AUC could not be calculated for some groups. Peak plasma concentrations (C_{max}) were observed between 0.5 and 2 hours post-dose, with no relevant sex-related differences. A decrease in systemic exposure was observed from Day 1 to Day 78. Dose-proportional increases in C_{max} and AUC were observed between 10 and 30 mg/kg/day, with slightly more than dose-proportional increases between 30 and 90 mg/kg/day.

The MAH's interpretation is consistent with ICH S11, which recognises that juvenile animal studies may be constrained by species-specific tolerability and that, when higher exposure cannot be achieved, regulatory evaluation should focus on whether the study was conducted at the maximum tolerated dose and whether all relevant developmental and toxicological endpoints were adequately assessed. These criteria have been met.

At the NOAEL, observed findings were limited to non-adverse clinical signs, minor clinical pathology changes and minimal increases in liver weight without histopathological correlates. No adverse effects relevant to paediatric risk were identified. When integrated with the available clinical data, including completed paediatric studies and ongoing long-term follow-up, no new or unexpected safety signals have been observed in children and adolescents.

Risk mitigation measures are in place, including intensive clinical monitoring, ECG assessments, laboratory evaluations, DSMB oversight and routine pharmacovigilance activities, which adequately address the residual uncertainty associated with the absence of an exposure margin.

4.2.2. Other toxicity studies

The MAH conducted a GLP-compliant juvenile toxicity study with mexiletine hydrochloride (HCl) to support a line extension application for the inclusion of a paediatric indication for Namuscla® capsules.

The daily pre- and post-weaning oral administration of Mexiletine to juvenile Sprague Dawley rats at doses of 10, 30 or 90 mg/kg/day (expressed in Mexiletine) for approximately 3 months was associated at 90 mg/kg/day with few clinical signs of hypersalivation, some slight changes in clinical pathology

parameters (increase in WBC counts and GLDH levels) and produced a minimal and transient increase in liver weights with no corresponding microscopic findings.

Since all findings were considered to be non-adverse and there was no Mexiletine-related effect on growth measurements, neurobehavioral tests, sexual maturation, oestrous cycles, mating performance and early gestation, the No Observed Adverse Effect Level was set at 90 mg/kg/day of Mexiletine (or 108 mg/kg/day of Mexiletine HCl) for both sexes under the study conditions.

4.2.3. Ecotoxicity/environmental risk assessment

Table 2: **Screening**

Substance (INN/Invented Name):	mexiletine hydrochloride		
CAS-number (if available):	5370-01-4		
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107/117/123	< 2.6	Potential PBT: Y/N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	< 2.6	not B
	BCF	L/kg_{ww}	B/vB/not B
Persistence	DT50 Values are derived from the OECD 308 or OECD 307 study below and have been recalculated to 12°C or ready biodegradability	D	P/vP/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The active substance is considered to be not PBT, nor vPvB		

Table 3: ***Phase I***

Phase I			
Calculation	Value	Unit	Conclusion
PEC_{sw}, *default/refined*	2.5/0.00425	µg/L	≥ 0.01 threshold: Y/N
Other concerns (e.g., chemical class)			Y/N

Considering the presented data for the Environmental Risk Assessment of the API present in this medicinal product, namely the PECsw after refinement, and the PBT/vPBT criteria, the main pharmacologically active substance present in Namuscla is not likely to pose any additional environmental concern. $PEC_{surfacewater}$ for Mexiletine is below the action limit of 0.01 µg/L and Mexiletine is not a PBT substance as log K_{ow} does not exceed 4.5. In addition, the inclusion of mitigation measures of the environmental presence of the API also are in line with the established guideline, and will contribute for a significant environmental presence of the active substance.

$PEC_{surfacewater}$ for mexiletine is below the action limit of 0.01 µg/L and mexiletine is not a PBT substance as log K_{ow} does not exceed 4.5. Consequently, a Phase II risk assessment is not required.

4.3. Overall discussion and conclusions on non-clinical aspects

4.3.1. Discussion

The MAH conducted a GLP-compliant juvenile toxicity study with mexiletine hydrochloride (HCl) to support a line extension application for the inclusion of a paediatric indication for Namuscla® capsules. No additional non-clinical pharmacodynamic, pharmacokinetic, or general toxicological studies were submitted. This approach is considered acceptable in the context of the current application.

Concentrations of mexiletine in rat K2-EDTA plasma samples were determined using a validated LC-MS/MS method. Quality Control and calibration standard data were acceptable according to the requirements of the FDA Guidance for Industry, and the EMA guidance.

The systemic exposure at the NOAEL in juvenile rats does not exceed human exposure at the proposed clinical dose. Exposure margins (rat/human) are ≤1 for C_{max} and clearly <1 for AUC, particularly at PND84, where AUC margins are as low as approximately 0.1–0.3. Consequently, a conventional safety margin based on systemic exposure is not demonstrated, and human exposure exceeds animal exposure at the NOAEL for AUC. The MAH's interpretation is consistent with ICH S11, which recognises that juvenile animal studies may be constrained by species-specific tolerability and that, when higher exposure cannot be achieved, regulatory evaluation should focus on whether the study was conducted at the maximum tolerated dose and whether all relevant developmental and toxicological endpoints were adequately assessed. These criteria have been met.

At the NOAEL, observed findings were limited to non-adverse clinical signs, minor clinical pathology changes and minimal increases in liver weight without histopathological correlates. No adverse effects relevant to paediatric risk were identified. When integrated with the available clinical data, including completed paediatric studies and ongoing long-term follow-up, no new or unexpected safety signals have been observed in children and adolescents.

Risk mitigation measures are in place, including intensive clinical monitoring, ECG assessments, laboratory evaluations, DSMB oversight and routine pharmacovigilance activities, which adequately address the residual uncertainty associated with the absence of an exposure margin.

Considering the presented data for the Environmental Risk Assessment of the API present in this medicinal product, namely the PECsw after refinement, and the PBT/vPBT criteria, the main pharmacologically active substance present in Namuscla is not likely to pose any additional environmental concern. In addition, the inclusion of mitigation measures of the environmental presence of the API also are in line with the established guideline, and will contribute for a significant environmental presence of the active substance.

4.3.2. Conclusions

The extension application to add two new strengths and expand the indication of Namuscla to paediatric patients with non-dystrophic myotonia is supported by a GLP non-clinical juvenile toxicity study and clinical and pharmacokinetic data. Despite the absence of new non-clinical pharmacodynamic studies, the well-established mechanism of action of mexiletine remains relevant, justifying its expected benefit in reducing muscle stiffness and improving relaxation in this population.

The non-clinical data package includes a juvenile toxicity study supporting a NOAEL of 90 mg/kg/day; however, systemic exposure at this dose is significantly lower than that observed in humans at the proposed clinical dose, raising concerns regarding the absence of an adequate safety margin. The

MAH's interpretation is consistent with ICH S11, which acknowledges that juvenile animal studies may be limited by species-specific tolerability and that, in the absence of higher achievable exposure, evaluation should focus on confirmation of dosing at the maximum tolerated dose and adequate assessment of relevant developmental and toxicological endpoints, both of which were met. At the NOAEL, findings were limited to non-adverse clinical signs, minor clinical pathology changes and minimal increases in liver weight without histopathological correlates, with no effects relevant to paediatric risk identified. When considered together with the available paediatric clinical data and ongoing follow-up, no new or unexpected safety signals have been observed. Risk mitigation measures, including clinical monitoring, ECG and laboratory assessments, DSMB oversight and routine pharmacovigilance, are in place and adequately address residual uncertainty related to the absence of an exposure margin.

The presented data are satisfactory and allow to conclude that no environmental concerns are likely to result from the approval of Namuscla, hard capsules, 75 mg + 100mg.

5. Clinical aspects

5.1. Introduction

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 2.4.3.).

5.1.2. Tabular overview of clinical trials

Table 4: Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Phase 3					
MEX-NM-301 (completed)	Open-label, non-comparative study, multi-centre, single arm, interventional study 8-week treatment period with overall 22-month duration	Subjects were enrolled sequentially in 2 cohorts by age groups Cohort 1 – Adolescents aged 12 to <18 yrs, were enrolled first. If no safety concerns were observed (based on data evaluation by the DSMB), and the dose for the age group 6 to <12 yrs was confirmed by PK model,	Adolescents (aged 12 to <18 yrs) and children (aged 6 to <12 yrs) with Myotonic Disorders	Safety, Efficacy (primary endpoints) and PK	Total of 12 subjects; Cohort 1: 7 subjects (4 female and 3 males; mean age 13.4 yrs); Cohort 2: 5 subjects (3 female and 2 males; mean age 8.2 yrs)

		enrolment for Cohort 2 began. Cohort 2 – Children aged 6 to <12 yrs, were enrolled Dose titration phase: patients received mexiletine starting at an age-appropriate dose (as evaluated by the investigator and based on body weight) at a frequency of once a day. Dose was up-titrated every 14 days based on tolerability of mexiletine up to a maximum of three-times a day Maintenance phase: patients continued to receive mexiletine at the best-tolerated dose from the titration phase for further 4 weeks. The mexiletine total daily dose was based on body weight and ranged from 186 to 500 mg mexiletine during the maintenance period			

RD = randomised; DB = double blind; PC = placebo controlled; SA = single arm; OL =open label; yrs = years; SC = sub-cutaneous; Q4W = every 4 weeks; Q2W = every 2 weeks

5.2. Clinical pharmacology

5.2.1. Methods

The MAH provided the details about the analytical method used for the quantification of Mexiletine in the plasma samples of the patients in the study MEX-NM-301. Overall, the obtained data is considered acceptable form the analytical point of view.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

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 was 200 mg mexiletine HCl formulated as hard capsules for oral use containing 167 mg of mexiletine. Following a PIP, new paediatric formulations were developed consisting of 75 mg and 100 mg mexiletine strengths with identical qualitative composition to the 200 mg mexiletine strength. In order to extend the use of mexiletine to paediatric patients aged from 6 to up to 18 years old, the

MAH performed an Open-label, non-Comparative Study to Evaluate the Steady-State Pharmacokinetics, Safety, and Efficacy of Mexiletine in Adolescents and Children with Myotonic Disorders (study MEX-NM-301). In addition, a modelling and simulation study population pharmacokinetic study was also presented. This follows the PIP and PDCO already concluded for a compliance with the agreed PIP procedure.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

The population PK model used data from adult studies, U79-0321 and MYOMEX and paediatric data from a published source, Leheup *et al*. 1986 and a study conducted by Lupin (Study 4).

Mexiletine follows a 2-compartment pharmacokinetic model with proportional variability for the interindividual variability on CL and the residual error. Interindividual variability on the other PK parameters was not estimable, likely due to the limited data available for modelling. Body weight, added via an allometric function to the power of 0.75 for CL and Q, and 1 for V and V2, improved the description of the data and this was consistent with the originally developed model. None of the other covariates tested, age, creatinine clearance, age group, or dose, were found to improve the model fit and therefore the base model and the final model were the same.

The model qualification was performed via a visual prediction check and bootstrap technique. These showed the robustness of the model and excellent predictive performance.

Prior to the enrolment of the youngest subject cohort, simulations were performed based on body weight of 25 kg and 75 kg using the PK parameters from the base model. These simulations showed good agreement with a dose of ~75 mg TID for a 25 kg paediatric patient and ~100 mg TID for a 35 kg patient as compared to the exposure of 200 mg in a 75 kg adult patient. These simulations were used to inform dosing in the young patient cohort, 6-12 years old, in Study 4.

5.2.2.2.2. Physiology based pharmacokinetic model

Not applicable

5.2.2.3. Absorption

The popPK model included both IV and oral administered data. Bioavailability was considered 100%.

5.2.2.4. Bioequivalence

The 75 mg and 100 mg formulations have been developed as dose proportional formulations to the already approved 200 mg formulation EU/1/18/1325/001-004. In line with the 200 mg the manufacturing site is the same as the 75mg and 100mg. Also, the same API source, same formulation and same manufacturing process are used. The manufacturing process of the 75 mg and 100 mg capsule is identical to that of the 200 mg capsule up to the point of encapsulation. Dissolution is very fast in all the required dissolution media for all the formulations.

5.2.2.5. Distribution

A two-compartment model with IV and first order absorption, lag time, and first order elimination adequately described the mexiletine concentration data was found to best fit of all the available data from the 4 studies.

5.2.2.6. Metabolism

No new information was provided. However, it is known that mexiletine undergoes extensive hepatic metabolism (approximately 90% of the administered dose). At least 11 metabolites of mexiletine – products of oxidation, deamination, and reduction reactions – have been identified, most of which are eliminated as glucuronide conjugates (Study U79-0317 and published data). The majority of these metabolites does not appear to be pharmacologically active, the exception being MHM (m-hydroxymexiletine), the urinary excretion of which represents < 2% of the administered dose, and recently found to be ~2-fold more potent than the parent molecule in *in vitro* assays.

5.2.2.7. Elimination

From the base model, the typical value for mexiletine CL was estimated to be 28.21 L/h. Body weight was added to the model as a covariate via an allometric power function at a value of 0.75 on CL. The typical elimination half-life was 10h.

5.2.2.8. Dose proportionality and time dependency

The popPK model assumed both first order absorption and elimination. This is compatible with dose proportionality, as previously described for the drug.

5.2.2.9. Pharmacokinetics in the target population

Data in the paediatric population come from the phase 3 study MEX-NM-301. This was an open-label, multi-centre, single arm, interventional study to describe the steady-state PK, safety, and efficacy of mexiletine in paediatric patients (6 to <18 years of age) with myotonic disorders. Patients who meet the eligibility criteria were enrolled stepwise, sequentially in 2 cohorts by age groups.

Cohort 1 – Adolescents aged 12 to <18 years, were enrolled first. If no safety concerns were observed (based on data evaluation by the Data Safety Monitoring Board [DSMB]), and the dose for the age group 6 to <12 years was confirmed by PK model, enrolment for Cohort 2 began.

Cohort 2 – Children aged 6 to <12 years, were enrolled.

The overall treatment duration for each cohort was approximately 56 days (8 weeks): a dose titration phase of 4 weeks and the maintenance phase of 4 weeks. The overall study duration was approximately 22 months.

Dose dependent increases in mexiletine concentrations were observed (i.e., direct relationship between dose and exposure) at Day 42. The mean (GM) $C_{max,ss}$ and $AUC_{tau,ss}$ values at the maximum dose (501 mg, delivered as 1x167 capsule, TID) were 1392.21 µg/L and 8551.64 µg/L, respectively on Day 42.

5.2.2.10. Special populations

In the popPK covariate analysis, the creatine plasma value was not correlated to the CL of the model. This goes in line with the known elimination of mexiletine where only 10-15% is eliminated unchanged. Overall, no dose adjustment is needed in renal impaired patients.

No new information was provided regarding hepatic impairment. The previously recommendation of dose increased only after at least 2 weeks of treatment is to be followed.

In the popPK model, a slight trend appeared to be evident for sex on CL and this effect was tested but was not found to be significant.

Weight influences both the Clearance and the Volume of distribution in an allometric way. Due to this, the dosing for the paediatric population is staggered based on the patient weight.

The PIP was considered compliant with the agency's decisions by the PDCO. Of relevance, the PDCO considered that extrapolation of the paediatric population efficacy would be based on the adult efficacy data based on similar exposure-response relationship.

5.2.2.11. Pharmacokinetic interaction studies

5.2.2.11.1. Special populations

Being under therapeutic use since 1975, the DDIs for mexiletine are fairly well known. Those are mainly due to the fact that Mexiletine is a substrate of both CYP2D6 and CYP1A2, as well as a potent inhibitor of CYP1A2. These facts are well documented in the SmPC as well as the well-known DDIs with mexiletine.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

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 of the delay of muscle relaxation.

5.2.3.2. Primary and secondary pharmacology

No new information was provided.

5.2.3.3. Pharmacokinetics/pharmacodynamics (PK/PD)

As explained before, the PDCO considered that extrapolation of the paediatric population efficacy would be based on the adult efficacy data based on similar exposure-response relationship. As such, the MAH did not provide any new data on PD nor on the PK-PD relationship. This is acceptable.

5.2.3.4. Dose selection and therapeutic window

Dose selection was based on body weight aiming at similar exposures when compared to the adult population.

5.2.3.5. Overall discussion and conclusions on clinical pharmacology

5.2.3.6. Discussion

Methods

The MAH provided the details about the analytical method used for the quantification of Mexiletine in the plasma samples of the patients in the study MEX-NM-301. Overall, the obtained data is considered acceptable form the analytical point of view.

PopPK analysis

The MAH presented a popPK study with the data from 4 studies, the U79-03121 study in healthy volunteers (1), the MYOMEX study, conducted in patients with myotonia (2), the Leheup et al. (1986) study (3), which is a case report of mexiletine administration in an 11-month old child with myotonia, and (4) Study 4 (MEX-NM-301), an open-label non-comparative study to evaluate the steady-state pharmacokinetics, safety, and efficacy of mexiletine in adolescents and children with myotonic disorders that was agreed in the PIP. The initial model including the first 3 studies (with IV and oral data) was already assessed in the original application and was also the basis of the proposed weight-based dosing used in the PIP study 4. In this application, the final popPK study, including also all the available data from study 4 was assessed.

The used methodology included a base model search and models of increased complexity were tested. The final base model consisted of a two-compartment model with IV and first order absorption, lag time, and first order elimination. Inter-individual variability, as a proportional error model, was included on CL but not on any of the other pharmacokinetic parameters as model convergence was not achieved. A proportional error model was used to describe the intraindividual residual variability. All the model parameters were determined with good precision and their values were according to the described ones in the literature. Covariate inclusion was initially made by a search of a correlation between the ETA (interindividual variability) values for CL *versus* the available categorical and continuous variables. Since no specific correlation or trend was observed, consistent with the previously developed model, the effect of body weight on clearance and volume of distribution was kept fixed, using allometric exponents (0.75 for CL and Q, and 1 for V1 and V2). Based on this, and although other co-variate search approaches were possible, the one taken by the MAH was deemed acceptable.

The final model resulted in acceptable GOF plots and the bootstrap analysis also confirmed the quality of the obtained parameters. The MAH presented the pcVPC of all the data and also on the study 4 by cohort. In the first, there seems to be a good agreement on the median trend although, regarding variability, some overprediction on the upper percentiles is observed. Regarding the study 4 data, due to the low amount of data and the superimposition of the simulation bands, it is not possible to fully identify any major flaw in the model, that can be considered, thus, fit for purpose.

Based on the obtained final model, the MAH simulated the PK for 25 kg and 35 kg children with a dose regime of 75 mg TID and 100 mg TID and compared to an adult with 70 kg and a regime of 200 mg TID. The Values seem to overlap. These simulations were further expanded for all weight bands

expected to be observed in paediatric patients from 6 to 18 years old. The obtained exposures were compared to the ones obtained with the adult data showing similar values.

Absorption

Mexiletine is probably a BCS class I drug with complete absorption. The popPK model, that included data from both IV and Oral routes, considered an oral bioavailability of 100%.

In the PIP clinical study 4, 75 mg and 100 mg paediatric formulations were used. These were developed as dose proportional formulations to the already approved 200 mg formulation. In addition, the dissolution profiles in the required multi-media were always very fast (with more than 85% dissolved at 15 minutes). Overall, all formulations may be considered bioequivalent.

Distribution

According to the popPK model, the distribution of mexiletine follows a two-compartmental kinetics with a Vss of around 5.3 L/Kg. This value is similar to the one previously described.

Elimination

The popPK model assumed a first-order elimination with a CL value of 28.2 L/h for a 70 kg subject. This results in a terminal elimination half-life of around 10h. This is the typical value for an CYP2D6 normal metabolizer.

No new information was provided. However, it is known that mexiletine undergoes extensive hepatic metabolism (approximately 90% of the administered dose). At least 11 metabolites of mexiletine – products of oxidation, deamination, and reduction reactions – have been identified, most of which are eliminated as glucuronide conjugates (Study U79-0317 and published data). The majority of these metabolites does not appear to be pharmacologically active, the exception being MHM (m-hydroxymexiletine), the urinary excretion of which represents < 2% of the administered dose, and recently found to be ~2-fold more potent than the parent molecule in *in vitro* assays.

The MAH reported than no prospective CYP2D6 genotyping or phenotyping was performed to identify poor metabolizers among enrolled children However, both individualized dosing and therapeutic drug monitoring were used to manage exposure, and no severe toxicity attributable to poor metabolism was observed. Since a CYP2D6 poor metabolizer subject is expected to present a conservatively $t_{1/2}$ of 14 hours thus it is reasonable to expect that steady-state mexiletine levels will be reached after 7 days, irrespective of the patient's CYP450 polymorphism and/or renal or hepatic function. In this context, the up-titration protocol, combined with clinical monitoring, is expected to control the risks associated with altered mexiletine pharmacokinetics.

Dose proportionality and time dependency

The popPK model assumed both first order absorption and elimination. This is compatible with dose proportionality, as previously described for the drug.

Intra- and inter-individual variability

The popPK model only included inter-individual variability in the Clearance. With a value of 66%, it can be considered as moderate to high. This may be due to the fact that metabolism is subjected to genetic polymorphism.

Pharmacokinetics in the target population

The observed PK in the study 4 resulted in C_{max} values ranging from 0.45 mg/L to 1.53 mg/L. According to the MAH, both C_{max} and AUC seem to show a dose dependent increase in mexiletine concentrations. However, the administration protocol considers a weight dependent dose increase and similar exposures were expected to be seen in the end. According to the protocol, mexiletine titration could be discontinued due to tolerability issues. As a result, some patients may not have reached the target dose and could have been underdosed. This, together with the small sample size, may explain the observation of a slight dose dependent increase in mexiletine concentrations. Nevertheless, when observing the relationship of C_{max}/AUC vs dose/kg, no further dose dependency was observed. This goes in line with the PopPK model predictions.

The MAH reported that the therapeutic range of 0.500 to 2.000 mg/L, established in adults with myotonia based on efficacy and safety data, was used as the reference for all paediatric exposure comparisons. In the original application, the day 18 C_{min} and C2h of 600 mg/day on the MYOMEX study resulted in values from approx. 0.2 to 2.0 mg/L. Other studies with similar doses but administered to patients with other diseases resulted in ranges of concentrations from 0.1 to 3 mg/L. So, in general, the proposed values may be accepted. Regarding the possibility of extrapolation of efficacy from adults to children, the MAH argue that Myotonic disorders are skeletal-muscle ion-channelopathies characterized by impaired muscle relaxation and episodic or persistent stiffness, that although may present at differing ages, the fundamental pathophysiology, molecular mechanisms, and clinical manifestations of myotonia are highly conserved across age groups. In particular, molecular mechanisms do not change with age and children manifest the same defective channel biology as adults. This was generally accepted by the PDCO.

Special populations

In the popPK covariate analysis, the creatine plasma value was not correlated to the CL of the model. This goes in line with the known elimination of mexiletine where only 10-15% is eliminated unchanged. Overall, no dose adjustment is needed in renal impaired patients.

No new information was provided regarding hepatic impairment. The previously recommendation of dose increased only after at least 2 weeks of treatment is to be followed.

In the popPK model, a slight trend appeared to be evident for sex on CL and this effect was tested but was not found to be significant.

Weight influences both the Clearance and the Volume of distribution in an allometric way. Due to this, the dosing for the paediatric population is staggered based on the patient weight.

The PIP was considered compliant with the agency's decisions by the PDCO. Of relevance, the PDCO considered that extrapolation of the paediatric population efficacy would be based on the adult efficacy data based on similar exposure-response relationship.

Pharmacokinetic interactions studies

Being under therapeutic use since 1975, the DDIs for mexiletine are fairly well known. Those are mainly due to the fact that Mexiletine is a substrate of both CYP2D6 and CYP1A2, as well as a potent inhibitor of CYP1A2. These facts are well documented in the SPC as well as the well-known DDIs with mexiletine.

5.2.3.7. Conclusions

In general, the children PK and the bridge to adult efficacy data is well described in this application, specially taking in consideration the rarity of the condition. The exposure results expected to be obtained by the proposed regime in the paediatric population were shown to be similar to the ones observed in the adult population.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

Dose-response studies have not been performed although pivotal trial has a dose-escalation phase.

5.3.2. Main study

5.3.2.1. MEX-MN-301

5.3.2.1.1. Study title

An Open-label, non-Comparative Study to Evaluate the Steady-State Pharmacokinetics, Safety, and Efficacy of Mexiletine in Adolescents and Children with Myotonic Disorders.

5.3.2.1.2. Study design

Open-label, multi-centre, single arm, interventional study to describe the steady-state PK, safety, and efficacy of mexiletine in paediatric patients (6 to <18 years of age) with myotonic disorders. Patients who meet the eligibility criteria were enrolled stepwise, sequentially in 2 cohorts by age groups. The overall treatment duration for each cohort was approximately 56 days (8 weeks): a dose titration phase of 4 weeks and the maintenance phase of 4 weeks. The overall study duration was approximately 22 months (Figure 2).

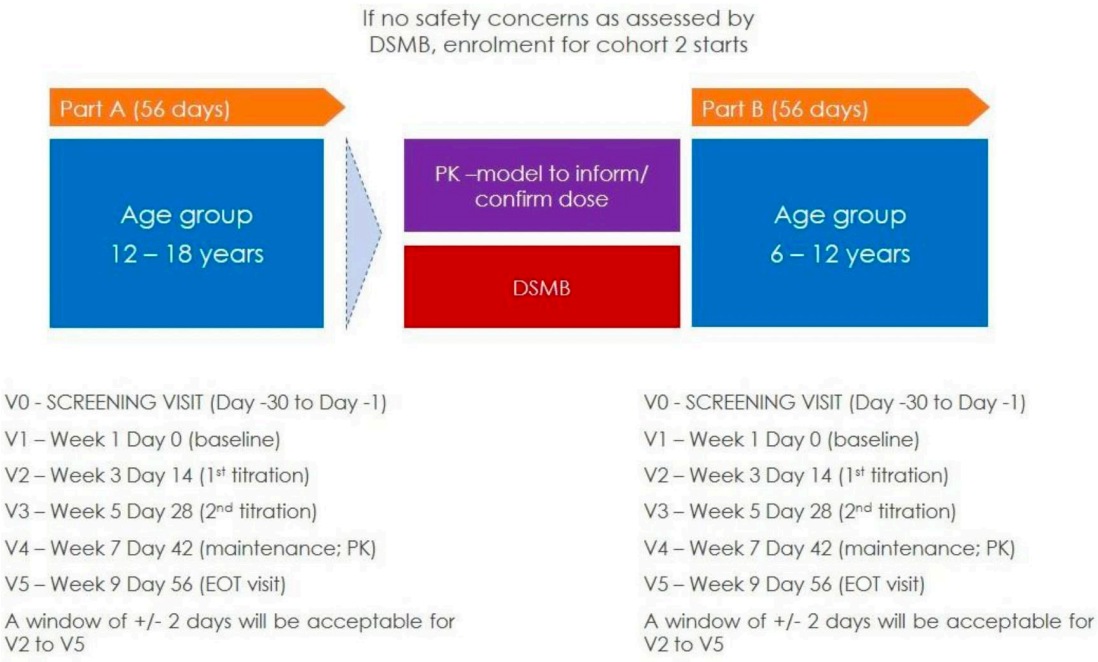

Figure 1. Schematic representation of study MEX-NM-301 design

5.3.2.1.2.1. Treatment

Patients who met the eligibility criteria were enrolled stepwise, sequentially in two cohorts by age groups.

- *Cohort 1* – Adolescents aged 12 to <18 years, were enrolled first. If no safety concerns were observed (based on data evaluation by the Data Safety Monitoring Board [DSMB]), and the dose for the age group 6 to <12 years was confirmed by PK model, enrolment for Cohort 2 began.
- *Cohort 2* – Cohort 2 enrolled children aged 6 to < 12 years, both inclusive. The dosing for this cohort was confirmed by the PK model based on PK data obtained from the adolescents' cohort prior to commencing.

The overall treatment duration for each cohort was approximately 56 days (8 weeks): a dose titration phase of 4 weeks and the maintenance phase of 4 weeks. The overall study duration was approximately 22 months.

Namuscla is formulated as hard gelatine capsules. Namuscla was started as a once-a-day (QD) treatment regimen (in the morning) and the dose was escalated every 2 weeks as per investigator judgement depending on the patient response and tolerability. Dose was escalated to BID at Day 14 (morning and evening) and TID at Day 28 (morning, midday and evening). The starting doses and the planned dose escalations of Namuscla (mexiletine hydrochloride) by weight are presented below.

Body weight in kg	Mexiletine total daily dose[1]		
	Week 1 – 2	Week 3 – 4	Week 5 - 6 and Maintenance (Week 7 – 8)
20 < 30 kg	62 mg (as 1 x 62 mg capsules)	124 mg (as 2 x 62 mg capsules)	186 mg (as 3 x 62 mg capsules)
30 < 40 kg	83 mg (as 1 x 83 mg capsule)	166 mg (as 2 x 83 mg capsules)	249 mg (as 3 x 83 mg capsules)
40 < 60 kg	124 mg (as 2 x 62 mg capsules)	248 mg (as 4 x 62 mg capsules)	372 mg (as 6 x 62 mg capsules)
≥ 60 kg	167 mg (as 1 x 167 mg capsule)	333 mg (as 2 x 167 mg capsules)	500 mg (as 3 x 167 mg capsules)

1 Administered as Mexiletine HCl 75 mg capsules (containing 62 mg of mexiletine), Mexiletine HCl 100 mg capsules (containing 83 mg of mexiletine) or Mexiletine HCl 200 mg capsules (containing 167 mg of mexiletine).

Dose Escalation: Patients/caregivers were instructed to commence Namuscla by taking one capsule a day with their breakfast for the first 2 weeks. The first dose was given at the clinic (Day 0) and sufficient medicine for 2 weeks was dispensed at this visit. During the third week (at V2) patients/caregivers were instructed to increase their Namuscla dose by taking a second capsule with their next meal (dinner). During the fifth week (at V3) patients/caregivers were instructed to add a third capsule with their third meal and continue with three capsules thereafter (around breakfast, lunch and dinner). Study medication was preferably taken with meals around approximately the same time daily. Date, time and dose of medicine (1 cap, 2 caps) taken was recorded in the patient diary on a daily basis.

Each patient was dispensed study drug capsule in sufficient quantity until next study visit. Patients took the study medication as prescribed by the investigator, preferably with food and at the same time daily. For patients who were not able to swallow capsules, capsule contents were opened and sprinkled on food or mixed with milk/juice. At the time of the study, only the 200 mg strength was approved for marketing as Namuscla. The lower strengths were investigational products (IPs) that had been developed according to the requirements of paediatric dosing. The mexiletine total daily dose was based on body weight and ranged from 186 to 500 mg during the maintenance period.

Reduction of Study Medication doses was allowed in the event of side effects (based on investigator decision). Details of dose reduction, temporary discontinuation along with reasons for the same, were recorded in the CRF.

5.3.2.1.2.2. Randomisation

Not applicable.

5.3.2.1.2.3. Blinding

Not applicable.

5.3.2.1.2.4. Patient population

Two clinical research centres located in France participated in the Study (Hopital Necker-Enfants Malades and Hopital Armand Trousseau).

Inclusion Criteria:

1. Male or female patients aged ≥ 6 and < 18 years who are able to comply with the study conditions
2. A genetically confirmed diagnosis of NDM or DM (DM1or DM2)
3. Presence of clinical symptoms of myotonia (hand grip myotonia, myotonia in the leg muscles, any other myotonia symptoms)
4. No significant cardiac abnormalities as determined by a cardiologist's assessment of the ECG and echocardiogram performed within 3 months prior to enrolment in the study. (if not done within 3 months before trial, ECG and echocardiogram assessments will be performed at screening)
5. No history of any significant liver disorder
6. Patients receiving mexiletine treatment agree to stop treatment at least 7 days prior to initiation of treatment with Namuscla
7. Patients receiving other antimyotonic treatment agree to stop treatment for at least 7 times the half-life of respective drug
8. Laboratory investigations for haematology, biochemistry, and urinalysis at screening are within normal range, or showing no clinically relevant abnormal values, as judged by the Investigator
9. Female patients of childbearing potential must be using an acceptable form of birth control as determined by the Investigator (e.g., oral contraception, implantable, injectable/transdermal hormonal contraception, intrauterine device (IUD), barrier methods), tubal ligation or have a vasectomized partner or are practicing abstinence.
10. Patients able to provide assent to study participation and a parent or legal guardian able to sign written informed consent prior to study entry.

Exclusion Criteria:

1. Any contra-indication to mexiletine as listed in the Namuscla Summary of Product Characteristics (SmPC):
    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 (class Ia, Ic, III antiarrhythmics): Co-administration of mexiletine and antiarrhythmics inducing torsades de pointes (class Ia: quinidine, procainamide, disopyramide, ajmaline; class Ic: encainide, flecainide, propafenone, moricizine; class III: amiodarone, sotalol, ibutilide, dofetilide, dronedarone, vernakalant) increases the risk of potentially lethal torsades de pointes.

l. Co-administration with medicinal products with narrow therapeutic index

2. Any other neurological or psychiatric condition that might affect the assessment of the study measurements
3. Any clinically significant illness, laboratory findings, ECG, or other clinical symptoms, which in the opinion of the Investigator could affect the patient's optimal participation in the study
4. Strong inducer or inhibitor of CYP2D6 or CYP1A2 within 7 days prior to study drug administration
5. Any concurrent illness, or medications which could affect the muscle function
6. Seizure disorder, diabetes mellitus requiring treatment by insulin
7. Pregnant or breastfeeding
8. Concurrent participation in any other clinical trial.

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1. Primary objectives

The co-primary objectives of this study are:

- To evaluate the safety of mexiletine in adolescents (aged 12 to <18 years) and children (aged 6 to <12 years) for the treatment of myotonic disorders
- To evaluate the efficacy of mexiletine for the treatment of myotonic disorders

The number of patients in this study was not hypothesis driven; rather as agreed with PDCO. Thus, the endpoints, either with the wording "primary" or "secondary", were all not statistically powered.

5.3.2.1.3.2. Estimand for the primary objective

No estimands were defined.

5.3.2.1.3.3. Secondary objectives

- To evaluate the efficacy of mexiletine for the treatment of myotonic disorders as assessed by patient-reported outcomes
- To evaluate effectiveness and tolerability of mexiletine as captured by Clinical Global Impression (CGI) scale indices
- To determine changes in health-related quality-of-life as measured by the PedsQL Quality of Life and Neuromuscular module.
- To determine the steady-state pharmacokinetics (PK) of mexiletine in children (6 to <12 years) and adolescents (aged 12 to <18 years)

- To assess the acceptability of the capsule formulation.
- To assess palatability of alternative administration (capsule content with milk/juice or sprinkled over yoghurt) by 5-point facial hedonic scale correlated with 100-point VAS

5.3.2.1.3.4. Estimands for the secondary objectives

No estimands were defined.

5.3.2.1.4. Results

5.3.2.1.4.1. Participant flow and numbers analysed

The study started on 03 September 2021 and ended on 13 June 2024. From 14 subjects screened, 2 were excluded (1 withdrew consent and 1 screen failure). Remaining 12 subjects completed the study (12/12). No subjects withdrew or were discontinued early from the study after initiating treatment with IMP. The ITT and PP analysis populations included all 12 enrolled subjects with no exclusions (Figure 2).

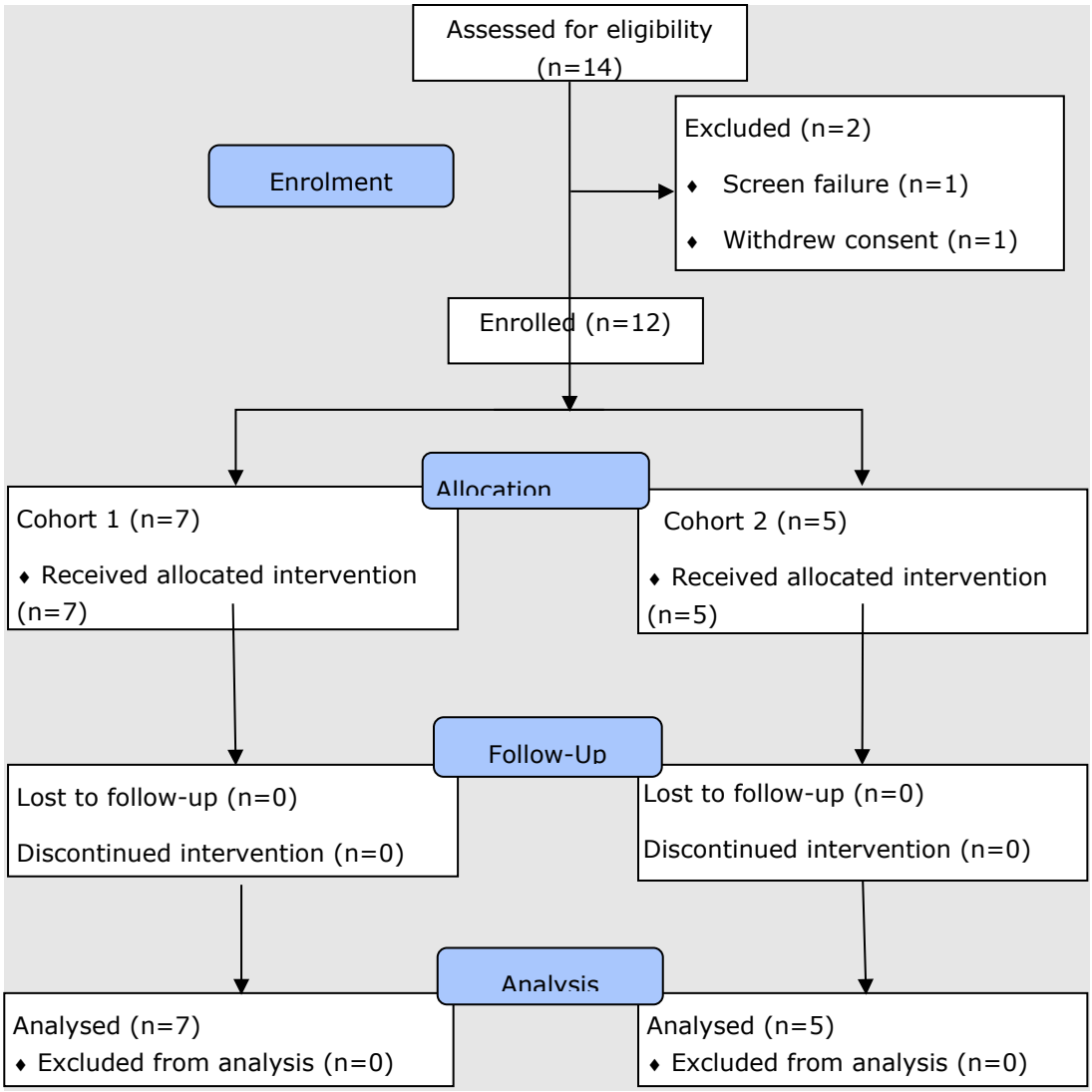

Figure 2. Participant flow

5.3.2.1.4.2.Deviations from study plan

No deviations from study plan were reported.

5.3.2.1.4.3. Baseline data

A total of 7 subjects were enrolled in Cohort 1; 4 female (57.1%) and 3 males (42.9%). The mean age of the study subjects was 13.4 years (range from 12 to 16 years). The mean body mass index (BMI) of the study subjects was 20.6 kg/m^2 (range from 12.9 to 24.9 kg/m^2). A total of 5 subjects were enrolled in Cohort 2; 3 female (60%) and 2 males (40%).

The mean age of the study subjects was 8.2 years (range from 6 to 10 years). The mean body mass index (BMI) of the study subjects was 17.1 kg/m^2 (range from 16.2 to 18.5 kg/m^2).

Baseline myotonic disorder type by cohort group is detailed in the table below.

***Table 5*. Listing of baseline myotonic disorders type by cohort group**

	Cohort 1		Cohort 2	
NDM	**5**	Chloride channelopathy or Thomsen disease (3) Congenital myotonia linked to CLCN1 gene (2)	**5**	Chloride channelopathy or Thomsen disease (3) Paramyotomia congenita (2)
DM1	**2**			

CLCN1: Chloride Voltage-Gated Channel 1; DM: Myotonic dystrophy type 1; NDM: Nondystrophic myotonia

Most subjects (58.3%) reported significant medical history. The most frequently reported SOCs were Immune system disorders including preferred terms of dust allergies (2 subjects), food allergies (1 subject), and seasonal allergies (1 subject). Other medical history was reported by 7 subjects (58.3%). The most frequently reported SOCs were Injury, poisoning and procedural complications including the preferred term of fall (5 subjects). Similar rates of medical history were reported between cohorts.

Prior medication use was reported by 4 subjects (33.3%); 3 subjects in Cohort 1 and 1 subject in Cohort 2. The most frequently reported pharmacological class was antihistamines including the standard term of levocetirizine (2 subjects). Concomitant medication use was reported by 7 subjects (58.3%); 6 subjects in Cohort 1 and 1 subject in Cohort 2. The most frequently reported pharmacological class was Analgesic/Antipyretic including the standard term of paracetamol (4 subjects). No prohibited medications were reported during the study.

5.3.2.1.4.4. Outcomes and estimation

Primary Efficacy analysis

Visual Analogue Scale (VAS)

A summary of the VAS scale results for stiffness, pain, and fatigue are provided in the table below (ITT population and PP population).

Table 6. Summary of Visual Analogue Scale (ITT Population/PP Population)

VAS Test Name	Visit	Statistics	Cohort 1 (N = 7)	Cohort 2 (N = 5)	Total (N = 12)
Stiffness	Baseline	n	7	3	10
		Mean (SD)	68.4 (23.04)	64.3 (40.70)	67.2 (26.94)
		Median	77.0	73.0	75.0
		Min, Max	23, 90	20, 100	20, 100
	Visit 2	n	7	3	10
		Mean (SD)	35.0 (27.31)	54.3 (30.66)	40.8 (28.17)
		Median	28.0	58.0	36.0
		Min, Max	2, 80	22, 83	2, 83
	Change from baseline to Visit 2	n	7	3	10
		Mean (SD)	-33.4 (24.72)	-10.0 (28.00)	-26.4 (26.64)
		Median	-21.0	2.0	-21.0
		Min, Max	-67, -6	-42, 10	-67, 10
	Visit 3	n	7	3	10
		Mean (SD)	25.6 (30.09)	49.0 (19.00)	32.6 (28.50)
		Median	14.0	54.0	25.5
		Min, Max	3, 88	28, 65	3, 88
	Change from baseline to Visit 3	n	7	3	10
		Mean (SD)	-42.9 (29.59)	-15.3 (43.02)	-34.6 (34.23)
		Median	-52.0	-35.0	-47.5
		Min, Max	-74, 10	-45, 34	-74, 34
	Visit 4	n	7	3	10
		Mean (SD)	21.9 (30.76)	8.3 (7.23)	17.8 (26.18)
		Median	6.0	12.0	9.0
		Min, Max	0, 85	0, 13	0, 85
	Change from baseline to Visit 4	n	7	3	10
		Mean (SD)	-46.6 (30.04)	-56.0 (46.70)	-49.4 (33.27)
		Median	-52.0	-61.0	-56.5
		Min, Max	-77, -1	-100, -7	-100, -1
	Visit 5 (End of Study)	n	7	3	10
		Mean (SD)	14.7 (19.86)	42.7 (30.62)	23.1 (25.56)
		Median	3.0	26.0	16.0
		Min, Max	2, 50	24, 78	2, 78
	Change from baseline to Visit 5 (End of Study)	n	7	3	10
		Mean (SD)	-53.7 (19.62)	-21.7 (27.50)	-44.1 (25.77)
		Median	-54.0	-22.0	-50.5
		Min, Max	-75, -21	-49, 6	-75, 6

Pain	Baseline	n	7	3	10
		Mean (SD)	15.7 (17.40)	7.3 (6.66)	13.2 (15.11)
		Median	13.0	9.0	11.0
		Min, Max	1, 50	0, 13	0, 50
	Visit 2	n	7	3	10
		Mean (SD)	4.7 (5.19)	4.3 (6.66)	4.6 (5.27)
		Median	3.0	1.0	2.0
		Min, Max	0, 12	0, 12	0, 12
	Change from baseline to Visit 2	n	7	3	10
		Mean (SD)	-11.0 (18.33)	-3.0 (4.36)	-8.6 (15.59)
		Median	-3.0	-1.0	-2.0
		Min, Max	-47, 3	-8, 0	-47, 3
	Visit 3	n	7	3	10
		Mean (SD)	7.6 (16.14)	13.3 (21.39)	9.3 (16.83)
		Median	2.0	2.0	2.0
		Min, Max	0, 44	0, 38	0, 44
	Change from baseline to Visit 3	n	7	3	10
		Mean (SD)	-8.1 (27.32)	6.0 (21.28)	-3.9 (25.39)
		Median	-11.0	2.0	-6.5
		Min, Max	-46, 43	-13, 29	-46, 43
	Visit 4	n	7	3	10
		Mean (SD)	5.9 (7.58)	11.0 (19.05)	7.4 (11.19)
		Median	1.0	0.0	0.5
		Min, Max	0, 18	0, 33	0, 33
	Change from baseline to Visit 4	n	7	3	10
		Mean (SD)	-9.9 (20.05)	3.7 (18.77)	-5.8 (19.72)
		Median	-13.0	0.0	-7.0
		Min, Max	-42, 13	-13, 24	-42, 24
	Visit 5 (End of Study)	n	7	3	10
		Mean (SD)	2.1 (2.91)	11.7 (20.21)	5.0 (10.84)
		Median	0.0	0.0	0.0
		Min, Max	0, 7	0, 35	0, 35
	Change from baseline to Visit 5 (End of Study)	n	7	3	10
		Mean (SD)	-13.6 (18.32)	4.3 (19.86)	-8.2 (19.65)
		Median	-13.0	0.0	-7.0
		Min, Max	-50, 2	-13, 26	-50, 26

Weakness and fatigue	Baseline	n	7	3	10
		Mean (SD)	34.9 (24.70)	39.3 (14.57)	36.2 (21.42)
		Median	32.0	44.0	34.5
		Min, Max	5, 80	23, 51	5, 80
	Visit 2	n	7	3	10
		Mean (SD)	29.7 (25.70)	38.0 (17.06)	32.2 (22.83)
		Median	19.0	33.0	27.0
		Min, Max	3, 81	24, 57	3, 81
	Change from baseline to Visit 2	n	7	3	10
		Mean (SD)	-5.1 (24.07)	-1.3 (30.62)	-4.0 (24.45)
		Median	0.0	-18.0	-9.0
		Min, Max	-33, 37	-20, 34	-33, 37
	Visit 3	n	7	3	10
		Mean (SD)	25.4 (24.05)	32.3 (14.50)	27.5 (21.06)
		Median	26.0	32.0	29.0
		Min, Max	2, 66	18, 47	2, 66
	Change from baseline to Visit 3	n	7	3	10
		Mean (SD)	-9.4 (33.85)	-7.0 (27.07)	-8.7 (30.47)
		Median	-6.0	-19.0	-12.5
		Min, Max	-46, 54	-26, 24	-46, 54
	Visit 4	n	7	3	10
		Mean (SD)	25.0 (28.33)	34.7 (14.15)	27.9 (24.52)
		Median	17.0	27.0	26.5
		Min, Max	0, 82	26, 51	0, 82
	Change from baseline to Visit 4	n	7	3	10
		Mean (SD)	-9.9 (41.87)	-4.7 (28.57)	-8.3 (36.83)
		Median	-20.0	-17.0	-18.5
		Min, Max	-48, 77	-25, 28	-48, 77
	Visit 5 (End of Study)	n	7	3	10
		Mean (SD)	13.9 (12.40)	22.3 (27.47)	16.4 (16.94)
		Median	11.0	8.0	10.0
		Min, Max	0, 37	5, 54	0, 54
	Change from baseline to Visit 5 (End of Study)	n	7	3	10
		Mean (SD)	-21.0 (22.91)	-17.0 (41.87)	-19.8 (27.26)
		Median	-26.0	-36.0	-27.0
		Min, Max	-48, 10	-46, 31	-48, 31

Abbreviations: N = Number of subjects in specified cohort; n = Number of subjects in specified category.
Reference listing 16.2.6.1

Numerical reductions (improvement) from baseline were observed with VAS scale results for stiffness in each cohort and overall at all visits; the mean (SD) VAS change from baseline at Visit 5 (EOS) was -53.7 (19.62), -21.7 (27.5), and -44.1 (25.77) in Cohort 1, Cohort 2, and overall, respectively.

Some numerical reductions (improvement) from baseline were observed with VAS scale results for pain; the mean (SD) VAS change from baseline at Visit 5 (EOS) was -13.6 (18.32), 4.3 (19.86), and -8.2 (19.65) in Cohort 1, Cohort 2, and overall, respectively.

Numerical reductions (improvement) from baseline were observed with VAS scale results for weakness and fatigue in each cohort and overall at all visits; the mean (SD) VAS change from baseline at Visit 5 (EOS) was -21.0 (22.91), -17.0 (41.87), and -19.8 (27.26) in Cohort 1, Cohort 2, and overall, respectively.

FACES (FAS)

Two of the 5 subjects in Cohort 2 completed the FAS scale (FAS scale only utilized in children aged 6 to 8 years (subset of Cohort 2)). The FAS stiffness, pain, and weakness/fatigue results were variable over time. The mean (SD) change from baseline in FAS stiffness scores at Visit 5 (EOS) was -3 (1.41) in Cohort 2. The mean (SD) change from baseline in FAS pain scores at Visit 5 (EOS) was -1 (1.41) in Cohort 2. The mean (SD) change from baseline in FAS weakness/fatigue scores at Visit 5 (EOS) was 2 (0) in Cohort 2.

A summary of the FAS scores results for stiffness, pain, and fatigue are provided in the table below (ITT population and PP population).

Table 7. Summary of FACES Scores (FAS) (ITT Population/PP Population)

FAS Test Name	Visit	Statistics	Cohort 1 (N = 7)	Cohort 2 (N = 5)	Total (N = 12)
Stiffness	Baseline	n	0	2	2
		Mean (SD)	NE	5.0 (1.41)	5.0 (1.41)
		Median	NE	5.0	5.0
		Min, Max	NE	4, 6	4, 6
	Visit 2	n	0	2	2
		Mean (SD)	NE	6.0 (2.83)	6.0 (2.83)
		Median	NE	6.0	6.0
		Min, Max	NE	4, 8	4, 8
	Change from baseline to Visit 2	n	0	2	2
		Mean (SD)	NE	1.0 (4.24)	1.0 (4.24)
		Median	NE	1.0	1.0
		Min, Max	NE	-2, 4	-2, 4

	Visit 3	n	0	2	2
		Mean (SD)	NE	5.0 (1.41)	5.0 (1.41)
		Median	NE	5.0	5.0
		Min, Max	NE	4, 6	4, 6
	Change from baseline to Visit 3	n	0	2	2
		Mean (SD)	NE	0.0 (2.83)	0.0 (2.83)
		Median	NE	0.0	0.0
		Min, Max	NE	-2, 2	-2, 2
	Visit 4	n	0	2	2
		Mean (SD)	NE	5.0 (4.24)	5.0 (4.24)
		Median	NE	5.0	5.0
		Min, Max	NE	2, 8	2, 8
	Change from baseline to Visit 4	n	0	2	2
		Mean (SD)	NE	0.0 (5.66)	0.0 (5.66)
		Median	NE	0.0	0.0
		Min, Max	NE	-4, 4	-4, 4
	Visit 5 (End of Study)	n	0	2	2
		Mean (SD)	NE	2.0 (0.00)	2.0 (0.00)
		Median	NE	2.0	2.0
		Min, Max	NE	2, 2	2, 2
	Change from baseline to Visit 5 (End of Study)	n	0	2	2
		Mean (SD)	NE	-3.0 (1.41)	-3.0 (1.41)
		Median	NE	-3.0	-3.0
		Min, Max	NE	-4, -2	-4, -2
Pain	Baseline	n	0	2	2
		Mean (SD)	NE	4.0 (0.00)	4.0 (0.00)
		Median	NE	4.0	4.0
		Min, Max	NE	4, 4	4, 4
	Visit 2	n	0	2	2
		Mean (SD)	NE	6.0 (0.00)	6.0 (0.00)
		Median	NE	6.0	6.0
		Min, Max	NE	6, 6	6, 6
	Change from baseline to Visit 2	n	0	2	2
		Mean (SD)	NE	2.0 (0.00)	2.0 (0.00)
		Median	NE	2.0	2.0
		Min, Max	NE	2, 2	2, 2

	Visit 3	n	0	2	2
		Mean (SD)	NE	5.0 (4.24)	5.0 (4.24)
		Median	NE	5.0	5.0
		Min, Max	NE	2, 8	2, 8
	Change from baseline to Visit 3	n	0	2	2
		Mean (SD)	NE	1.0 (4.24)	1.0 (4.24)
		Median	NE	1.0	1.0
		Min, Max	NE	-2, 4	-2, 4
	Visit 4	n	0	2	2
		Mean (SD)	NE	4.0 (0.00)	4.0 (0.00)
		Median	NE	4.0	4.0
		Min, Max	NE	4, 4	4, 4
	Change from baseline to Visit 4	n	0	2	2
		Mean (SD)	NE	0.0 (0.00)	0.0 (0.00)
		Median	NE	0.0	0.0
		Min, Max	NE	0, 0	0, 0
	Visit 5 (End of Study)	n	0	2	2
		Mean (SD)	NE	3.0 (1.41)	3.0 (1.41)
		Median	NE	3.0	3.0
		Min, Max	NE	2, 4	2, 4
	Change from baseline to Visit 5 (End of Study)	n	0	2	2
		Mean (SD)	NE	-1.0 (1.41)	-1.0 (1.41)
		Median	NE	-1.0	-1.0
		Min, Max	NE	-2, 0	-2, 0
Weakness and fatigue	Baseline	n	0	2	2
		Mean (SD)	NE	4.0 (2.83)	4.0 (2.83)
		Median	NE	4.0	4.0
		Min, Max	NE	2, 6	2, 6
	Visit 2	n	0	2	2
		Mean (SD)	NE	5.0 (1.41)	5.0 (1.41)
		Median	NE	5.0	5.0
		Min, Max	NE	4, 6	4, 6
	Change from baseline to Visit 2	n	0	2	2
		Mean (SD)	NE	1.0 (4.24)	1.0 (4.24)
		Median	NE	1.0	1.0
		Min, Max	NE	-2, 4	-2, 4

Visit 3	n	0	2	2
	Mean (SD)	NE	5.0 (4.24)	5.0 (4.24)
	Median	NE	5.0	5.0
	Min, Max	NE	2, 8	2, 8
Change from baseline to Visit 3	n	0	2	2
	Mean (SD)	NE	1.0 (1.41)	1.0 (1.41)
	Median	NE	1.0	1.0
	Min, Max	NE	0, 2	0, 2
Visit 4	n	0	2	2
	Mean (SD)	NE	7.0 (1.41)	7.0 (1.41)
	Median	NE	7.0	7.0
	Min, Max	NE	6, 8	6, 8
Change from baseline to Visit 4	n	0	2	2
	Mean (SD)	NE	3.0 (1.41)	3.0 (1.41)
	Median	NE	3.0	3.0
	Min, Max	NE	2, 4	2, 4
Visit 5 (End of Study)	n	0	2	2
	Mean (SD)	NE	6.0 (2.83)	6.0 (2.83)
	Median	NE	6.0	6.0
	Min, Max	NE	4, 8	4, 8
Change from baseline to Visit 5 (End of Study)	n	0	2	2
	Mean (SD)	NE	2.0 (0.00)	2.0 (0.00)
	Median	NE	2.0	2.0
	Min, Max	NE	2, 2	2, 2

Abbreviations: N = Number of subjects in specified cohort; n = Number of subjects in specified category; NE = Not Evaluable.
Reference listing 16.2.6.1

Clinical Assessment of Myotonia (Functional Assessment)

A summary of the clinical assessments of myotonia results, including handgrip (primary outcome), is provided in the table below (ITT population and PP population).

Table 8. Summary of clinical assessment of myotonia (ITT Population/PP Population)

Test Name	Visit	Statistics	Cohort 1 (N = 7)	Cohort 2 (N = 5)	Total (N = 12)
Hand Grip Myotonia Test score	Baseline	n	7	5	12
		Mean (SD)	0.326714 (0.1023958)	0.369200 (0.2858124)	0.344417 (0.1894799)
		Median	0.307000	0.317000	0.312000
		Min, Max	0.21400, 0.48800	0.15200, 0.85400	0.15200, 0.85400
	Visit 2	n	7	5	12
		Mean (SD)	0.265714 (0.0884076)	0.367000 (0.2547705)	0.307917 (0.1748893)
		Median	0.265000	0.277000	0.271000
		Min, Max	0.15800, 0.41400	0.17700, 0.81300	0.15800, 0.81300
	Change from baseline to Visit 2	n	7	5	12
		Mean (SD)	-0.061000 (0.0915460)	-0.002200 (0.0824057)	-0.036500 (0.0892041)
		Median	-0.056000	0.004000	-0.041500
		Min, Max	-0.18300, 0.06300	-0.11100, 0.11200	-0.18300, 0.11200
	Visit 3	n	5	5	10
		Mean (SD)	0.230200 (0.0651821)	0.376400 (0.3168135)	0.303300 (0.2289867)
		Median	0.217000	0.223000	0.220000
		Min, Max	0.15500, 0.31100	0.16800, 0.91900	0.15500, 0.91900
	Change from baseline to Visit 3	n	5	5	10
		Mean (SD)	-0.098400 (0.0660856)	0.007200 (0.0850129)	-0.045600 (0.0908334)
		Median	-0.090000	0.025000	-0.048500
		Min, Max	-0.20600, -0.02800	-0.13500, 0.07800	-0.20600, 0.07800
	Visit 4	n	6	5	11
		Mean (SD)	0.262167 (0.1363956)	0.326800 (0.2575378)	0.291545 (0.1922797)
		Median	0.231000	0.199000	0.205000
		Min, Max	0.14000, 0.51400	0.17300, 0.78000	0.14000, 0.78000
	Change from baseline to Visit 4	n	6	5	11
		Mean (SD)	-0.074667 (0.1141642)	-0.042400 (0.0820567)	-0.060000 (0.0974372)
		Median	-0.088000	-0.025000	-0.074000
		Min, Max	-0.19200, 0.13600	-0.16800, 0.03400	-0.19200, 0.13600
	Visit 5 (End of Study)	n	6	5	11
		Mean (SD)	0.271833 (0.1303770)	0.256400 (0.1091435)	0.264818 (0.1154511)
		Median	0.215500	0.204000	0.204000
		Min, Max	0.14700, 0.46800	0.16200, 0.40200	0.14700, 0.46800
	Change from baseline to Visit 5 (End of Study)	n	6	5	11
		Mean (SD)	-0.065000 (0.1027424)	-0.112800 (0.2136099)	-0.086727 (0.1554118)
		Median	-0.075500	0.006000	-0.074000
		Min, Max	-0.22500, 0.09000	-0.45200, 0.05200	-0.45200, 0.09000

Leg muscles (Timed-up and go [TUG] test)	Baseline	n	7	5	12
		Mean (SD)	7.964 (1.8168)	7.702 (1.8943)	7.855 (1.7673)
		Median	8.000	7.000	7.590
		Min, Max	5.00, 11.00	5.93, 10.90	5.00, 11.00
	Visit 2	n	7	5	12
		Mean (SD)	7.334 (1.4767)	8.626 (1.1530)	7.873 (1.4544)
		Median	7.270	9.000	7.700
		Min, Max	5.40, 10.00	7.00, 10.00	5.40, 10.00
	Change from baseline to Visit 2	n	7	5	12
		Mean (SD)	-0.630 (1.6882)	0.924 (1.9977)	0.018 (1.9095)
		Median	-0.100	1.000	0.000
		Min, Max	-3.73, 1.00	-1.90, 3.20	-3.73, 3.20
	Visit 3	n	7	5	12
		Mean (SD)	7.537 (1.6001)	8.400 (0.5477)	7.897 (1.3050)
		Median	7.000	8.000	8.000
		Min, Max	5.40, 10.00	8.00, 9.00	5.40, 10.00
	Change from baseline to Visit 3	n	7	5	12
		Mean (SD)	-0.427 (2.4832)	0.698 (2.0616)	0.042 (2.2901)
		Median	-1.540	1.320	0.100
		Min, Max	-2.80, 4.00	-2.90, 2.07	-2.90, 4.00
	Visit 4	n	6	5	11
		Mean (SD)	7.870 (2.0051)	8.388 (2.0675)	8.105 (1.9476)
		Median	7.420	8.110	7.840
		Min, Max	5.96, 11.00	6.00, 11.70	5.96, 11.70
	Change from baseline to Visit 4	n	6	5	11
		Mean (SD)	-0.172 (2.3533)	0.686 (3.3533)	0.218 (2.7327)
		Median	0.130	1.330	0.800
		Min, Max	-4.00, 3.00	-4.90, 4.02	-4.90, 4.02
	Visit 5 (End of Study)	n	7	5	12
		Mean (SD)	7.511 (1.9029)	7.900 (0.8944)	7.673 (1.5186)
		Median	7.220	8.000	7.610
		Min, Max	5.57, 10.00	7.00, 9.00	5.57, 10.00
	Change from baseline to Visit 5 (End of Study)	n	7	5	12
		Mean (SD)	-0.453 (2.7055)	0.198 (1.8729)	-0.182 (2.3196)
		Median	-0.780	0.820	0.410
		Min, Max	-5.00, 3.00	-2.90, 2.00	-5.00, 3.00

Action myotonia in eyelid muscles	Baseline	n	7	5	12
		Mean (SD)	0.714 (0.4880)	1.720 (2.0425)	1.133 (1.3839)
		Median	1.000	1.000	1.000
		Min, Max	0.00, 1.00	0.20, 5.20	0.00, 5.20
	Visit 2	n	6	5	11
		Mean (SD)	0.833 (0.4082)	4.080 (4.3488)	2.309 (3.2439)
		Median	1.000	1.000	1.000
		Min, Max	0.00, 1.00	1.00, 10.20	0.00, 10.20
	Change from baseline to Visit 2	n	6	5	11
		Mean (SD)	0.000 (0.0000)	2.360 (2.6130)	1.073 (2.0616)
		Median	0.000	0.800	0.000
		Min, Max	0.00, 0.00	0.00, 5.40	0.00, 5.40
	Visit 3	n	7	5	12
		Mean (SD)	0.600 (0.5033)	5.040 (5.7661)	2.450 (4.1780)
		Median	1.000	1.000	1.000
		Min, Max	0.00, 1.00	1.00, 13.40	0.00, 13.40
	Change from baseline to Visit 3	n	7	5	12
		Mean (SD)	-0.114 (0.3024)	3.320 (3.9411)	1.317 (2.9707)
		Median	0.000	0.800	0.000
		Min, Max	-0.80, 0.00	0.00, 8.20	-0.80, 8.20
	Visit 4	n	6	5	11
		Mean (SD)	0.713 (0.4528)	5.880 (8.2080)	3.062 (5.8593)
		Median	1.000	1.000	1.000
		Min, Max	0.00, 1.00	0.00, 19.40	0.00, 19.40
	Change from baseline to Visit 4	n	6	5	11
		Mean (SD)	-0.120 (0.2939)	4.160 (6.2119)	1.825 (4.5249)
		Median	0.000	0.800	0.000
		Min, Max	-0.72, 0.00	-0.40, 14.20	-0.72, 14.20
	Visit 5 (End of Study)	n	6	5	11
		Mean (SD)	0.833 (0.4082)	3.920 (5.4801)	2.236 (3.8333)
		Median	1.000	1.000	1.000
		Min, Max	0.00, 1.00	1.00, 13.60	0.00, 13.60
	Change from baseline to Visit 5 (End of Study)	n	6	5	11
		Mean (SD)	0.000 (0.0000)	2.200 (3.4928)	1.000 (2.4900)
		Median	0.000	0.800	0.000
		Min, Max	0.00, 0.00	0.00, 8.40	0.00, 8.40

Right-hand flexor muscles	Baseline	n	7	5	12
		Mean (SD)	1.486 (0.9582)	1.780 (1.8281)	1.608 (1.3187)
		Median	1.400	1.000	1.200
		Min, Max	0.00, 3.00	0.50, 5.00	0.00, 5.00
	Visit 2	n	6	5	11
		Mean (SD)	1.267 (0.3933)	1.540 (1.2402)	1.391 (0.8443)
		Median	1.100	1.200	1.200
		Min, Max	1.00, 2.00	0.10, 3.40	0.10, 3.40
	Change from baseline to Visit 2	n	6	5	11
		Mean (SD)	-0.467 (0.6408)	-0.240 (0.9915)	-0.364 (0.7827)
		Median	-0.200	0.000	0.000
		Min, Max	-1.60, 0.00	-1.60, 0.70	-1.60, 0.70
	Visit 3	n	6	5	11
		Mean (SD)	1.250 (0.6124)	3.680 (5.4509)	2.355 (3.6990)
		Median	1.000	1.000	1.000
		Min, Max	0.50, 2.00	1.00, 13.40	0.50, 13.40
	Change from baseline to Visit 3	n	6	5	11
		Mean (SD)	-0.150 (1.4335)	1.900 (3.6442)	0.782 (2.7360)
		Median	-0.450	0.500	0.000
		Min, Max	-2.00, 2.00	0.00, 8.40	-2.00, 8.40
	Visit 4	n	6	5	11
		Mean (SD)	1.045 (0.5515)	1.500 (0.8832)	1.252 (0.7215)
		Median	1.000	1.000	1.000
		Min, Max	0.27, 2.00	0.60, 2.50	0.27, 2.50
	Change from baseline to Visit 4	n	6	5	11
		Mean (SD)	-0.355 (1.3799)	-0.280 (1.3103)	-0.321 (1.2808)
		Median	-0.500	0.000	0.000
		Min, Max	-2.00, 2.00	-2.50, 1.00	-2.50, 2.00
	Visit 5 (End of Study)	n	6	5	11
		Mean (SD)	1.167 (0.4082)	1.360 (0.4980)	1.255 (0.4390)
		Median	1.000	1.200	1.000
		Min, Max	1.00, 2.00	1.00, 2.20	1.00, 2.20
	Change from baseline to Visit 5 (End of Study)	n	6	5	11
		Mean (SD)	-0.233 (1.3292)	-0.420 (1.3461)	-0.318 (1.2719)
		Median	-0.200	0.000	0.000
		Min, Max	-2.00, 2.00	-2.80, 0.50	-2.80, 2.00

Abbreviations: N = Number of subjects in specified cohort; n = Number of subjects in specified category.
Reference listing 16.2.6.2

The results of the clinical assessments of myotonia scores were variable over time.

The mean (SD) change from baseline in hand grip myotonia test scores at Visit 5 (EOS) was -0.06 (0.10), -0.11 (0.21), and -0.09 (0.16) in Cohort 1, Cohort 2, and overall, respectively.

Secondary Efficacy analysis

The mean (SD) change from baseline in leg muscles (timed-up and go [TUG] test) test scores at Visit 5 (EOS) was -0.45 (2.7), 0.20 (1.8), and -0.18 (2.3) in Cohort 1, Cohort 2, and overall, respectively.

The mean (SD) change from baseline in action myotonia in eyelid muscles test scores at Visit 5 (EOS) was 0 (0), 2.2 (3.5), and 1.0 (2.5) in Cohort 1, Cohort 2, and overall, respectively.

The mean (SD) change from baseline in right-hand flexor muscles test scores at Visit 5 (EOS) was -0.23 (1.3), -0.42 (1.35), and -0.32 (1.27) in Cohort 1, Cohort 2, and overall, respectively.

Summary of Paediatric Quality of Life (Pedsql) Questionnaire

Numerical improvement from baseline were observed with all Pedsql scores in each cohort and overall at Visit 5. The mean (SD) change from baseline in total Pedsql score by patient at Visit 5 (EOS) was 11.7 (12.92), 14.4 (10.36), and 12.8 (11.49) in Cohort 1, Cohort 2, and overall, respectively. The mean (SD) change from baseline in total Pedsql score by parent at Visit 5 (EOS) was 12.1 (10.67), 6.8 (15.97), and 9.9 (12.75) in Cohort 1, Cohort 2, and overall, respectively.

Summary of Neuromuscular Modules

The mean (SD) change from baseline in total neuromuscular module results by patient at Visit 5 (EOS) was 11.7 (10.69), 5.0 (3.75), and 9.3 (9.18) in Cohort 1, Cohort 2, and overall, respectively. The mean (SD) change from baseline in total neuromuscular module results by parent at Visit 5 (EOS) was 4.4 (5.06), -1.0 (20.09), and 2.2 (12.98) in Cohort 1, Cohort 2, and overall, respectively.

Myotonia Behaviour Scale (MBS)

The mean (SD) change from baseline in MBS scores at Visit 5 (EOS) was -1.7 (1.11), -0.2 (0.84), and -1.1 (1.24) in Cohort 1, Cohort 2, and overall, respectively.

Clinical Global Impression (CGI)

CGI scores of "very efficient" or "good" at visit 5 were reported in 11 of 12 subjects (92%).

5.3.2.1.4.5. Pre-defined and post-hoc subgroup analyses

No subgroup analyses were planned nor relevant ad hoc subgroup analyses were performed.

5.3.3. Clinical studies in special populations

***Table 9*: Clinical studies in special populations**

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	0	0
Hepatic impairment** patients (Subjects number /total number)	0	0
Paediatric patients >6 years and <18 years (Subjects number /total number)	0	12/14
Paediatric patients <6 years (Subjects number /total number)	0	0/10 (planned/ongoing)
Age 65-74 (Subjects number /total number)	N/A	N/A
Age 75-84 (Subjects number /total number)	N/A	N/A
Age 85+ (Subjects number /total number)	N/A	N/A

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

5.3.5. Supportive study(ies)

PIP Study 8 - Population Pharmacokinetic Analysis of Mexiletine in Healthy Volunteers and Myotonic Patients.

The objective of this analysis was to characterize the pharmacokinetic profile of mexiletine in healthy individuals and patients in order to support dosing recommendations in children with myotonic disorders and to fulfil the requirements of the Paediatric Investigation Plan EMEA-002012-PIP01-16-M05, last modification approved 19 July 2024.

- The first aim was to use the population pharmacokinetic model for mexiletine previously developed (Report: Mexiletine preliminary population PK analysis, June 2017), based on previous pharmacokinetic studies in adult subjects and in one paediatric patient to verify the dosing of paediatric patients.
- The second aim to was analyse all the available mexiletine concentration data for all patients and to investigate the potential sources of variability in drug exposure.

The population PK model used data from adult studies, U79-0321 and MYOMEX, and paediatric data from a published source, Leheup et al 1986 and a study conducted by Lupin (Study 4). All subjects who had taken the study medication and for whom complete dosing information was available were included in the analysis. The data consisted of 319 valid mexiletine concentrations from 30 adults and 13 paediatric subjects.

This population pharmacokinetic analysis was conducted to fulfil the extrapolation, modelling, and simulation component of the Paediatric Investigation Plan, EMEA-002012-PIP01-16-M05, last modification approved 19 July 2024. Population PK modelling and simulations were conducted for mexiletine for dose selection within paediatric subsets. In addition, dose linearity and potential accumulation as well as variability among subjects was investigated.

Prior to the enrolment of the youngest subject cohort, simulations were performed based on body weight of 25 kg and 75 kg using the PK parameters from the base model. These simulations showed good agreement with a dose of ~75 mg TID for a 25 kg paediatric patient and ~100 mg TID for a 35 kg patient as compared to the exposure of 200 mg in a 75 kg adult patient. These simulations were used to inform dosing in the young patient cohort, 6-12 years old, in Study 4.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.7. Overall discussion and conclusions on clinical efficacy

5.3.7.1. Discussion

The MAH ied for a Line and Paediatric extension Application for Namuscla (mexiletine) to add two strengths of hard capsules for oral use (75 mg and 100 mg mexiletine HCL corresponding to 62.48 mg and 83.31 mg of mexiletine, respectively) and to extend the current indication for adults for the 'symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders' to children and adolescents from 6 to up to 18 years of age.

Myotonic disorders are a heterogeneous group of hereditary rare diseases with only symptomatic treatment. Based on epidemiological data, approximately 2 in 10,000 people are affected with myotonic disorders in the EU. Mexiletine was granted orphan designation for 'treatment of myotonic disorders' and is the only approved product for NDM disorders in adults.

The pivotal study supporting this application is the MEX-MN-301 Study to evaluate the safety, efficacy and steady-state PK of mexiletine in adolescents (aged 12 to <18 years) and children (aged 6 to <12 years) with myotonic disorders. MEX-MN-301 Study was an open-label, multi-centre, single arm, interventional study where patients who meet the eligibility criteria were enrolled stepwise, sequentially in 2 cohorts by age groups. Primary and secondary objectives are relevant and clearly defined. Sample size was not hypothesis driven (at least 10 evaluable subjects) and the efficacy endpoints chosen were based on those commonly used in routine clinical practice for adults, modified according to the patient's age and ability to participate (VAS and FAS score for muscle stiffness, pain; Functional Assessment of myotonia; Pedsql Questionnaire; Neuromuscular Modules; MBS; CGI). These issues were reviewed and accepted by the Paediatric Committee (PDCO) as part of the PIP approval process and therefore, all endpoints are not statistically powered. Data was collected and analysed only descriptively.

A total of 12 subjects were enrolled in the pivotal study: 7 subjects in Cohort 1 (4 female and 3 males; mean age 13.4 years) and 5 subjects in Cohort 2 (3 female and 2 males; mean age 8.2 years). Discrepancies between the 2 cohort groups (age, height, weight and BMI) were expected due to the protocol study design itself. There were no subject withdrawals, discontinuations, or losses to follow-up. Compliance was good, no major protocol deviations were reported, and all enrolled subjects were

included in both ITT and PP analyses. The potential impact of including 2 subjects in Cohort 1 with myotonic dystrophy type 1 (DM1) on the overall study results, particularly regarding the heterogeneity of the population and how this might affect the interpretation of efficacy and safety outcomes was not addressed by the MAH. Nevertheless, due to the limited size of the population of the pivotal study, the extension of the indication to the paediatric population should rely in the extrapolation from the data in adults through a PK bridge (see MO) and this is not expected to be influenced by the type of myotonic dystrophy of the patients; as such, no issue is being raised on this aspect.

Results from the VAS (n=10) and FAS scale (n=2, aged 6-8 years) for stiffness, pain, and fatigue (primary outcomes) suggest that mexiletine may improve these key symptoms of myotonia in the paediatric population, particularly stiffness, where findings were more consistent. There was a small improvement in hand grip myotonia scores by the end of the study across both cohorts - overall mean SD change from baseline -0.09 (0.16). Functional assessments of myotonia and motor performance, however, yielded inconsistent and, at best, modest changes of uncertain clinical relevance. While patients generally reported improvements in neuromuscular symptoms, parent-reported outcomes were less consistent, especially in Cohort 2. This aligns with Myotonia Behaviour Scale results, which suggest, by the end of the study, a modest overall improvement in the impact of myotonia on daily activities, with more pronounced changes in older children (Cohort 1). Numerical improvements from baseline were observed with all Pedsql scores (Physical, Emotional, Social, and School Functioning) at Visit 5, supporting a positive trend in perceived quality of life during the treatment period, for both patients and parents. Clinical Global Impression (CGI) scores at visit 5 indicated that 11 out of 12 subjects rated the efficacy of treatment as 'very efficient' or 'good', reinforcing the perception of treatment benefit.

Besides MEX-MN-301, 3 other studies were agreed in current PIP: PIP study 8, MEX-NM-303 and MEX-MN-401. PIP study 8 had PK sampling on day 42 of pivotal study to characterize the pharmacokinetic profile of mexiletine patients in order to support dosing recommendations in children with MD and to fulfil the requirements of the paediatric investigation plan (PIP). Results demonstrated good concordance between predicted paediatric exposures and the reference adult exposure. It concluded that a dose of approximately 75 mg three times daily (TID) for a 25 kg paediatric patient and 100 mg TID for a 35 kg patient yielded exposure levels comparable to those observed with a 200 mg TID dose in a 75 kg adult. MEX-NM-303 is an ongoing open-label extension study to evaluate the long-term safety and efficacy of mexiletine in the patients of pivotal trial. MEX-MN-401 (Pegasus Study) is an ongoing long-term observation registry study to evaluate the long-term efficacy and safety of mexiletine in paediatric patients with myotonic disorders (from birth to less than 6 years of age). MEX-MN-301, PIP study 8, MEX-NM-303 and MEX-MN-401 are the 4 studies agreed in the current PIP.

The MAH discusses a 0.500 to 2.000 mg/L therapeutic exposure range. However, for the figures provided, the MAH simulated the adult reference population based on 70 kg subjects and this was depicted in the figures. Ideally, the target exposure from adults should be based on the exposure were efficacy and safety have been established, either from observed exposure in the adult pivotal trial(s) or simulated using the adult body weight range from the pivotal trials. The different body weight dosing does however match simulated adult exposure (based on 1000 simulated 70 kg adults) and using the whole adult body weight range would have increased the target exposure range. The proposed doses in children weighing 20 kg or more are thus expected to be effective and safe and can be accepted. However, the used modelling does not allow to make the same conclusion in patients' population weighing less than 20 kg. Therefore, the weight limit was included to the indication.

Based on the review of clinical data and the above-mentioned reports, the CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.3.7.2. Conclusions on the clinical efficacy

In general, the pivotal trial (MEX-MN-301 Study) showed improvements from baseline in VAS results for stiffness, pain, and weakness/fatigue across both cohorts and in the overall population. Numerical improvements were also noted in most other clinical meaningful efficacy assessments, including FAS, clinical assessments of myotonia, PedsQL and MBS. CGI scores are supporting. In the context of an orphan disease with high unmet medical need, the interpretation of these findings is inherently limited by the small sample size and the absence of formal statistical testing. Some other concerns were discussed and resolved during the procedure. The proposed PI changes are in accordance with the Line and Paediatric extension Application for Namuscla.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The two main studies contributing to the safety data are MEX-NM-301 (PIP 4) and the ongoing study MEX-NM-303 (PIP 7).

The primary data to support the safety and efficacy of mexiletine in paediatric patients with myotonic disorders are derived from MEX-NM 301 (PIP 4) study which included 12 paediatric patients. This was an open-label, multi-centre, single arm, interventional, study to evaluate the safety, steady-state PK, and efficacy of mexiletine for the treatment of myotonia in paediatric population aged 6 to <18 years.

Patients who met the eligibility criteria were enrolled stepwise, sequentially in two cohorts by age groups.

- *Cohort 1* – Adolescents aged 12 to <18 years, both inclusive were enrolled first. Based on the Data Safety Monitoring Board (DSMB) assessment and recommendations enrolment for Cohort 2 was started.
- *Cohort 2* – Cohort 2 enrolled children aged 6 to < 12 years, both inclusive. The dosing for this cohort was confirmed by the PK model based on PK data obtained from the adolescents' cohort prior to commencing.

The study comprised a screening period of 30 days, a dose-titration period of 4 weeks, and a maintenance period of 4 weeks. After the last visit, all patients were offered follow-up in clinical study MEX-NM-303 (PIP Study 7).

In the pivotal paediatric study MEX-NM-301, safety data were collected prospectively using a combination of site-based assessments, structured visits, and patient-reported tools to ensure comprehensive safety surveillance.

Safety data were collected via direct clinical assessments, laboratory testing (biochemistry, haematology, urinalysis), ECGs, Holter monitoring, and patient interviews.

Additional safety monitoring components: Electrocardiogram (ECG) assessments at 6 visits across the study period, cardiac ultrasound at screening and EOS, Holter monitoring at screening and EOS, clinical laboratory analyses at baseline, Day 28, and EOS, Adverse event monitoring at every visit, including unsolicited reports and patient diary entries.

5.4.2. Patient exposure

The safety database consists primarily of two interventional clinical studies in paediatric patients with myotonic disorders (non-dystrophic myotonias, NDM):

Study ID	Title/Design	Status	Contribution to Safety
MEX-NM-301	Open-label, non-comparative Phase 3 study evaluating PK, safety, and efficacy of mexiletine in paediatric patients (6 to <18 years)	**Completed** (Sep 2021 – Jun 2024)	**Primary**
MEX-NM-303	Open-label, long-term safety extension in paediatric patients who completed MEX-NM-301	**Ongoing**	Not included in current analysis

The patient disposition and exposure as of cut-off (13th June 2024) of Mex-NM-301 study are shown below.

Exposure Type	Number of Patients
Patients enrolled	14
Patients exposed to at least 1 dose (Safety Population)	12
Patients in proposed therapeutic dose range	12
Patients with long-term safety data >6 months or >12 months	12* (follow-up endpoint at ~Day 56 only)
Blinded, placebo-controlled	0
Open-label study	1 (MEX-NM-301)
Post-marketing / Compassionate use	0

*Note: Long-term safety (>6 months) is expected to be addressed through ongoing Study MEX-NM-303.

The study met the agreed Paediatric Investigation Plan (PIP) requirements: ≥5 children aged 6 to <12 years (n=5) and ≥5 adolescents aged 12 to <18 years (n=7).

Although the safety population (N=12) may appear limited, the rarity of non-dystrophic myotonias in the paediatric population, combined with the inherent challenges of enrolling children with ultrarare neuromuscular disorders, justifies the size of this database.

The demographic and anthropometry characteristics of safety population (MEX-NM-301 study) are described on the table below.

		Cohort 1	Cohort 2	Total
Characteristic (Unit)	**Statistics**	**(N = 7)**	**(N = 5)**	**(N = 12)**
Gender				
Female	n (%)	4 (57.1)	3 (60.0)	7 (58.3)
Male	n (%)	3 (42.9)	2 (40.0)	5 (41.7)
Age (Years)	n	7	5	12
	Mean (SD)	13.4 (1.62)	8.2 (1.79)	11.3 (3.14)
	Median	13.0	8.0	12.0
	Min, Max	12, 16	6, 10	6, 16
Weight at baseline (kg)	n	7	5	12
	Mean (SD)	53.8 (14.58)	26.4 (5.52)	42.4 (18.07)
	Median	58.1	26.0	38.7
	Min, Max	27.3, 68.5	21.0, 32.6	21.0, 68.5
Height at baseline (cm)	n	7	5	12
	Mean (SD)	160.5 (9.36)	123.5 (9.69)	145.1 (21.08)
	Median	163.5	125.0	147.8
	Min, Max	145.5, 171.0	113.0, 133.0	113.0, 171.0
BMI at baseline (Kg/m^2)	n	7	5	12
	Mean (SD)	20.6 (4.08)	17.1 (1.00)	19.1 (3.55)
	Median	22.5	16.6	18.2
	Min, Max	12.9, 24.9	16.2, 18.5	12.9, 24.9

All participants had genetically confirmed non-dystrophic myotonia (e.g., SCN4A, CLCN1 mutations) with documented functional impairment. No healthy subjects or adult controls were included.

Long-term safety (>6 or 12 months) is expected to be captured in MEX-NM-303, which remains ongoing and is part of the paediatric development program.

5.4.3. Adverse events

In MEX-NM-301 (PIP 4) study, TEAEs were reported in 6 subjects (85.7%), 1 subject (20%), and 7 subjects (58.3%) in Cohort 1, Cohort 2, and overall, respectively. No deaths, serious TEAEs, or TEAEs leading to study discontinuation were reported.

The table below shows an overall summary of the TEAEs in safety population.

	Cohort 1 (N = 7)		Cohort 2 (N = 5)		Total (N = 12)	
	n (%)	E	n (%)	E	n (%)	E
Subjects with TEAE	6 (85.7)	23	1 (20.0)	1	7 (58.3)	24
Subjects with Serious TEAEs	0	0	0	0	0	0
Subjects with Study Drug Related TEAEs	2 (28.6)	9	0	0	2 (16.7)	9
Subjects with TEAEs of Specific Interest	0	0	0	0	0	0

Abbreviations: N = Number of subjects in specified cohort; n = Number of subjects in specified category; E = Events. Note 1: Percentages are based on the number of subjects in respective cohort in safety population.

Overall, 7 of 12 subjects (58.3%) reported TEAEs. The most frequently reported SOC category was Gastrointestinal disorders including the most frequently reported TEAEs (preferred term) of abdominal pain (3 subjects (25%) with 3 events) and nausea (3 subjects (25%) with 4 events). All TEAEs were considered mild in severity and most were considered not related or unlikely related to study medication (15 of 24 TEAEs; 62.5%). Two subjects reported 9 related TEAEs (Cohort 1).

- 301-1-103 (Cohort 1) – headache, nausea, vertigo, cardiac palpitations, diarrhoea, All TEAEs were reported as mild and related to study medication. All caused dosing delay and resolved.
- 301-1-104 (Cohort 1) – abdominal pain, nausea (2 events), asthenia, pallor. All TEAEs were considered related to study medication (1 nausea event unrelated). Drug was withdrawn temporarily. All TEAEs resolved.

No deaths or serious TEAEs were reported.

The AEs by SOC and PT for both Cohorts, are represented in the table below:

	Cohort 1		Cohort 2		Total	
System Organ Class	**(N = 7)**		**(N = 5)**		**(N = 12)**	
Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Subjects having at least one TEAE	6 (85.7)	23	1 (20.0)	1	7 (58.3)	24
Gastrointestinal disorders	4 (57.1)	9	0	0	4 (33.3)	9
Abdominal pain	3 (42.9)	3	0	0	3 (25.0)	3
Nausea	3 (42.9)	4	0	0	3 (25.0)	4
Diarrhoea	1 (14.3)	1	0	0	1 (8.3)	1
Vomiting	1 (14.3)	1	0	0	1 (8.3)	1
Nervous system disorders	3 (42.9)	3	0	0	3 (25.0)	3
Headache	2 (28.6)	2	0	0	2 (16.7)	2
Hypoaesthesia	1 (14.3)	1	0	0	1 (8.3)	1
Infections and infestations	2 (28.6)	2	0	0	2 (16.7)	2
Nasopharyngitis	2 (28.6)	2	0	0	2 (16.7)	2
Cardiac disorders	1 (14.3)	1	0	0	1 (8.3)	1
Palpitations	1 (14.3)	1	0	0	1 (8.3)	1
Ear and labyrinth disorders	1 (14.3)	1	0	0	1 (8.3)	1
Vertigo	1 (14.3)	1	0	0	1 (8.3)	1
General disorders and administration site conditions	1 (14.3)	1	0	0	1 (8.3)	1

Asthenia	1 (14.3)	1	0	0	1 (8.3)	1
Injury, poisoning and procedural complications	1 (14.3)	1	0	0	1 (8.3)	1
Ligament sprain	1 (14.3)	1	0	0	1 (8.3)	1
Musculoskeletal and connective tissue disorders	1 (14.3)	1	0	0	1 (8.3)	1
Musculoskeletal chest pain	1 (14.3)	1	0	0	1 (8.3)	1
Renal and urinary disorders	1 (14.3)	1	0	0	1 (8.3)	1
Proteinuria	1 (14.3)	1	0	0	1 (8.3)	1
Reproductive system and breast disorders	1 (14.3)	1	0	0	1 (8.3)	1
Amenorrhoea	1 (14.3)	1	0	0	1 (8.3)	1
Respiratory, thoracic and mediastinal disorders	0	0	1 (20.0)	1	1 (8.3)	1
Asthma	0	0	1 (20.0)	1	1 (8.3)	1
Skin and subcutaneous tissue disorders	1 (14.3)	1	0	0	1 (8.3)	1
Alopecia	1 (14.3)	1	0	0	1 (8.3)	1
Vascular disorders	1 (14.3)	1	0	0	1 (8.3)	1
Pallor	1 (14.3)	1	0	0	1 (8.3)	1

Adverse drug reactions

Below, we provide a summary overview of the characteristics and impact of the ADRs that occurred during the MEX-NM-301 study:

- Number of patients with related AEs (ADRs): 2 out of 12 subjects (16.7%)
- Number of ADRs: 9
- Populations affected: Only patients in Cohort 1 (12–<18 years); no ADRs reported in Cohort 2 (6–<12 years)
- Severity: All ADRs were mild
- Reversibility: All reactions were resolved or resolving following temporary discontinuation or dose delay
- Impact on study**:** No permanent discontinuation; no events led to serious complications

No evidence of non-clinical correlation with these events was identified. There were no quality or manufacturing issues (e.g., impurities, excipients, or immunogenicity concerns) associated with the occurrence of ADRs.

The confirmed ADRs of Mexiletine in MEX-NM-301Paediatric Study are shown in the table below:

System Organ Class (MedDRA)	Preferred Term (PT)	Subjects Affected N (%) [Cohort]	No. of Events	Action Taken	Outcome	Causality Rationale
Gastrointestinal disorders	Nausea	2 (28.6%) [C1]	3	Dose delayed; withdrawn temporarily	Resolved/resolving	Temporal relationship, recurrence after dosing, known class effect of

System Organ Class (MedDRA)	Preferred Term (PT)	Subjects Affected N (%) [Cohort]	No. of Events	Action Taken	Outcome	Causality Rationale
						Na+ channel blockers
	Abdominal pain	1 (14.3%) [C1]	1	Withdrawn temporarily	Resolved	Onset after mexiletine initiation; resolved after withdrawal
	Diarrhoea	1 (14.3%) [C1]	1	Dose delayed	Resolved	Strong temporal association; class effect; resolved without sequelae
Nervous system disorders	Headache	1 (14.3%) [C1]	1	Dose delayed	Resolved	Common with mexiletine class; resolved with dose postponement
	Vertigo	1 (14.3%) [C1]	1	Dose delayed	Resolved	Temporal association; known adverse effect in adult use
Cardiac disorders	Palpitations	1 (14.3%) [C1]	1	Dose delayed	Resolved	Effect consistent with Na+ channel modulation; no ECG abnormality; resolved without intervention
General disorders and administration site conditions	Asthenia	1 (14.3%) [C1]	1	Withdrawn temporarily	Resolved	Reversible, fatigue onset during treatment; resolved upon drug withdrawal
Vascular disorders	Pallor	1 (14.3%) [C1]	1	Withdrawn temporarily	Resolved	Occurred during active treatment; resolved with no recurrence

Abbreviations: C1 = Cohort 1 (12 to <18 years) Dose delayed = temporary pause in dosing (e.g. 1–2 days); withdrawn temporarily = interruption >2 days Causality rationale = Assessment based on investigator judgment, temporal association, expected class effects

The selection and classification of ADRs are adequately substantiated by temporal association, consistency with the known class (sodium channel blockers), and positive response to temporary withdrawal. Given the known safety profile of mexiletine in adults, and the absence of any unexpected or serious ADRs in this paediatric population, the risk profile is considered acceptable.

There are no signals of product quality issues or formulation-related toxicity.

The listed events, particularly gastrointestinal and CNS symptoms, are in line with the pharmacological activity of mexiletine and align with observed adult data. These events were included in section 4.8 of the proposed SmPC for the paediatric population.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Adverse Events of Special Interest (AESIs) are specific events that require focused assessment due to their possible linkage to the mechanism of action, known class effects, or non-clinical findings relevant to mexiletine. AESIs are typically selected based on:

- Known risks from adult experience with mexiletine and similar sodium channel blockers.
- Potential for class-specific, serious, or unexpected toxicity (e.g., hepatic injury, proarrhythmia, severe dermatologic reactions).
- Regulatory precedent and post-marketing safety data.

For paediatric patients with non-dystrophic myotonia (NDM), AESIs for mexiletine were prospectively monitored:

- Cardiac arrhythmias and conduction disturbances (proarrhythmia, new ECG abnormalities)

  1 subject experienced palpitations (mild, not serious), managed with temporary dose interruption, resolved without sequelae. No serious arrhythmia, conduction block, or cardiac deaths occurred. Continuous ECG and Holter monitoring showed no new significant abnormalities.

- Severe hepatotoxicity (hepatitis, acute liver failure)

  No cases of hepatitis, hepatic failure, severe cutaneous reaction, GI bleed, or cytopenia were observed.

- Severe hypersensitivity reactions (e.g., DRESS, Stevens-Johnson Syndrome)
- Neurologic events (seizures, severe CNS effects)

  1 subject experienced mild event of vertigo, temporally related to dosing, resolved after dose delay. No seizures or severe CNS adverse effects.

- Severe gastrointestinal reactions (GI bleeding, peptic ulcer)
- Other events of regulatory or clinical concern (e.g., severe hematologic reactions)

These AESIs were chosen because of evidence from adult and paediatric clinical experience and the non-clinical profile of mexiletine, as well as regulatory requirements for surveillance of antiarrhythmic class effects.

None Serious Adverse Events and deaths were reported in the paediatric cohort during the study.

The next table shows the rationale for ADR classification classified by SOC, PT, number of patients and events:

System Organ Class (MedDRA SOC)	Preferred Term (PT)	Patients Affected N (%) [Cohort 1, N=7]	No. of Events	Action Taken with IMP	Outcome	Rationale for ADR Classification
Gastrointestinal disorders	Nausea	2 (28.6%)	3	Temporarily withdrawn/delay	Resolved/resolving	Temporal relationship, known class effect, response to treatment interruption
	Abdominal pain	1 (14.3%)	1	Treatment interruption	Resolved	Onset after treatment, resolved with discontinuation

System Organ Class (MedDRA SOC)	Preferred Term (PT)	Patients Affected N (%) [Cohort 1, N=7]	No. of Events	Action Taken with IMP	Outcome	Rationale for ADR Classification
	Diarrhoea	1 (14.3%)	1	Dose delay	Resolved	Associated with timing of administration, quick resolution
Nervous system disorders	Headache	1 (14.3%)	1	Dose delay	Resolved	Known side effect for class, resolved with dose delay
	Vertigo	1 (14.3%)	1	Dose delay	Resolved	Consistent with expected CNS effects
Cardiac disorders	Palpitations	1 (14.3%)	1	Dose delay	Resolved	Dose-related pharmacodynamic effect, quickly reversible
General disorders and administration conditions	Asthenia	1 (14.3%)	1	Temporary withdrawal	Resolved	Fatigue linked with peak dosing period, resolved after break
Vascular disorders	Pallor	1 (14.3%)	1	Temporary withdrawal	Resolved	Resolved without intervention, likely linked to underlying AE above

5.4.5. Discontinuation due to adverse events

In the MEX-NM-301 study (PIP 4), in both Cohorts - Cohort 1 (adolescents: 12 to <18 years) and Cohort 2 (children: 6 to <12 years) - no patients permanently discontinued treatment or withdrew from the study due to adverse events (AEs). Therefore, no study discontinuations or permanent treatment discontinuations attributable to AEs or serious adverse events (SAEs) occurred.

However, two subjects experienced temporary interruptions or dose delays due to AEs that were identified as related to mexiletine (i.e., adverse drug reactions – ADRs). These were all mild in intensity, non-serious, and reversible without long-term consequences.

Cohort	Patients with Dose Delay or Temporary Withdrawal	No. of Events (E)
Cohort 1	2 (28.6%)	6
Cohort 2	0	0
Total	2 (16.7%)	6

All adverse events in Cohort 1 that led to dose delays or interruptions, by subject, were as follows:

- Subject 301-1-103: Headache, nausea, vertigo, palpitations, diarrhoea (mild)
  - Action: Dose delay in all events
  - Justification: Events occurred in temporal association with treatment and resolved post-interruption
- Subject 301-1-104: Abdominal pain, nausea, asthenia, pallor (mild)
  - Action: Treatment temporarily withdrawn

- Justification: AEs deemed related; all resolved rapidly after discontinuation

The table below shows the actions that were taken in response to TEAE.

Action Taken for TEAE	Cohort 1 (N=7)	Cohort 2 (N=5)	Total (N=12)
None	6 (85.7%), 18 E	0, 0 E	6 (50.0%), 18 E
Medication Given	4 (57.1%), 5 E	1 (20.0%), 1 E	5 (41.7%), 6 E
Hospitalisation	0	0	0
Non-drug Treatment	0	0	0
Patient Withdrawn	0	0	0
Other	0	0	0

There were no SAEs and no use of non-drug treatment or hospitalisation due to TEAEs. All patients who experienced TEAEs continued in the study after appropriate measures.

These interventions indicate adequate tolerability management and reversibility of the related AEs.

5.4.6. Safety in special populations

This safety summary is based on integrated data from non-clinical pharmacology/toxicology and clinical safety findings from the paediatric MEX-NM-301 study of mexiletine for non-dystrophic myotonia (NDM).

No clinically relevant or statistically significant gender-related differences in AE incidence, severity, or type were observed. Both male and female subjects exhibited a comparable tolerability and safety profile.

Due to the limited sample size and lack of a comparator or adult data, it was not possible to thoroughly assess the relationship between exposure levels and adverse events. All adverse drug reactions (ADRs) appeared to be dose and time related, and they resolved with temporary dose adjustments.

***Table 10*: AEs by Range**

MedDRA System Organ Class	Preferred Term	Cohort 1 (12–18 yrs, N=7, %)	Cohort 2 (6–12 yrs, N=5, %)	Total (N=12, %)	Serious AE (N)	Hospitalisation	Life-Threatening	Disability	Medically Significant	Drop-out Due to AE
Nervous system disorders	Headache, Vertigo	2 (28.6)	0 (0)	2 (16.7)	0	0	0	0	0	0
Gastrointestinal	Nausea, Diarrhoea, Abdominal pain	3 (42.9)	0 (0)	3 (25.0)	0	0	0	0	0	0
Cardiac disorders	Palpitations	1 (14.3)	0 (0)	1 (8.3)	0	0	0	0	0	0

MedDRA System Organ Class	Preferred Term	Cohort 1 (12–18 yrs, N=7, %)	Cohort 2 (6–12 yrs, N=5, %)	Total (N=12, %)	Serious AE (N)	Hospitalisation	Life-Threatening	Disability	Medically Significant	Drop-out Due to AE
General disorders	Asthenia	1 (14.3)	0 (0)	1 (8.3)	0	0	0	0	0	0
Vascular disorders	Pallor	1 (14.3)	0 (0)	1 (8.3)	0	0	0	0	0	0
Infections & Infestations	Nasopharyngitis	2 (28.6)	0 (0)	2 (16.7)	0	0	0	0	0	0
Respiratory disorders	Asthma	0 (0)	1 (20.0)	1 (8.3)	0	0	0	0	0	0

Note: For all categories, no serious AEs**,** no fatalities**,** no hospitalisations, and no drop-outs due to AE occurred.

5.4.7. Immunological events

Not applicable.

5.4.8. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted with mexiletine in the clinical development program described (MEX-NM-301 and related studies). The clinical safety data are therefore limited to observations from single-arm, open-label exposure in the paediatric population. The SmPC includes established interaction warnings based on data available from the AIM marketing authorisation and published literature.

Pharmacokinetic Interactions

- Mexiletine is primarily metabolized by hepatic CYP450 isozymes (notably CYP2D6 and CYP1A2); thus, co-administration with inhibitors or inducers of these enzymes could alter mexiletine plasma concentrations.
- **No clinical PK interaction data** were generated in the paediatric study population.
- Known from adult data and SmPC:
    - CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) may increase mexiletine levels.
    - Enzyme inducers (e.g., rifampicin, phenytoin) could reduce mexiletine efficacy.
    - Caution is also warranted with CYP1A2 substrates and inhibitors.

Pharmacodynamic Interactions

- Mexiletine has antiarrhythmic and weak CNS stimulant activity; additive or antagonistic pharmacodynamic effects may occur with:
    - Other antiarrhythmics (risk of arrhythmia or QT prolongation)
    - Beta-blockers (additive cardiac effects)
    - CNS active drugs (potential for additive neurological adverse effects)
- No clinically significant pharmacodynamic interaction was identified in the provided paediatric safety dataset.

Clinically Relevant Concomitant Use

- Data from MEX-NM-301 did not involve systematic reporting of concomitant use of interacting drugs due to the paediatric, rare-disease, low-comorbidity population.
- No clinically relevant safety signals or unexpected adverse events were observed due to co-medication.

Clinical Perspective for Older Populations

Although the studied population did not include elderly patients, older adults are likely to be polymedicated, including: antiarrhythmics, beta-blockers, calcium channel blockers, antidepressants or antipsychotics, antiepileptics, medications affecting CYP enzymes. Due to this fact and in the absence of clinical drug-drug interaction studies in this application means caution is especially warranted in older patients with polypharmacy.

SmPC warnings from AIM approval regarding these interactions remain appropriate and should be reflected in labelling.

5.4.9. Vital signs and laboratory findings

Laboratory parameters were assessed primarily at screening, Day 28, and Day 56 or at end of study.

Overall, no clinically significant alterations from baseline were reported in haematology or biochemistry labs. No consistent pattern indicating renal or hepatic toxicity. Electrolyte monitoring highlighted the importance of maintaining normal electrolyte balance to mitigate cardiac risk but did not reveal treatment-related adverse imbalances. One isolated mild urinary protein finding was unrelated and did not lead to clinical concerns. Vital signs and cardiac assessments did not reflect emergent safety concerns.

The safety laboratory data, cardiac monitoring, and physical examination findings are supportive and consistent with the known safety profile of mexiletine.

The absence of clinically meaningful laboratory deviations or cardiac conduction abnormalities supports the safety of mexiletine in the studied paediatric population.

Laboratory and ECG-based monitoring recommendations in the SmPC are justified and should be maintained.

The single mild, unrelated TEAE in urinalysis does not warrant additional safety measures.

These findings align with known mexiletine safety profile and support existing lab monitoring recommendations in the SmPC.

5.4.10. Post marketing experience

Not applicable.

5.4.11. In vitro biomarker test for patient selection for safety

Not applicable.

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

General Discussion and Key Findings

The clinical safety data for mexiletine in the paediatric population with non-dystrophic myotonia derive primarily from the open-label, single-arm MEX-NM-301 study involving 12 patients aged 6 to <18 years. The data set represents the totality of paediatric safety experience submitted to date, complemented by established adult safety data.

Patient exposure

Although limited in size (N=12), the exposure meets PIP requirements and reflects the rarity of the condition. The follow-up duration (~8 weeks per patient) is relatively short, and long-term safety data are awaited from the ongoing open-label extension study MEX-NM-303.

Safety profile

The profile is consistent with the known class effects of mexiletine and sodium channel blockers, characterized mainly by mild gastrointestinal and neurological adverse drug reactions (ADRs) such as nausea, abdominal pain, headache, and vertigo.

Serious adverse events (SAEs)

None were reported in the paediatric trial, with no deaths, hospitalizations or discontinuations due to AEs. This aligns with non-clinical toxicity studies which did not indicate serious organ toxicity at therapeutic doses.

Specific risk factors

No specific patient subgroup appeared to be at increased risk of ADRs. Dose-dependent effects and reversibility upon dosing interruption were observed. Monitoring of cardiac conduction parameters and electrolytes is prudent given mexiletine's electrophysiological effects and potential pro-arrhythmic risk.

Compliance to Regulatory Requirements

- The clinical safety data, even though limited, fulfil the agreed Paediatric Investigation Plan (PIP) obligations.

- The data adhere to relevant ICH guidelines (e.g., ICH E2A, E2E) and EMA procedural guidance.
- Safety monitoring measures, including ECG assessments, laboratory tests, and patient diaries, were adequate and sufficient for this rare, paediatric population.

Limitations:

- The limited population size and short duration of exposure raise some uncertainties about long-term safety, especially in younger children and other special populations such as infants or patients with comorbidities.
- Lack of safety data in elderly and renal/hepatic impaired patients could be discussed regarding labelling and risk minimisation in those groups.
- Absence of placebo or comparator data limits the ability to fully attribute ADRs causally, though existing evidence is compelling.

Conclusions and Recommendations for SmPC and Opinion

- The absence of serious safety signals and low discontinuation rate supports a positive benefit-risk ratio.
- Monitoring recommendations for ECG and electrolytes should be explicitly maintained.
- The lack of observed long-term safety data should be transparently noted.
- Warnings should be included extending known adult adverse reactions cautiously to paediatric use.

Benefit-Risk Key Findings and Uncertainties

- Benefit-risk remains positive given the unmet medical need for mexiletine in paediatric NDM and the observed manageable safety profile.
- Uncertainty exists regarding rare or delayed effects and in special populations not studied.
- Continuous pharmacovigilance and data from study MEX-NM-303 will be important in reducing uncertainty.

Additional Considerations

- No immediate need detected for a Scientific Advisory Group (SAG) meeting.
- No triggers currently for a GCP or GMP inspection based on safety data.

5.4.12.1.2. Adverse drug reactions in the SmPC

The ADRs proposed by the MAH for inclusion in the SmPC are described above.

The proposed Table describing adverse drug reactions in paediatric patients is based on observations only in two paediatric patients who each reported single ADRs (except nausea). Such information does not allow to draw any conclusions neither about the quantitative, nor qualitative differences between observations in paediatric patients and ADR profile known in adults. Therefore, the it was proposed to remove the Table describing the ADRs in paediatric patients and modify the proposed text:

The safety assessment in children and adolescents was studied in the ~~Phase III study~~ MEX-NM-301 ***study*** *in which 12 paediatric patients aged from 6 to 18 years and weighing at least 20 kg received mexiletine (see section 5.1). Two (2) of these patients reported adverse* ***drug*** *reactions. Adverse* ***drug*** *reactions established for adults are considered applicable to children and adolescents.*

5.4.12.2. Conclusions on clinical safety

Mexiletine was generally well-tolerated in the completed paediatric study (MEX-NM-301), with no deaths, serious adverse events (SAEs), permanent treatment discontinuations, or unanticipated safety signals observed. A total of 7 out of 12 patients (58.3%) reported treatment-emergent adverse events (TEAEs), all of which were mild in intensity.

The most commonly reported TEAEs were:

- Nausea (25% of subjects, 4 events)
- Abdominal pain and headache: consistent in nature with known class effects
- Vertigo, diarrhoea, pallor, and asthenia: less frequent but plausibly related

All adverse drug reactions (ADRs) observed were consistent in type, severity, and anticipated reversibility with the adult experience for mexiletine (i.e., per Namuscla SmPC, 2023). No dose reductions or early treatment withdrawals occurred. Two subjects required temporary interruption or delayed dosing due to ADRs, all of which subsequently resolved.

The safety profile observed in paediatric patients was aligned with the established data in adults and no new safety signals emerged. The observed adverse reactions and physiological effects (e.g., cardiac conduction stability, lab values) are consistent with historical safety data from antiarrhythmic uses of mexiletine.

While the short-term safety data presented are supportive, limitations remain due to:

- Small sample size (N=12)**,** reflecting the ultra-rare nature of the disease;
- Short treatment duration (8 weeks exposure per subject);
- Absence of safety data in special populations (e.g., children <6 years, elderly, renal/hepatic impairment);
- No long-term safety data (>6 months) currently available.

These limitations are being addressed through the ongoing long-term extension study (MEX-NM-303) and should be closely monitored through enhanced pharmacovigilance efforts.

Final Remarks

- The observed safety profile in the studied paediatric population supports the **favourable benefit–risk balance** of mexiletine.

- Continued follow-up, risk minimisation, and data from the extension study (MEX-NM-303) are essential to further characterise the long-term safety of mexiletine in children.

6. Risk management plan

The MAH submitted an updated RMP version 4.0 with this application. Addressing the requests, the MAH submitted updated RMP versions, with final version 5.3 (signed off 24 March 2026).

6.1. Safety specification

6.1.1. Proposed safety specification

The MAH proposed an inclusion of the new important potential risk – Dispensing and medication errors due to introduction of the new strengths of the product.

***Table 11*: Summary of safety concerns in the proposed RMP version 5.2, final sign-off 18 Feb 2026**

Summary of safety concerns	
Important identified risks	• Severe cutaneous adverse drug reactions (SCARs) • Cardiac arrhythmia • Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine • Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
Important potential risks	• Increased frequency of seizure episodes in patients with epilepsy • Off-label use in DM1 and DM2 patients • Dispensing and medication errors
Missing information	• Long term use in adult patients with myotonic disorders • Effect on fertility and use in pregnancy • Safety in elderly • Use in patients with severe renal impairment • Long-term safety in paediatric population

6.1.2. Discussion on proposed safety specification

No changes of the safety specification were initially proposed by the MAH. Nevertheless, the following updates were requested by the PRAC to reflect the currently available data on the paediatric population as well as data until DLP of the updated RMP, version 5.2:

Part II Module SII, SIII and SIV were updated with the summary of relevant non-clinical and clinical data, including the MYOMEX study, two RCTs by Logigian et al (2010) and the PIP study MEX-NM-301.

Part II Module SV was updated to reflect the current post-authorisation exposure.

Part II Module SVII – Identified and potential risks

Important identified risks (IIR)

No changes in the IIR were proposed by the MAH. The current list of IIR is supported by the PRAC. Data presented for the paediatric indication do not raise additional safety concerns.

Important potential risks (IPR)

The MAH´s proposal for inclusion of the new important potential risk "Dispensing and medication errors" in the RMP version 5.1 has not been supported by the PRAC. Medication errors associated with the introduction of multiple product strengths cannot be ruled out, nevertheless, medication errors are routinely monitored and described in the PSURs. No other additional risk minimisation measures were proposed to cover this risk. The proposed paediatric dosage completely differs from the adult dosage, and it is sufficiently described in the table in posology section of the SmPC. Moreover, differentiation in colour of capsules and outer packaging is applied. It was therefore considered sufficient by the PRAC to discuss the medication errors (with a special focus on paediatric patients) in the PSURs. The broader term "Medication errors" already includes dispensing errors, as it covers the mistakes in all medication stages - prescribing, storing, dispensing, preparation and administration of a medicine. The proposed IPR "Dispensing and medication errors" was removed from the list of safety concerns in the RMP version 5.2.

The IPR "Off-label use in children" was removed from the list of safety concerns in the light of the paediatric line extension of the product.

Missing information

No changes in missing information were proposed by the MAH. Based on the data on paediatric extension, it was suggested by the PRAC and agreed by the MAH to include "Long-term safety in paediatric population". As a part of currently agreed PIP, there is an ongoing open-label extension study MEX-NM-303 to evaluate the long-term safety and efficacy of mexiletine in the patients of pivotal trial (6-18 years). Furthermore, MEX-MN-401 (Pegasus Study) is an ongoing long-term observation registry study to evaluate the long-term efficacy and safety of mexiletine in paediatric patients with myotonic disorders (from birth to less than 6 years of age).

The PRAC recommended amendments of the proposed summary of safety concerns:

Summary of safety concerns	
Important identified risks	1. Severe cutaneous adverse drug reactions (SCARs) 2. Cardiac arrhythmia 3. Risk of toxicity of CYP1A2 substrates with narrow therapeutic window such as theophylline, caffeine or tizanidine 4. Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
Important potential risks	5. Increased frequency of seizure episodes in patients with epilepsy ~~6. Off-label use in children under the age of 6 years~~ 6. Off-label use in DM1 and DM2 patients ~~8. Medication errors~~
Missing information	7. Long term use in adult patients with myotonic disorders 8. Effect on fertility and use in pregnancy 9. Safety in elderly 10. Use in patients with severe renal impairment 11. Long-term safety in paediatric population

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

The MAH did not propose any changes to the additional pharmacovigilance activities.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities that are in place for the product (including the specific adverse reaction follow-up questionnaires for the risk of cardiac arrhythmia) are considered satisfactory. No change is warranted.

6.2.2.2. Additional pharmacovigilance activities

Additional pharmacovigilance activities that are in place for the product are considered satisfactory. No change is warranted.

6.3. Plans for post-authorisation efficacy studies

Not applicable.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

No changes of the routine risk minimisation activities were proposed.

The MAH has proposed an update of the additional risk minimisation measures to include the new strengths of the authorised product in the Educational guide for Healthcare Professionals and Patient Card.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Routine pharmacovigilance activities that are in place for the product are considered satisfactory. No change is warranted.

6.4.2.2. Additional risk minimisation measures

For the Important Identified Risk of "Cardiac arrhythmia" and "Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment", the following additional risk minimisation measures are in place:

- Educational guide for Healthcare Professionals for risk of cardiac arrhythmia and risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment
- Patient Card

These educational tools (additional RMM) were formally updated to include the paediatric strengths of the product. Furthermore, the correct name of the educational tool for patient (Patient Card) was

consistently applied throughout the entire RMP. The wording of the Patient Card in the Annex 6 has been updated to reflect the use in paediatric population and the possible role of parents/caregivers.

PRAC endorsed the additional RMM as proposed in the updated RMP version 5.3.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI is considered acceptable.

The RMP Annexes are considered acceptable.

The MAH is notified that the RMP Part VI is a stand-alone document, that shall be publicly available.

6.6. Overall conclusion on the Risk Management Plan

The PRAC considers that the updated risk management plan version 5.3 is acceptable.

7. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.1. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The MAH discussed a 0.500 to 2.000 mg/L therapeutic exposure range. However, for the figures provided, the MAH simulated the adult reference population based on 70 kg subjects and this was depicted in the figures. Ideally, the target exposure from adults should be based on the exposure were efficacy and safety have been established, either from observed exposure in the adult pivotal trial(s) or simulated using the adult body weight range from the pivotal trials. The different body weight dosing does however match simulated adult exposure (based on 1000 simulated 70 kg adults) and using the whole adult body weight range would have increased the target exposure range. The proposed doses in children weighing 20 kg or more are thus expected to be effective and safe and can be accepted. However, the used modelling does not allow to make the same conclusion in patients' population weighing less than 20 kg. Therefore, the weight limit was included to the indication.

8.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

9. Benefit-risk assessment

9.1. Therapeutic context

Mexiletine hydrochloride 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. 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 of the delay of muscle relaxation.

A Marketing Authorisation was granted to Namuscla (mexiletine) with Orphan Drug Designation to Lupin Europe GmbH on 18 December 2018 for the therapeutic indication 'symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. 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.

9.1.1. Disease or condition, proposed therapeutic indication

Myotonic disorders are a heterogeneous group of hereditary rare (orphan) diseases with no known cure and only symptomatic treatment. A common and defining feature of myotonic disorders is myotonia which is a malfunction of muscular ion channels, usually chloride or sodium channels 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.

Myotonia is caused by skeletal muscle fibre hyperexcitability. 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. Consequently, the underlying cause of myotonic disorders are skeletal ion channelopathies mainly affecting sodium or chloride ion channels.

Electrophysiological studies on resting conductance of chloride, potassium, sodium, and calcium ions have revealed considerable insight into the pathophysiological mechanisms.

The two myotonic dystrophies (type 1 and 2; DM1 and DM2, respectively) are autosomal dominant and multi-systemic disorders caused by an accumulation of expanded, non-coding RNAs, containing repetitive CUG and CCUG elements. 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. Frequently weakness, cataracts, conduction defects, insulin insensitivity, balding, hyperhidrosis, hypersomnia, and respiratory failure occur. DM2 is not normally diagnosed until adulthood and, in general, has clinical symptoms that are usually milder than DM1.

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. 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. 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. The intensity of symptoms ranges from mild (late onset) to life-threatening.

Mexiletine is the only approved product for the symptomatic treatment of non-dystrophic myotonic disorders in adults. As well as the approved 200 mg strength, new paediatric formulations were developed consisting of 75 mg and 100 mg mexiletine HCL strengths, hard capsules for oral use. The MAH requested to add these new strengths (corresponding to 62.48 mg and 83.31 mg of mexiletine, respectively) for paediatric population and to extend the current indication for adults for the symptomatic treatment of myotonia in patients with non-dystrophic myotonic disorders to children and adolescents from 6 to up to 18 years of age.

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2 of this document.

Mexiletine is the only approved product for proposed therapeutic indication (symptomatic treatment of non-dystrophic myotonic disorders).

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. of this document.

The pivotal study supporting this application is the MEX-MN-301 Study to evaluate the safety, efficacy and steady-state PK of mexiletine in adolescents (aged 12 to <18 years) and children (aged 6 to <12 years) with myotonic disorders. It was an open-label, multi-centre, single arm, interventional study where patients who met the eligibility criteria were enrolled stepwise, sequentially in two cohorts by age groups: Cohort 1 – Adolescents aged 12 to < 18 years; and Cohort 2 – enrolled children aged 6 to < 12 years. Primary and secondary objectives were relevant and clearly defined. Sample size was not hypothesis driven (at least 10 evaluable subjects) and the efficacy endpoints chosen were based on

those commonly used in routine clinical practice for adults, modified according to the patient's age and ability to participate (VAS and FAS score for muscle stiffness, pain; Functional Assessment of myotonia; Pedsql Questionnaire; Neuromuscular Modules; MBS; CGI). These issues were reviewed and accepted by the PDCO as part of the PIP approval process and therefore, all endpoints are not statistically powered.

Namuscla was started as a once-a day (QD) treatment regimen (in the morning) and the dose was escalated every 2 weeks as per investigator judgement depending on the patient response and tolerability. Dose was escalated to BID at Day 14 (morning and evening) and TID at Day 28 (morning, midday and evening). The mexiletine total daily dose was based on body weight and ranged from 186 to 500 mg mexiletine during the maintenance period. Total treatment duration was 8-week.

A total of 12 subjects were treated with mexiletine in this study; 7 subjects in Cohort 1 (4 female and 3 males; mean age 13.4 years) and 5 subjects in Cohort 2 (3 female and 2 males; mean age 8.2 years). All subjects (100%) completed the study. Both the ITT and PP analysis populations included all 12 enrolled subjects, with no exclusions or major protocol deviations, resulting in similar data tables.

9.3. Favourable effects

Data was collected and analysed only descriptively. Numerical reductions (improvement) from baseline were observed with VAS scale results for stiffness, pain, and weakness/fatigue in each cohort and overall. The results of other clinical efficacy assessments including FAS, clinical assessments of myotonia, Pedsql, and MBS were variable over time but in general improvement was observed. MBS scores improved from baseline to EOS for 8/12 (66.7%), remained the same for 3/12 (25.0%), and worsened for 1/12 (8.3%) patients. Mean MBS scores decreased across all cohorts between baseline and EOS. CGI scores of "very efficient" or "good" at visit 5 were reported in 11 of 12 subjects (92%).

9.3.1. Uncertainties and limitations about favourable effects

Subjects in MEX-NM-301 Study were recruited from two hospitals in France. Considering the genetic basis and the high familial prevalence of myotonic disorders (12 out of 14 subjects had at least one close relative affected), the MAH was requested to provide a more comprehensive characterization of myotonic disorders with respect to their geographical and ethnicity distribution. A correlation between this characterization and the demographics of the study population, including possible familial relationships was requested. Furthermore, a critical discussion was requested on the potential limitations associated with the small sample size and the possible overrepresentation of individuals from a single geographical area, familial clusters, or specific ethnic backgrounds, which may impact the generalizability of results. The MAH clarified that myotonic dystrophy (DM) and non-dystrophic myotonias (NDM) often show familial clustering due to autosomal inheritance, with most cases reported predominantly in Caucasian populations. The rarity and ultrarare prevalence of these conditions, combined with familial clustering and the limited patient pool, justify the typical diagnosis at specific centers. Nevertheless, despite potential limitations in study epidemiology, it is recognized that the observed patterns support the role of specialized centers and family networks in identifying eligible patients, with paediatric prevalence aligning closely with adult patterns, particularly for DM1.

Since the approval of the use of mexiletine is mainly based on a extrapolation from adults 3 main issues were questioned: 1) the possibility of extrapolation of efficacy from adults to children; 2) the discussion on the therapeutic window for mexiletine; and 3) the simulations of the PK for the full paediatric population under assessment.

Regarding 1) the MAH argues that Myotonic disorders are skeletal-muscle ion-channelopathies characterized by impaired muscle relaxation and episodic or persistent stiffness, that although may present at differing ages, the fundamental pathophysiology, molecular mechanisms, and clinical manifestations of myotonia are highly conserved across age groups. In particular, molecular mechanisms do not change with age and children manifest the same defective channel biology as adults. This was generally accepted by the PDCO.

Regarding 2) The MAH reported that the therapeutic range of 0.500 to 2.000 mg/L, established in adults with myotonia based on efficacy and safety data, was used as the reference for all paediatric exposure comparisons. In the original application, the day 18 Cmin and C2h of 600 mg/day on the MYOMEX study resulted in values from approx. 0.2 to 2.0 mg/L. Other studies with similar doses but administered to patients with other diseases resulted in ranges of concentrations from 0.1 to 3 mg/L. So, in general, the proposed values may be accepted.

Regarding 3) The MAH provided new simulations showing the simulated plasma profile of an 8 h administration where weight groups were stratified into bins (20 kg, 24.5 kg, 29 kg; 30 kg, 34.5 kg, 39 kg; 40 kg, 49.5 kg, 59 kg) and the obtained C_{max}, C_{min} and AUC values (Mean and range) obtained within each group. However, the assessment of the data was not easily interpretable because no boxplots were presented as requested in the "modelling and simulation: Question and answers – How should results/predictions of pharmacokinetics analysis be presented to facilitate decision making about the adequacy of the proposed dosing regimen in paediatric patients?" from November 2018. The target exposure from adults was requested to be clearly defined and presented for comparison. In addition to the requested boxplots, it was also requested to plot the primary PK parameters as a function of body weight with reference lines for the adult population. Of relevance for all these requests, it was not clear that the presented simulations were at steady state since the C0h concentrations are lower than the C8h concentrations. In addition, the values presented do not seem to compare well to the previously presented PK parameters for the 25 kg, and 35 kg subject simulations:

It was acknowledged that the dose optimization is made in a weekly base evaluation of the clinical response. However, it was not yet clear if the proposed dosing regimen will result in a similar exposure, based on the simulated C_{max} and C_{min} values provided. The MAH provided the new simulations as requested. A justification was also provided regarding the nonattendance on steady state conditions observed in the response to the previous round of questions. This was due to the simulation of multiple doses without the inclusion of a steady state flag. This is acceptable.

The new simulations do show that the concentration profiles, both in their central tendency and variability, do seem similar between the different weight bands when taken in consideration the different dose regime in each main group (62 mg TID for 20-30 kg, 83 mg TID for 30-40 kg, 124 mg TID for 40-60 mg and 167 mg TID more than 60 kg). This was also confirmed in the simulated PK parameters ($C_{max,ss}$, $C_{min,ss}$ and $AUC_{tau,ss}$). In the different comparisons, similar box (Q1 and Q3) to the 70 kg adult were basically observed, included within the observed adult *in vivo* exposures. Although some whiskers and extreme values were observed outside these limits, these were independent of the weight bands and doses administered, being also observed in the adult population simulations.

Overall, the simulations do show that the exposures obtained in the paediatric population are within the ones observed in the adult population when the proposed dose regime is considered.

Primary outcomes

The small sample size limits definitive conclusions. Results from the VAS (n=10) and FAS scale (n=2, children aged 6-8 years) for stiffness, pain, and fatigue (primary outcomes) suggest that mexiletine

may improve these key symptoms of myotonia in the paediatric population, particularly stiffness, where findings were more consistent.

There was a small improvement in hand grip myotonia scores by the end of the study across both cohorts [overall mean SD change from baseline -0.09 (0.16)].

Secondary outcomes

Functional assessments of myotonia and motor performance, however, yielded inconsistent and, at best, modest changes of uncertain clinical relevance.

While patients generally reported improvements in neuromuscular symptoms, parent-reported outcomes were less consistent, especially in Cohort 2. This aligns with Myotonia Behaviour Scale results, which suggest, by the end of the study, a modest overall improvement in the impact of myotonia on daily activities, with more pronounced changes in older children (Cohort 1).

Numerical improvements from baseline were observed with all Pedsql scores (Physical, Emotional, Social, and School Functioning) at Visit 5, supporting a positive trend in perceived quality of life during the treatment period, for both patients and parents. Clinical Global Impression (CGI) scores at visit 5 indicated that 11 out of 12 subjects had their treatment efficacy rated as 'very efficient' or 'good', reinforcing the perception of treatment benefit.

Interpretation of these findings, however, is limited by the small sample size and the absence of statistical testing.

MEX-NM-303 is an ongoing open-label extension study to evaluate the long-term safety and efficacy of mexiletine in the patients of pivotal trial.

9.4. Unfavourable effects

The clinical safety data for mexiletine in the paediatric population with non-dystrophic myotonia derive primarily from the open-label, single-arm MEX-NM-301 study involving 12 patients aged 6 to <18 years. The data set represents the totality of paediatric safety experience submitted to date, complemented by established adult safety data. Although limited in size (N=12), the exposure meets PIP requirements and reflects the rarity of the condition. The follow-up duration (~8 weeks per patient) is relatively short, and long-term safety data are awaited from the ongoing open-label extension study MEX-NM-303.

In light of the observed data and class effects of mexiletine, the following safety areas are recommended for inclusion in the **Safety Specification** of the Risk Management Plan (RMP):

Important Identified Risks	**Source/Justification**
Gastrointestinal ADRs (e.g., nausea, abdominal pain)	Frequently observed in clinical studies; pharmacologically expected; dose-related
Central nervous system ADRs (e.g., headache, vertigo)	Consistent with class effect and reported in paediatric study
Cardiac electrophysiological effects (e.g., palpitations)	Known arrhythmogenic potential in susceptible individuals; observed in safety dataset
Important Potential Risks	**Source/Justification**
Proarrhythmic effects in at-risk patients	Based on mexiletine's class profile; ECG/QT monitoring required

Use in patients with hepatic or renal impairment	No safety data from these populations; caution advised
Cumulative or delayed toxicity from long-term use	Lack of data beyond 8 weeks in paediatric patients

Missing Information	**Source/Justification**
Long-term safety in paediatric patients (>6/12 months)	MEX-NM-303 ongoing; no current data submitted
Safety in children <6 years	Study population limited to 6 years and older
Use in elderly	Not studied in current program; class effects may be amplified in older populations
Use in pregnancy	No clinical safety experience; non-clinical data suggest risk at high exposures

9.4.1. Uncertainties and limitations about unfavourable effects

While the short-term safety data presented are supportive, limitations remain due to:

- Small sample size (N=12), reflecting the ultra-rare nature of the disease;
- Short treatment duration (8 weeks exposure per subject);
- Absence of safety data in special populations (e.g., children <6 years, elderly, renal/hepatic impairment);
- No long-term safety data (>6 months) currently available.

These limitations are being addressed through the ongoing long-term extension study (MEX-NM-303) and should be closely monitored through enhanced pharmacovigilance efforts.

9.5. Effects Table

The pivotal trial (MEX-NM-301) was an open-label, non-comparative study, single arm, interventional study with a total of 12 subjects enrolled. All endpoints were not statistically powered. Data was collected and analysed only descriptively. The protocol of this study was reviewed and accepted by the PDCO as part of the current PIP approval process.

Table 12: Effects Table for Namuscla

Effect (short description)	Treatment			Uncertainties/ Strength of evidence	Ref
ITT/PP population change from baseline to EOS	**Cohort 1** Mean Change (SD)	**Cohort 2** Mean Change (SD)	**Total** Mean Change (SD)	No statistical testing conducted	**MEX-NM-301**
Stiffness VAS	7/7 -53.7 (19.62)	3/5 -21.7 (27.50)	10/12 -44.1 (25.77)		

Effect (short description)	Treatment			Uncertainties/ Strength of evidence	Ref
Pain VAS	7/7 -13.6 (18.32)	3/5 4.3 (19.86)	10/12 -8.2 (19.65)		
Weakness and Fatigue VAS	7/7 -21.0 (22.91)	3/5 -17.0 (41.87)	10/12 -19.8 (27.26)		
Stiffness FAS	NE	2/5 -3.0 (1.41)	2/12 -3.0 (1.41)		
Pain FAS	NE	2/5 -1.0 (1.41)	2/12 -1.0 (1.41)		
Weakness and Fatigue FAS	NE	2/5 2.0 (0.00)	2/12 2.0 (0.00)		
Hand Grip Myotonia Test score	6/7 -0.065 (0.10)	5/5 -0.112 (0.21)	11/12 -0.086 (0.15)		
Leg muscles (Timed-up and go [TUG] test)	7/7 -0.453 (2.70)	5/5 0.198 (1.87)	12/12 -0.182 (2.31)		
Action myotonia in eyelid muscles	6/7 0.000 (0.00)	5/5 2.2 (3.49)	11/12 1.0 (2.49)		
Right-hand flexor muscles	6/7 -0.233 (1.32)	5/5 -0.420 (1.34)	11/12 -0.318 (1.27)		
Myotonia Behaviour Scale (MBS)	7/7 -1.7 (1.11)	5/5 -0.2 (0.84)	12/12 -1.1 (1.24)		

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; FAS: FACES scores, Family Adaptability and Cohesion Evaluation Scales; EoS: End of Study; NE: Not evaluable.

Due to the small number of patients, the efficacy and safety was established by an extrapolation approach and by confirming similar exposure (AUCss, Cmax,ss and Cmin,ss) of the proposed regime for children above 20 kg to the ones observed in the adult population, by means of a PopPK model.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

In general, improvements from baseline were observed in VAS results for stiffness, pain, and weakness/fatigue across both cohorts and in the overall population. Numerical improvements were

also noted in most other clinical meaningful efficacy assessments, including FAS, clinical assessments of myotonia, PedsQL and MBS. CGI scores are supporting.

All adverse drug reactions (ADRs) observed were consistent in type, severity, and anticipated reversibility with the adult experience for mexiletine (i.e., Namuscla SmPC). No dose reductions or early treatment withdrawals occurred. Two subjects required temporary interruption or delayed dosing due to ADRs, all of which subsequently resolved.

The safety profile observed in paediatric patients was aligned with the established data in adults and no new safety signals emerged. The observed adverse reactions and physiological effects are consistent with historical safety data from antiarrhythmic uses of mexiletine.

9.6.2. Balance of benefits and risks

In the context of an orphan disease with high unmet medical need, and taking into account that the pivotal trial protocol was reviewed and agreed by the PDCO, as well as the overall modest but consistent numerical improvements observed across clinically relevant endpoints, the B/R of Namuscla (mexiletine) 62 mg, 83 mg, and 167 mg hard capsules, for the symptomatic treatment of myotonia in children and adolescents (aged 6 to 18 years) with non-dystrophic myotonic disorders, could be considered positive.

The MAH provided new simulations showing the simulated plasma profile of an 8 h administration where weight groups were stratified into bins (20 kg, 24.5 kg, 29 kg; 30 kg, 34.5 kg, 39 kg; 40 kg, 49.5 kg, 59 kg) and the obtained C_{max}, C_{min} and AUC values (Mean and range) obtained within each group. However, the assessment of the data was not easily interpretable because no boxplots were presented as requested. The target exposure from adults was requested to be clearly defined and presented for comparison. In addition to the requested boxplots, it was also requested to plot the primary PK parameters as a function of body weight with reference lines for the adult population. Of relevance for all these requests, it was not clear that the presented simulations were at steady state since the C0h concentrations are lower than the C8h concentrations. In addition, the values presented do not seem to compare well to the previously presented PK parameters for the 25 kg, and 35 kg subject simulations:

It was acknowledged that the dose optimization is made in a weekly base evaluation of the clinical response. However, it was not yet clear if the proposed dosing regimen will result in a similar exposure, based on the simulated C_{max} and C_{min} values provided. The MAH provided the new simulations as requested. A justification was also provided regarding the nonattendance on steady state conditions observed in the response to the previous round of questions. This was due to the simulation of multiple doses without the inclusion of a steady state flag. This is acceptable.

The new simulations do show that the concentration profiles, both in their central tendency and variability, do seem similar between the different weight bands when taken in consideration the different dose regime in each main group (62 mg TID for 20-30 kg, 83 mg TID for 30-40 kg, 124 mg TID for 40-60 mg and 167 mg TID more than 60 kg). This was also confirmed in the simulated PK parameters ($C_{max,ss}$, $C_{min,ss}$ and $AUC_{tau,ss}$). In the different comparisons, similar box (Q1 and Q3) to the 70 kg adult were basically observed, included within the observed adult *in vivo* exposures. Although some whiskers and extreme values were observed outside these limits, these were independent of the weight bands and doses administered, being also observed in the adult population simulations. Ideally, the target exposure from adults should be based on the exposure were efficacy and safety have been established, either from observed exposure in the adult pivotal trial(s) or simulated using the adult body weight range from the pivotal trials. The different body weight dosing

does however match simulated adult exposure (based on 1000 simulated 70 kg adults) and using the whole adult body weight range would have increased the target exposure range. The proposed doses in children weighing 20 kg or more are thus expected to be effective and safe and can be accepted.

Overall, the simulations do show that the exposures obtained in the paediatric population are within the ones observed in the adult population when the proposed dose regime is considered. However, the used modelling does not allow to make the same conclusion in patients' population weighing less than 20 kg. Therefore, the weight limit was included to the indication.

The safety profile observed in paediatric patients was aligned with the established data in adults and no new safety signals emerged. The observed adverse reactions and physiological effects are consistent with historical safety data from antiarrhythmic uses of mexiletine.

Therefore, the observed safety profile in the studied paediatric population supports the favourable benefit–risk balance of mexiletine. Continued follow-up, risk minimisation, and data from the extension study (MEX-NM-303) are essential to further characterise the long-term safety of mexiletine in paediatric patients.

In conclusion, considering the resolved clinical pharmacology major objection on the extrapolation of adults' data to children, the B/R is considered positive.

9.7. Benefit-risk conclusions

The benefit-risk profile is considered positive.