18 October 2018
EMA/831802/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Namuscla

International non-proprietary name: mexiletine

Procedure No. EMEA/H/C/004584/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APD_{90}	Action potential duration at 90%
AP-HP	Assistance Publique Hôpitaux de Paris, Paris, France
API	Active Product Ingredient
ASM	Active substance manufacturer
ASMF	Active substance master file
ATX	Sea anemone toxin
AUC	Area under the concentration-time curve
BI	Boehringer Ingelheim
BCS	Biopharmaceutics classification system
CCI	Chronic constriction injury
CHMP	Committee for medicinal products for human use
Cmax	Maximum plasma concentration
CNS	Central nervous system
CoA	Certificate of analysis
CYP	Cytochrome P450
DM	Dystrophic myotonias
DM1	Dystrophic myotonia type 1
DMPK	Dystrophia Myotonica-Protein Kinase
DSC	Differential scanning calorimetry
EAD	Early after depolarisation
ECG	Electrocardiogram
ED50	Half-maximum efficient dose
EMG	Electromyography
GC	Gas chromatography
GD	gestation day(s)
GLP	Good laboratory practice
GMP	Good manufacturing practice
HED	Human equivalent dose
hERG	Human ether-à-go-go-related gene
HMM	Hydroxymethylmexiletine
HPLC	High-pressure liquid chromatography
HPLC-MS	High performance liquid chromatography mass spectrometry
IBD	International birth date
IC50	Half-maximum inhibitory concentration
ICa	Inward calcium current
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
IP	Intraperitoneal
IR	Infrared
IV	Intravenous

Ki	Inhibition constant
LD50	Median lethal dose
MAA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MC	Myotonia congenital
mHM	m-Hydroxymexiletine
N/A	Non-applicable
NDM	Non-dystrophic myotonias
NMR	Nuclear magnetic resonance
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PC	Paramyotonia congenital
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia
P-gp	P-glycoprotein
pHM	p-Hydroxymexiletine
PK	Pharmacokinetic
PND	Post-natal day
PNS	Peripheral nervous systems
PO	Oral
PRP	Patient-reported outcome
PSUR	Periodic Safety Update Report
PTZ	Pentetrazol
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RH	Relative Humidity
RPM	Revolutions per minute
RT	Relaxation time
SAE	Serious adverse event
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SNEL	Severe Neonatal Episodic Laryngospasm
SOC	System organ class
tid	Three times a day
TG	Thermo-Gravimetry
TRR	Time of righting reflex
UV	Ultraviolet
WT	Wild type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant LUPIN (EUROPE) LIMITED submitted on 26 June 2017 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Namuscla, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016.

Namuscla was designated as an orphan medicinal product EU/3/14/1353 on 19 November 2014. Namuscla was designated as an orphan medicinal product in the following indication: treatment of myotonic disorders.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Namuscla as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/namuscla

The applicant applied for the following indication:

Namuscla is indicated for the symptomatic treatment of myotonic disorders in adults.

The applicant has changed to Lupin Europe GmbH during the procedure at Day 121.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0155/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0155/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

New active Substance status

The applicant indicated the active substance mexiletine hydrochloride contained in the above medicinal

product to be considered as a known active substance.

Protocol assistance

The applicant did not seek Protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Kristina Dunder

The application was received by the EMA on	26 June 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	6 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	6 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 November 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	9 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	31 May 2018
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	6 July 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	7 September 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	18 September 2018
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	18 October 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Myotonic disorders are hereditary, rare diseases caused by a malfunction of skeletal ion channels (channelopathy) which share the main clinical symptom of muscle myotonia. Myotonic disorders comprise dystrophic myotonias (DM) and non-dystrophic myotonias (NDM).

The proposed indication is:

- Namuscla is indicated for the symptomatic treatment of myotonic disorders in adults.

Definition and Classification

Myotonic disorders (ICD-10 code G71.1) are a heterogeneous group of rare disorders linked by a common clinical symptom (myotonia) and characteristic electromyographical (EMG) features. Both groups of myotonic disorders (DM and NDM) can be further defined by genetic testing. A common feature of myotonic disorders is the associated malfunction of muscular ion channels which, in general, affects chloride or sodium channels (Kurihara, 2005).

In contrast to NDMs, DMs (type 1 and 2) are complex, multi-system disorders caused by an accumulation of expanded, non-coding RNAs, containing repetitive CUG and CCUG elements. Both DM types affect almost all human systems – not just skeletal muscles (Schoser et al., 2010). There is increasing evidence that the transcribed Dystrophia Myotonica-Protein Kinase gene (DMPK) pre-mRNA is directly toxic and results in abnormal splicing of other mRNA transcripts, including those of the muscle chloride ion channel (Turner et al., 2010).

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

2.1.2. Epidemiology

Prevalence

Based on epidemiological data, approximately 2 in 10,000 people are affected with myotonic disorders (which comprise the two main entities, DM and NDM) in the EU. Overall the prevalence rate of DM type 1 in the EU appears to be between 0.9 and 1.2 per 10,000 people (Magee et al., 1999; Siciliano et al., 2001; Norwood et al., 2009); the prevalence of type 2 is around 0.02 per 10,000 people (Norwood et al., 2009). Based on these data approximately 1 person in 10,000 is affected with DM in the EU. These estimations for type 1 and type 2 prevalence rates are supported by recent reviews on the topic (Udd et al., 2003; Wicklund, 2013).

2.1.3. Aetiology and pathogenesis

Aetiology

The causes of all myotonic disorders are different genetic aberrations which lead to a malfunction of muscular ion channels. All are hereditary and are either autosomal dominant or autosomal recessive disorders. An overview of myotonic disorders, the affected gene and ion channels, and the mode of inheritance are shown in Table 1 below.

Autosomal dominant DMs type 1 and 2 are not restricted to skeletal muscles (e.g. cataracts, conduction defects, insulin insensitivity, and respiratory failure) (Turner et al., 2010). The identified genetic cause underlying dystrophic myotonia type 1 (DM1) is related to a CTG trinucleotide expansion in the untranslated region of the DMPK on chromosome 19q13.3; for DM type 2, the underlying genetic cause is a CCTG repeat expansion on intron 1 of the zinc finger protein 9 gene on chromosome 3q21 (Jurkat-Rott et al., 2010b; Heatwole et al., 2013). These expansions form aggregated double stranded RNA within nuclei. The expanded RNA accumulates as double stranded structures in the nucleus and sequesters splicing regulators, rendering them unable to facilitate normal splicing of genes. The CLCN1 gene encodes the chloride channel and abnormal splicing of CLCN1 is thought to account for myotonia (Charlet-B. et al., 2002; Mankodi et al., 2002), although the precise pathophysiology is not entirely clear (Bernareggi et al., 2005). Cardiac dysfunction is partially explained by perturbed splicing and expression of troponin T (McNally et al., 2011).

For NDM disorders, the primary symptom is usually skeletal muscle stiffness caused by genes coding for skeletal ion channels. In general, mutations of either the CLCN1 gene coding for the skeletal voltage-dependent chloride channel or the SCN4A gene coding for the skeletal muscle voltage-gated sodium channel are responsible for ion channel malfunction (Jurkat-Rott et al., 2010a).

Pathophysiology

Myotonia is caused by skeletal muscle fibre hyperexcitability (Pusch, 2002). Membrane excitability, which is critical for skeletal muscle function, is regulated by ion channels. The underlying causes of myotonic disorders are skeletal ion channelopathies mainly affecting sodium or chloride ion channels (Trip et al., 2006). Clinically, a delayed muscle relaxation after voluntary or evoked muscle contraction is observed in both channelopathies (Logigian et al., 2005), while intermediary paralysis may also develop (in hyper- or hypokalaemic periodic paralysis).

In DM type 1, the length of the CTG trinucleotide expansion in the untranslated region of the DMPK gene is correlated with the onset and the severity of disease. This is not the case for type 2 (Turner et al., 2010).

Chloride 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. The skeletal muscle chloride channel also stabilises and regulates the electrical excitability of the muscle membrane.

In NDMs, mutations in the chloride channel decrease the chloride current in the physiological range and destabilise the muscle membrane, predisposing it to the hyperexcitability created by the accumulation of potassium in the t-tubules. Though potassium is normally present in the t-tubular lumen after an action potential, repetitive depolarisation of the sarcolemma (myotonia) only occurs when the chloride current cannot adequately buffer the cation load (Platt *et al*., 2009).

Sodium Channels

Mutations in the sodium channel result in multiple defects in channel gating and produce different disease phenotypes depending on the location of the mutation in the ion channel. The voltage-gated sodium channel, Nav1.4 (SCN4A), generates the action potentials that initiate muscle contraction in response to nerve stimulation. Immediately after the action potential, the channels undergo fast inactivation to prevent repetitive discharge. Sodium channelopathies possess altered channel gating that causes slowed or incomplete inactivation, or sometimes enhanced activation. Furthermore, the worsening of myotonia in response to low temperatures may result from cold-induced disruption of sodium channel slow inactivation. The net effect of these disturbances is an increase in sodium entry into the cell, which

prolongs the action potential duration and encourages persistent depolarisation of muscle fibres, causing myotonia. These mutations are known as gain-of-function due to their promotion of increased cell excitability (Platt *et al.*, 2009).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Clinical Manifestations

The diagnosis of myotonic disorders is based on medical history and examination of the patient and family members, in conjunction with judicious confirmatory laboratory and genetic testing.

Overall, myotonic disorders are a chronic life-long debilitating condition characterised by pain, fatigue, and muscle stiffness, resulting in frequent falls and disability (*Trip et al., 2009a*) – see also Table 2.5 1 for an overview.

DM is recognised by the presence of systemic features and the pattern of myotonia, i.e. distal and facial in type 1 and more proximal in type 2. Other features are a family history of maternally transmitted congenital disease in type 1 but not in type 2 and the presence of pain or muscle hypertrophy in type 2. Patients with DM1 mainly suffer from severe myotonia, pain, and extramuscular involvements such as cataracts, conduction defects, insulin insensitivity, balding, and respiratory failure. In general symptoms increase with aging, the life expectancy is reduced, and up to 50% of patients are at least partly wheelchair-bound shortly before they die. The most common causes of death are pneumonia/respiratory failure, cardiovascular disease, sudden death/arrhythmia and neoplasms. In patients with DM type 2, clinical symptoms are usually milder (*Turner et al., 2010).*

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

In the absence of systemic features and dystrophic weakness, a diagnosis of NDM becomes more likely. Several clinical and electrodiagnostic features help in making the distinction between chloride channelopathies or sodium channelopathies, and defined sub-entities based on clinical and EMG grounds (Michel *et al*., 2007) and, if necessary, are confirmed by genetic testing.

The major clinical manifestation of the NDMs is muscle stiffness as a consequence of the myotonia. Severe muscles stiffness drastically reduces the patient's ability to perform daily activities (Lehmann-Horn *et al*., 2004). Additional common symptoms include pain, weakness and fatigue – for an illustration of these symptoms please refer to the audiovisual material enclosed in Module 5.4 (Ginanneschi *et al*., 2017c). The intensity of symptoms ranges from mild (late onset) to life-threatening (neonatal presentation) (Matthews *et al*., 2010).

Particularly, sodium channelopathies can manifest in newborns as Severe Neonatal Episodic Laryngospasm (SNEL), characterised by muscle hypotonia and recurrent episodes of laryngospasm,

followed by apnoea. SNEL exhibits a spontaneous decrease in frequency and duration; this clinical phase is usually followed by myotonia (i.e., myotonia permanens or PC) (*Matthews et al., 2008*).

Table 1: Clinical Features of the Different Myotonias

	Dystrophic myotonia	**Non-dystrophic myotonia**				
	Dystrophic myotonia type 1 (DM1)	**Thomsen myotonia congenita (dominant)**	**Becker myotonia congenita (recessive)**	**Paramyotonia congenita**	**Periodic paralysis**	**Potassium-aggravating myotonia**
Gene	DMPK	Chloride channel (CLCN1)		Sodium channel (SCN4A)		
Locus	19q	7q	7q	17q	17q	17q
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant
Age of onset	Infancy to early adult	Infancy	Early childhood	Infancy	Infancy to early childhood	Childhood to early teens
Myotonia	Severe	Moderate to severe	Severe	Moderate to severe	Asymptomatic to severe	Asymptomatic to severe
Distribution of myotonia	Distal more than proximal	Generalised; face, arms > legs	Generalised; legs > face, arms	Face (eyelids), hands, thighs	Generalised if present	Proximal more than distal
Periodic weakness	No	No	Yes	Yes	Yes	No
Duration of weakness	None	None	Variable (transient on initiation of movement)	Minutes to days	Minutes to days	None
Progressive weakness	Yes	No	Some patients	No	Variable	No
Extramuscular involvement	Yes	No	No	No	No	No
Provocative factors	None	Cold, stress, pregnancy	Cold, stress, pregnancy	Cold, exercise (paradoxical myotonia), fasting	Cold, rest after exercise, fasting	Potassium, diet, delay after exercise
Alleviating factors	None	Exercise (warm-up effect)	Exercise (warm-up effect)	Warming	Carbohydrates, exercise	Exercise

2.1.5. Management

Current Treatment Options for Myotonic Disorders

Historically, many medications of various pharmacological classes have been administered in patients with symptomatic myotonia (*Trip et al., 2006*).

Mexiletine is a class Ib antiarrhythmic medication, structurally similar to lidocaine, that was initially developed as a treatment for ventricular arrhythmias with subsequent use in long QT syndrome (*Heatwole et al., 2013*). Mexiletine is the only medicinal product currently approved in the EU for the symptomatic treatment of myotonic disorders; this authorisation has been granted in France in 2010

through a national procedure. Mexiletine is currently registered in Hungary for the antiarrhythmic indication.

Besides mexiletine, other antiarrhythmics such as tocainide (Kwiecinski *et al*., 1992), flecainide (Desaphy *et al*., 2013), propafenone (Alfonsi *et al*., 2007) and procainamide (Finlay, 1982) have shown similar effects on sodium channel function and some efficacy on myotonic disorders. However, most of them cannot be recommended as treatment for myotonia, because of associated severe side effects.

Antiepileptics with sodium blocking properties have also been evaluated in myotonic disorders and were shown to have some efficacy, such as phenytoin (Kwiecinski *et al*., 1992) and carbamazepine (Sechi *et al*., 1983).

Rationale for the Use of Mexiletine

There is a substantial body of nonclinical and clinical evidence indicating that the cause of myotonic disorders is a malfunctioning of skeletal muscle ion channels, leading to a hyperexcitability of the muscle membrane. Despite the variability of pathophysiologies of the different genetic disorders broadly defined as "myotonic disorders", mexiletine exhibits a similar mode of action and efficacy in these various subtypes.

- With chloride channelopathies (such as MC and also DM1), the resting potential of the muscle cell is decreased, thereby destabilising the muscle membrane and predisposing it to hyperexcitability.
- With sodium channelopathies (such as PC), altered channel gating that causes slowed or incomplete inactivation (as well as occasionally enhanced activation) of action potentials is observed.

Mexiletine reduces or abolishes muscle hyperexcitability for both chloride and sodium ion channelopathies by inducing a slower influx of sodium (peak and late currents; sodium channel blocker) and probably a faster membrane repolarisation. The clinical usefulness of mexiletine resides in the ability to block sodium channels with a stronger potency in situations of excessive burst of action potentials (use-dependent block) and/or prolonged depolarisation (voltage-dependent block), as occurring in diseased tissues, rather than on physiological excitability (resting or tonic block). This blocking mechanism relies on the high-affinity drug binding to the receptor on the α-subunit of the channel when the latter is open and/or inactivated, and to a slow recovery from inactivation of the drug-bound channels during membrane repolarisation (De Luca *et al.*, 2000).

Mexiletine reduces the fast sodium influx into skeletal myocytes depending on the resting potential. As a consequence, the threshold for impulses is increased, and the depolarisation and conduction velocity is decreased. The repolarisation is increased and the effective refractory period shortened. In myotonic disorders, where the repolarisation of muscle cell membranes is impaired, the pharmacodynamic property of faster repolarisations and the slower influx of sodium are the mechanistic actions underlying the muscle relaxant effects of mexiletine in patients with muscular sodium or chloride channelopathies.

In different clinical series / cohort studies, clinical studies and also case reports, mexiletine was shown to reduce or abolish myotonia in the majority of patients with myotonic disorders. The mean hand grip relaxation time (RT) improved by approximately 50% in the mexiletine group as compared to the placebo group in patients with DM1 which was demonstrated in two randomised placebo-controlled trials (Logigian *et al.*, 2010). In patients with NDMs a multicentre randomised clearly has shown the efficacy of mexiletine treatment as demonstrated by a clear reduction of patient-reported outcome (PRO) measure – the severity score of muscle stiffness – and further secondary outcome measures (Statland *et al.*, 2012).

Mexiletine and unmet medical need - Submission of the Marketing Authorisation Application

The need for approved and available treatment options in the population with myotonic disorders is real. There is consensus, amongst the wider scientific community, that mexiletine is an effective treatment in both DM and NDM disorders (Deutsche Gesellschaft für Neurologie, 2012; Hoffman *et al.*, 2012; Heatwole *et al.*, 2013).

In the EU, there is currently no approved pharmacological treatment option available for patients (both adults and children) with myotonic disorders with the exception of France, where mexiletine is approved for the 'symptomatic treatment of myotonic syndromes' (in adults only). Other (off-label) pharmacological treatment options (see Section 1.2.1.6) are based on limited experience, appear less efficacious and / or are associated with a higher risk of severe side effects (Hoffman *et al.*, 2012; Heatwole *et al.*, 2013).

Consequently, there is a high medical need for approved, safe and effective treatment options for patients presenting with those types of disorders throughout the EU.

About the product

Pharmacological Class

Mexiletine is being developed as a sodium channel blocker for the symptomatic management of myotonic disorders in adults. The finished product is presented as capsules, each containing 167 mg of mexiletine (equivalent to 200 mg of mexiletine hydrochloride).

Mexiletine is a class Ib antiarrhythmic medication. It is structurally similar to lidocaine and was initially developed as a treatment for ventricular arrhythmias with subsequent use in long QT syndrome. Subsequently, mexiletine has gained acceptance as an effective antimyotonia therapy in both dystrophic and non-dystrophic myotonia (and for both the chloride and sodium channelopathies) (Kwiecinski *et al.*, 1992). Mexiletine acts by enhancing fast inactivation of sodium channels (Lehmann-Horn *et al.*, 1999; Jurkat-Rott *et al.*, 2001).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing mexiletine hydrochloride corresponding to 166.62 mg of mexiletine as active substance.

Other ingredients are:

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

Capsule shell: iron (III) oxide (E 172), titanium dioxide (E 171), and gelatin

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

2.2.2. Active Substance

General information

Mexiletine hydrochloride is a known active substance described in the Ph. Eur.

The chemical name of the active substance is (2RS)-1-(2,6-dimethylfenoxy)propan-2-amine hydrochloride corresponding to the molecular formula $C_{11}H_{17}NO \cdot HCl$. It has a relative molecular mass of 215.7 g/mol and the following structure:

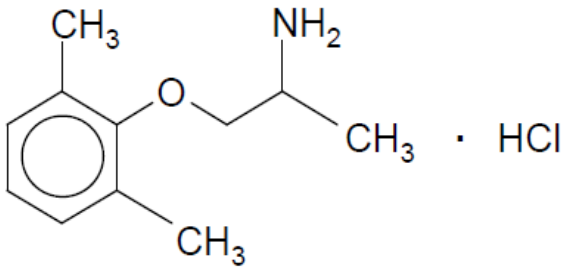


Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of IR, ^{1}H and ^{13}C NMR spectroscopic data, UV, elemental analysis and HPLC-MS. The solid state properties of the active substance were measured by DSC (differential scanning calorimetry), TG (thermogravimetry), IR (infrared spectroscopy), NMR spectra, and optical microscopy.

The active substance is a hygroscopic white crystalline powder, freely soluble in water, in methanol and in ethanol 95º.

The active substance exhibits stereoisomerism. It has one chiral center and exists as a racemic mixture of D and L forms.

Mexiletine hydrochloride shows polymorphism. Two polymorphic forms are known, Form I and Form II. The route of synthesis employed by the proposed manufacturer consistently produces the same polymorph. Form I can be converted to Form II by extreme heating (above 150°C). The two forms can be distinguished by their different infrared spectra.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is synthesized in 4 main steps using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Specification

The specification is in accordance with the Ph. Eur. monograph for mexiletine hydrochloride.

The active substance specification includes tests for appearance, identification (IR, test for chloride), solubility (Ph. Eur.), colour of solution (Ph. Eur.), clarity of solution (Ph. Eur.), pH (Ph. Eur), impurities

(HPLC), residual solvents (GC), loss on drying (weighting), water content (Ph. Eur.), sulphated ash (Ph. Eur), and assay (titration).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification and impurities testing has been presented.

Batch analysis data of 3 commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 commercial scale batches of active substance stored in the intended commercial package for up to 60 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 following parameters were tested*:* appearance, colour of solution, clarity of solution, chromatographic purity, loss on drying, water, assay, and assessment of packaging material. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. The stability data reveals that the active substance is chemically stable under all conditions studied. Based on assay levels and impurity levels there is no evidence of decomposition.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period without special storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as hard gelatin capsules, size 1 with a Swedish-orange cap and a Swedish-orange body, filled with a white powder.

The active substance is described in current European Pharmacopoeia. Two polymorphic forms of Mexiletine HCl are known, Form I and Form II. It is further concluded, that the route of synthesis employed consistently produces the same polymorph.

The compatibility of the active substance with the excipients is evaluated in the scope of stability testing of the finished product.

All the excipients used in the granulate blend formulation as proposed for marketing are well known and widely used in the pharmaceutical industry and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. At the time of the original formulation development (1970's), development studies were not required. The ingredients used are standard for the pharmaceutical form (hard capsules) and are considered suitable. Based on the extensive stability data available for the formulation and the long commercial history this is considered acceptable

The formulation proposed for marketing is the same as the clinical formulation tested in the pivotal clinical study, apart from the colorant for the hard capsules.

A risk assessment concerning any potential elemental impurities has been performed.

A dissolution method as quality control has been developed.

The manufacturing process is a standard process for the pharmaceutical form and consists of blending, wet granulation, fluid bed drying, sieving, blending/lubrication, encapsulation and packaging. Process evaluation data from the proposed commercial manufacturing site are provided.

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.

Manufacture of the product and process controls

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.

A process validation protocol has been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance, identification mexiletine (UV, HPLC), identification chloride (Ph. Eur.), identification iron oxide, identification titan dioxide, 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 specification parameters and acceptance criteria have been adequately defined and justified in line with relevant guidelines. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used 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.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Primary stability data from three commercial scale batches of finished product stored for up to 48 months under long term conditions (25 ºC / 60% RH), 12 months under intermediate conditions 30°C (± 2°C) / 65% 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, however they were not manufactured in the manufacturing site proposed for marketing.

Samples were tested for appearance, average unit mass, disintegration, assay, related substances and microbial contamination. Dissolution was not a part of the specification when these batches were tested however dissolution results are available from the historical stability batches. The analytical procedures used are stability indicating.

Three additional stability batches manufactured by the proposed manufacturing site for marketing were added to the stability program in April 2017. Three batches are tested after storage of 12 months at 25°C (± 2°C) / 60% RH, 30°C (± 2°C) / 65% RH and 40°C (± 2°C) / 75% RH for 6 months. Batches stored at

30°C (± 2°C) / 65% RH are only be tested in the event of out of specification results when testing batches stored at 40°C (± 2°C) / 75% RH.

Results are provided for three historical stability batches; 60 months data is presented for two batches and 36 months data for one batch, after storage at 25°C / 60% RH.

According to the applicable ICH recommendations, the data of three batches manufactured by the proposed manufacturing site support a shelf-life of 24 months; however, considering the extensive historical experience with the same formulation at other manufacturing sites, the CHMP concluded that the total stability data support the proposed 36 months shelf life. It is recommended that the applicant should submit additional stability data from the proposed manufacturing site confirming the proposed 36 months shelf life when available. In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No degradation has been observed.

Based on available stability data, the proposed shelf-life of 36 months and do not store above 30°C as stated in the SmPC (section 6.3) are acceptable.

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.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

At the time of the CHMP opinion, there was one minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. 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.

2.2.6. Recommendation 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 submit additional stability data supporting the proposed 36 months shelf life when available.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Class I antiarrhythmic agents and local anaesthetics, including mexiletine and lidocaine, exert their therapeutic effects by blocking voltage-gated sodium channels in a state-dependent manner. When channels are at the resting state at hyperpolarised potentials, the low affinity of mexiletine is revealed by tonic block, measured during brief infrequent depolarisations, with half-maximum inhibitory concentration (IC50) in the range of 236 to 294 µM in hNav1.4 transfected cells. The apparent affinity increases for depolarised channels, primarily due to a slow off-rate, and is the mechanistic basis for the antimyotonic, antiarrhythmic or antiepileptic action of mexiletine. Although the sodium currents recorded during electrophysiology studies are highly dependent on the test system and on the stimulation protocol, the literature indicates that the order of sensitivity of sodium channels to mexiletine is: cardiac channels > skeletal muscle channels > nervous channels.

Mexiletine is a chiral molecule with an asymmetric carbon at the amine end of the molecule. Although it was observed a two-fold higher activity of the R(-) stereoisomer on tonic block of skeletal muscle channels relative to the S(-) stereoisomer, this effect was not observed for the use-dependent block, which is relevant to the therapeutic indication of mexiletine, suggesting an absence of stereospecific effects of mexiletine in the indication of myotonia.

Concerning the pharmacological activity of mexiletine metabolites, m-Hydroxymexiletine (mHM) had a blocking effect similar to this of mexiletine in cells transfected with skeletal muscle channels Nav1.4, while this effect was almost twice this of mexiletine in cells transfected with cardiac channels Nav1.5. In addition to its blocking activity on cardiac sodium channels, mHM at the highest tested doses did not impair motor coordination in contrast to mexiletine, and showed cytotoxicity, suggesting mHM may be as effective as mexiletine, with less toxic effects. However, this metabolite represents less than 2% of the administered dose and is not likely to participate to the pharmacological effect of mexiletine. The other hydroxylated metabolites were found less active than mexiletine in blocking the skeletal muscle sodium channels. p-Hydroxymexiletine (PHM) and hydroxymethylmexiletine (HMM) are 5- to 10-fold less potent than mexiletine, while bis(hydroxymethyl)mexiletine and p-hydroxyhydroxymethylmexiletine are more than 50-fold less potent.

Concentrations $\geq$ 10 µM mexiletine were shown to be effective in the in vitro models of myotonia. Although these concentrations are high relative to the plasma therapeutic range (2.8 to 11 µM) observed in the MYOMEX study in myotonic patients, the rapid tissue uptake of mexiletine allows reaching 7-10 fold higher concentrations in the target tissues, in the range of the pharmacological concentrations found in the in vitro studies. In vivo studies conducted in animal models of myotonia confirmed the beneficial effects of mexiletine

Secondary pharmacodynamic studies

The secondary PD actions of mexiletine are related to its blocking effects on sodium channels other than the skeletal muscle channels Nav1.4. The blocking effects of mexiletine on the cardiac channels Nav1.5 are related to its antiarrhythmic effects as well as its effects in the long QT syndrome. The blocking effects of mexiletine on sodium channels from the CNS and PNS are related to its anticonvulsive, analgesic, local anaesthetic effects, as well as its effects on neuropathic pain.

Safety pharmacology programme

The outcome of the safety pharmacology evaluation of mexiletine suggests that adverse effects related to the mode of action of mexiletine are likely to occur on the cardiovascular and CNS systems upon administration of therapeutic doses. The effects identified include possible changes in the QRS, QTc and PR intervals, tachycardia, motor incoordination, ataxia, as well as mydriasis and salivation. The relevance of these findings to the clinical use of mexiletine is discussed in the clinical section, where these findings are compared to the adverse drug reactions (ADRs) observed in the MYOMEX clinical study and post-marketing data.

Cardiac system

The safety pharmacology effects of mexiletine on the cardiac system observed in *in vitro* studies consisted in negative chronotropic and inotropic effects observed at high concentrations in isolated guinea-pig atrium, with ED_{50} of 230 to 250 µM, more than 25-fold the plasma therapeutic concentration and are considered not relevant to the therapeutic use of mexiletine.

The effects of APD shortening effects in dog Purkinje fibres and ventricular muscle fibres, increased stimulus threshold and increased effective refractory time observed in guinea-pig atrium were observed at concentrations of 3.3 to 22 µM. These concentrations are in the therapeutic range of mexiletine and correspond to its pharmacological effects as a direct consequence of the inhibition of the cardiac channel Nav1.5.

An important safety effect of blocking the cardiac channel Nav1.5 is the increase in conduction time through the ventricular myocardium, which was assessed pre-clinically via the duration of the QRS interval. A slight increase (17%) in QRS duration was seen *in vitro* in rabbit ventricular wedge at concentrations within the therapeutic range, however no such effects were observed in telemetered rats tested at doses up to 45 mg/kg PO (HED of 7.3 mg/kg) and in telemetered dogs at 10 mg/kg PO (HED of 5.5 mg/kg) or 18 mg/kg IV (HED of 10 mg/kg). Since these HED's are in the range of 2 to 3-fold the therapeutic dose, and a possible increase of QRS interval was concluded from the toxicology studies and changes in QRS complex were seen in anaesthetised animals, increases in QRS duration may not be excluded following administration of therapeutic doses of mexiletine to patients. The possibility of observing ECG effects at the therapeutic dose is also supported by the publication of Cros *et al.* (2012), where decreased QTc and increased PR intervals were observed in conscious dogs treated PO with 10 mg/kg mexiletine.

The haemodynamic effects noted following administration of mexiletine were different between studies with anaesthetised and conscious animals. Bradycardia was often observed in studies with anaesthetised animals together with hypotension, while tachycardia was seen in conscious dogs at 18 mg/kg IV (HED of 10 mg/kg), as well as at 40 mg/kg PO in the 52-week toxicity study in dogs (HED of 22 mg/kg). This discrepancy might be explained by the anaesthetised status of animals, which generally received urethane at doses around 2 g/kg IP. As reported by Hara *et al.* (2002), urethane acts on neurotransmitter-gated ion channels and modifies the response to several neurotransmitters, resulting in modified chloride currents and in an anaesthetic effect. The results from studies testing conscious animals are expected to be more relevant to the therapeutic use of mexiletine.

Taken together, the overall results of the studies evaluating the cardiac safety pharmacology of mexiletine suggest that, upon administration of therapeutic PO doses, very slight cardiac effects (possible increased QRS, decreased QTc, increased PR intervals), tachycardia are likely to occur, which are related to the pharmacological properties of mexiletine.

Central nervous system

The results of the studies evaluating the safety pharmacology of mexiletine on the CNS suggest that administration of a therapeutic dose to humans may lead to motor coordination side effects at doses corresponding to the equivalent therapeutic dose in behavioural studies, while higher doses may lead to ataxia.

Other systems

The increased respiratory rate and decreased tidal volume noted following IV administration of mexiletine is of uncertain relevance to the PO route. Mexiletine had no significant effects on the gastrointestinal and renal systems upon PO administration.

Pharmacodynamic drug interactions

Superadditive effects have been evidenced with either PO or IV administration of mexiletine and antiarrhythmics (lidocaine, prajmalium, quinidine, procainamide), β-blockers (propranolol, bunitrolol) and a local anaesthetic (procaine). Other studies show that the convulsions induced by toxic doses of mexiletine can be abolished by previous administration of chlordiazepoxide, diazepam and oxazepam, as well as by phenobarbitone. The applicant has adequately discussed the clinical implications of superaddictive effects with β-blockers and procaine at pharmacological and toxicological levels. The conclusion that the use of β-blockers is not recommended, and procaine/procainamide is contraindicated in myotonic patients treated with mexiletine is acceptable. These conclusions have been reflected in the SmPC, as requested.

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetic studies discussed in this section do not provide an adequate basis for comparing and interpreting results from toxicology and clinical studies.

The analytical methods used for the determination of pharmacokinetic (PK) parameters of mexiletine included either radioactive detection following administration of [^{3}H]-mexiletine, reported by the Sponsor and the scientific literature or using HPLC methods coupled with various detection methods.

The PK data arise from toxicokinetic studies in rats and dogs and in monkeys, performed during 26week (PO dosing) and 4 weeks (IV dosing), respectively, which used radioactive material. Results from these studies thus report the PK fate of both mexiletine and its metabolites and give an indication of the PK of mexiletine. PK data are reported from the scientific literature and mainly consist in C_{max} determination, which is an important parameter for the PD effect of mexiletine.

Absorption

Studies conducted by BI and evaluating the PK of mexiletine following single oral (PO) doses are not available. The PK parameters following single PO doses to rats and dogs and intravenous (IV) doses to dogs are reported from the scientific literature. The PK parameters of mexiletine following repeated PO administration to rats and dogs up to 26 weeks and IV administration to monkeys for 4 weeks are reported from toxicokinetic studies. The little amount of data gathered on the PO bioavailability (97% in rats), absorption and drug accumulation agree with the human data (Module 2.7.2). The toxicokinetic studies conducted during the 26-week PO studies in rats and dogs and in the 4-week IV study in monkeys indicated a significant exposure to mexiletine in these studies, as well as a likely absence of drug accumulation. However, no dose proportionality and no gender effects have been evaluated for mexiletine.

Distribution

The tissue distribution studies have shown that mexiletine is rapidly and widely distributed in tissues within 15-30 min following PO administration of radioactive material and reaches tissue levels higher than the blood levels at all times. Using this route, the distribution is highest in the liver, then in the lungs, followed by kidneys, adrenals and other organs including heart and brain. The distribution of radioactivity has been determined in skeletal muscles from pregnant female rats following a PO dose of [^{3}H]-mexiletine, where the levels of tissue radioactivity suggest an 8-10-fold drug accumulation relative to plasma. The radioactivity was rapidly cleared from organs, the highest amounts of radioactivity being found in the liver and kidneys 6 hours after PO administration to rats and representing 5-7% of the maximal amount of radioactivity found in these organs 15-30 min after treatment. The high levels of radioactivity measured in liver and kidney are consistent with the liver metabolism of mexiletine, as well as with its urinary excretion.

The binding of mexiletine to plasma proteins represents about 50% and 75% in rats and dogs, respectively, an extent of the same range as humans.

Mexiletine crosses readily the placenta, leading to foetal blood levels similar to these of their mother.

Metabolism

Little information was identified on the metabolism of mexiletine in animals, in comparison to the extent of information available for humans. Experiments conducted with liver microsomes from animal origin showed the presence of metabolites found with human liver microsomes, with a large interspecies variability for mHM. Similarly, the Phase 1 and Phase 2 metabolites identified in rat and rabbit urine were also identified in humans. The little available information on the metabolism of mexiletine in the species tested in the safety and toxicology studies (mice, rats, rabbits, dogs and monkeys) does not allow establishing metabolic pathways specific to these species, as well as the relative amounts of metabolites formed in these species.

Although studies conducted with human liver microsomes have determined that CYP2D6, CYP1A2 and CYP2B6 are mainly involved in the catabolism of mexiletine, no such studies were identified in animals. Mexiletine has been found to be a potent inhibitor of CYP1A2 in mice. However no data on the effects of mexiletine on CYP induction or substrate properties were identified in rats, in rabbits and dogs, the species tested in the toxicology programme.

Excretion

Excretion of the radioactivity associated to the PO administration of [^{3}H]-mexiletine occurs mainly via the renal route (about 80% within 96 hours in dogs), while faecal excretion represents less than 10%. Mexiletine is excreted in milk to a daily extent expected to represent 1/20 of the daily therapeutic dose.

Pharmacokinetic drug interactions

The interaction of mexiletine with drug transporters has been evaluated only for the P-gp transporter, for which mexiletine is not expected to be a substrate. Non-clinical PK drug-drug interactions have been evaluated for lidocaine in rabbits, where drug interaction derived from the displacement of lidocaine from tissue binding sites by mexiletine resulted in increased plasma lidocaine concentrations

2.3.4. Toxicology

Single dose toxicity

The studies reported were conducted between 1968 and 1992. All toxicology studies performed in 1981 and later complied with the US FDA GLP regulations. The species tested in the toxicology programme included mice, rats, rabbits, dogs and monkeys, the species commonly used for this type of studies and for which exists a significant amount of background data. The toxicology studies include repeat-dose toxicity study in dogs, carcinogenicity studies in mice and rats and reproductive and developmental toxicity studies in rats and rabbits. Toxicology studies conducted before 1981 generally followed the state-of-the-art methods at this time. Their design and methods mostly comply with the ICH M3(R2) guideline as well as with the current guidelines on repeated dose toxicity, carcinogenicity (ICH S1) and reproductive and developmental toxicity (ICH S5[R2]), with the notable exception that no toxicokinetic studies were conducted in all but 2 studies.

The applicant presented data demonstrating that the acute toxicity of mexiletine has been determined in mice, rats, rabbits and dogs, using the oral, IV, IP, SC and IM routes. In all settings, symptomatology was similar across species and routes and related to the pharmacodynamics of mexiletine. At lower doses, ataxia and tremors were observed, followed by convulsions at higher doses, leading to death. The timing of occurrence and severity were related to the dose and routes of administration, highest doses leading to the most severe and earlier symptoms.

Table 2: Highest non lethal doses and LD_{50} of mexiletine in mice, rats, rabbits and dogs following acute treatment via the oral, IV, IP, SC and IM routes

Species	Treatment route	Highest non lethal dose (mg/kg)		LD_{50} (mg/kg)		Study Number
		Males	Females	Males	Females	
Mice	PO	160		260		U68-0169 p. 49
		< 200	< 200	310	400	U75-0252
		100	100	310	275	U76-0264
		---	200	---	320	U76-0262
	IV	30	40	43	50	U75-0252
		30	10	47.5	35	U76-0263
	IP	90	90	119	139	U76-0264
		100	110	125	140	U76-0263
		---	100	---	145	U76-0262
	SC	80		170		U68-0169 p. 50
		< 200	< 200	235	255	U75-0252
	IM	50	100	128	135	U75-0252
Rats	PO	100	100	275	240	U76-0264
		---	100	---	290	U76-0262
		< 100	< 100	330	400	U75-0252
		300		630		U68-0169 p. 51
		150	150	614	289	U84-0224
	IV	30	40	27	30	U75-0252

Species	Treatment route	Highest non lethal dose (mg/kg)		LD_{50} (mg/kg)		Study Number
		Males	Females	Males	Females	
		15	20	27.5	30	U76-0263
	IP	65 — 80	60 90 90	76 — 100	79 99 92.5	U76-0263 U76-0262 U76-0264
	SC	< 200	< 200	540	500	U75-0252
		150		720		U68-0169 p.52
	IM	50	100	260	190	U75-0252
Rabbits	PO	100	< 100	180	160	U75-0252
		300		~ 450		U68-0169 p. 53
Dogs	PO	175 75 64 (2 tablets)		356 112 113 (4 tablets)		U76-0245 U68-0169 p. 54 U81-0293
	IV	12.5 40		18.75 ~ 40-60		U76-0244 U68-0169 p. 56
	SC	65		~ 65-88		U68-0169 p. 55

The acute toxicity of the (R)-, (S)-enantiomer of mexiletine and of the racemate is not different following oral and IV administration to mice. The observed symptoms occur similarly and the maximum non lethal dose is not different via both routes. The LD_{50} of the (S)-enantiomer is lower than the (R)-enantiomer via the oral route, while they are similar for the IV route. No sex differences in the acute toxicity of the enantiomers were observed by either route.

Repeat dose toxicity

Considering repeat-dose toxicity in mice, mexiletine is considered to have been well tolerated by mice at oral doses of 40 and 80 mg/kg in a 4-week subacute oral (by gavage) toxicity study, although slight ataxia and reduced liver weight were noted at this latter dose as reported. Despite a reduced liver weight, the dose of 40 mg/kg is considered to be the NOAEL for mice in this study, since the applicant considered that this is not a treatment related effect. Nevertheless, no justification is given for this not to be considered an adverse effect, although it's acknowledged that this was only seen in a small percentage of animals across doses. At the dose of 160 mg/kg, mexiletine induced mortality, reduced body weight and food intake for the first treatment week, reduced liver and spleen weight and myocardial scars.

In rats, the oral dose of 40 mg/kg of mexiletine appears to be well tolerated by rats for 4 weeks (4-week subchronic oral (by gavage) toxicity study) and is the NOAEL for this study. The 100mg/kg dose causes ataxia and convulsions were seen at 250 mg/kg. These higher doses appear to have no adverse effects on body weight, food and water consumption. Mexiletine caused an increase of cholesterol levels in all groups, together with a slight dose-dependent liver enlargement of females, significant at the high dose tested. A mild decrease in total proteins was also noted in males at the high dose. These effects were reversed during the recovery period. No other findings have been observed.

In both 26-week chronic oral (by gavage) toxicity studies in rats, the NOAEL is considered to be the same. Sprague-Dawley rats appear to be more sensitive to the convulsive effects (observed already at 80mg/kg in these animals) in comparison to CD-C.O.B.S. rats.

No significant effects were noted on body weight, food and water consumption, haematology and urinalysis at any doses up to 250 mg/kg for 4 weeks in Study U76-0266 and up ot 120 mg/kg for 26 weeks in Studies U73-0218 and U75-0256.

Slightly increased ALP and SGPT levels were noted in females after 4 weeks treatment at 250 mg/kg in Study U76-0266, and the argument of the applicant is that these were possibly due to low control values, while slight and significant increased levels of cholesterol were noted at all doses in both sexes. All

parameters appear to return to normal values after the 6-week recovery period. No significant changes in clinical chemistry were noted at doses up to 120 mg/kg for 26 weeks in Studies U73-0218 and U75-0256. At necropsy, increased liver weight was observed in females treated at 250 mg/kg for 4 weeks in Study U76-0266, with no histopathological correlate. Fatty degeneration of liver was observed with a slightly higher incidence and severity in animals treated at 120 mg/kg for 26 weeks in Study U73-0218, and not in Study U75-0256 at the same dose. The relevance of these findings in the liver remains unknown at these medium and high doses, and it's described that signs of recovery were observed for these findings. Other changes in organ weights included decreased thymus weight at all doses up to 250 mg/kg for 4 weeks in Study U76-0266 (not observed in studies with longer duration). In all cases, there were no histopathological correlates to these findings and the findings were reversible according to the study reports. Taken together, the findings reported led to NOAELs of 40 mg/kg for all 3 Studies U76-0266, Study U73-0218 and U75-0256, independent of the treatment duration.

When mexiletine was administered orally in food to rats for 13 to 78 weeks, the observed mortality was not significantly increased at the highest doses tested and for durations up to 78 weeks.

Slight growth retardation was observed at doses ≥ 60 mg/kg for 13 weeks in Study U69-0198, ≥ 90 mg/kg for 26 weeks in Study U76-0256 and 240 mg/kg in Study U76-0242. This was accompanied by a slightly reduced food intake and increased water intake. Ataxia was noted in animals receiving the highest dose of 200 mg/kg for 26 weeks in Study U76-0256.

Changes in clinical chemistry liver markers were once more observed when using this route. These included increased ALP and cholesterol values at 13 weeks and SGPT at 26 weeks, which were considered by the applicant to be due to low control levels. Although this might be true, the fact that also cholesterol and total bilirubin were slightly increased (to values that were not considered biologically significant) along with increased levels of SGPT and ALP (noted at 240 mg/kg from 13 weeks upwards in the 78-week Study U76-0242), the liver clearly remains as a target organ for toxicity. At necropsy, reversible liver fatty infiltration was observed at doses ≥ 60 mg/kg for 13 weeks in Study U69-0198, males being more affected than females. Similar observation made in males treated at 200 mg/kg in Study U76-0256 was considered within the range of the background data, although the liver weight of both sexes was significantly increased at this dose.

The NOAELs for these studies were 30 mg/kg for 13 weeks in Study U69-0198 (doses tested: 15, 30, 60 and 150 to 200 mg/kg), 90 mg/kg for 26 weeks in Study U76-0256 (doses tested: 40, 90 and 200 mg/kg) and 40 mg/kg for 78 weeks in Study U76-0242 (doses tested: 20, 40 and 240 mg/kg). In view of the doses tested in these studies, the overall NOAEL for rats treated with mexiletine for up to 78 weeks is 90 mg/kg. This assumption is considered satisfactory. As expected, manifestations of toxicity due to mexiletine are higher when the IV route of administration is used. This is consistent with previous observations already considered when looking at Single Dose Toxicity.

Considering dogs, dogs treated orally with mexiletine exhibited signs of convulsive state with incidence and severity increasing with dose. Growth retardation was noted in the early phase of Studies U75-0255 and U74-0196, and food consumption was not altered except for males from the 52-week Study U74-0196, where it was increased in males. Growth retardation had previously been reported in rodents under repeat dose toxicity testing. Heart rates were slightly increased 1 and 2 hours after treatment in the 52-week Study U74-0196, with no effects on the ECG and the transmission time. The QRS interval was increased at all doses in the 25-week Study U75-0255. Necropsy revealed possibly increased liver fat content or fatty degeneration at 40 mg/kg in Study U73-0217. Liver fatty infiltration was observed in 1 animal treated at 30 mg/kg in the 13-week Study U76-0238, at ≥20 mg/kg in the 27-week Study U73-0217. Liver siderosis was seen at ≥20 mg/kg in the 27-week Study U73-0217, and ≥10 mg/kg in the 52-week Study U74-0196. Generalised congestion was seen in 2 females treated at 40 mg/kg in the 25-week Study U75-0255. In the 52-week Study U74-0196, prematurely dead animals had severe

plethora in large parenchymas and haemorrhages in several organs, confirmed by the histopathological observations. Histopathological changes included fatty degeneration of myocardial fibres in animals treated with 9 and 15/20/30 mg/kg in the 13-week Study U76-0238, in animals treated at 5 and 10 mg/kg in the 27-week Study U73-0217. Similar changes were noted at 5 mg/kg in the 52-week Study U74-0196. Taken together, the results of the repeat dose toxicity studies in dogs led to NOAELs of 3 mg/kg for 13 weeks in Study U76-0238, 10 mg/kg for 25 weeks in Study U75-0255, 5 mg/kg for 27 weeks in Study U73-0217 and 10 mg/kg for 52 weeks in Study U74-0196.

Dogs receiving IV doses of mexiletine experienced dose dependent effects. No deaths occurred at the doses tested. Body weight gain and food intake were significantly reduced in females treated for 4 weeks at 12 mg/kg in Study U71-0154. Significantly increased heart rates were observed a 13.5 mg/kg in Study U71-0154. No effects were observed on the PR, QRS, QT and QTc intervals in this study. In Study U82-0384, where measurements took place before treatment, mexiletine did not affect the baseline heart rate. At necropsy, apart the findings at the injection sites related to the injection technique, no macroscopic or microscopic changes were noted.

Two signs of fatty degeneration of liver cells and myocardial fibres have been identified and are not reported in the Tabulated list of ADRs of the SmPC. Both signs have not been identified in the latest PSUR edited by BI and covering the period from October 2005 to October 2008. This PSUR concerns 486,077 patient years (marketed product) and approx. 7,740 patient years (clinical trials) for this period. The following occurrences were reported using the SOCs of Cardiac Disorders (no AE related to fatty degeneration of myocardial fibres), Hepatobiliary Disorders (Hepatic lesion, 1 SAE), Investigations (no AE of fatty degeneration of liver cells and myocardial fibres) and Metabolic disorders (Hypercholesterolaemia, 1 SAE). Therefore, these findings may be expected to be of very low expectancy and no specific measures are envisaged.

In monkeys, intravenous administration of mexiletine resulted in ataxia, occasional nystagmus, salivation and occasional tonico-clonic convulsions at 12 mg/kg. Slight decreases in body weight and food consumption were observed in animals from this group. No effects were noted on heart rates, ECG and conduction time, however heart rates were high before treatment due to animal agitation. No ophthalmic effects of mexiletine were noted at any doses, as well as in haematology and clinical chemistry parameters. At necropsy, local irritation was noted in the animals receiving the dose of 12 mg/kg. Occasional lymphocytic infiltrations with eosinophilic cell necrosis, as well as fine to moderate fatty deposits of individual cells and Kupffer cells were observed with the same severity in the liver of almost all animals from all groups, although the incidence of fatty deposits in the liver may suggest a drug effect at 4.5 and 12 mg/kg. The NOAEL of mexiletine in this study was 4.5 mg/kg.

Two *in vitro* reverse mutation studies were conducted. In both studies, mexiletine was not found to be cytotoxic and had no mutagenic effects in any strains of bacteria.

Carcinogenicity

The applicant provided information on the carcinogenic potential of mexiletine evaluated in 2 long term studies in mice for 78 weeks (Study U82-0381) and in rats for 2 years (Study U83-0309). In both studies, mexiletine was administered orally in food and was well tolerated up to the highest doses tested, 160 mg/kg in mice and 240 mg/kg in rats. No effect was noted on mortality and the clinical signs observed corresponded to those generally observed in the elderly animals. Mexiletine decreased dose-dependently the body weight and food intake of animals during the study. This should be considered under the previous observations noted in the repeat dose toxicity studies. The absence of exposure data in the carcinogenicity studies and the incomplete genotoxicity testing hampers to evaluate the carcinogenicity risk of mexiletine.

The applicant was requested to submit during assessment a critical assessment of the carcinogenicity studies and in particular of the following points:

- The studies tested mexiletine mixed in food at doses of 40, 80 and 160 mg/kg in mice and 60, 120 and 240 mg/kg in rats. No toxicokinetic studies were performed and the animal's exposure was therefore not directly measured;
- An indirect evaluation of the animal's exposure to mexiletine was done in both studies by weighing weekly the amount of food eaten by the animals and by adjusting the concentration of mexiletine mixed in food according to the weekly measured body weight and food intake. This is considered not satisfactory given the significant variations in mexiletine concentrations in food (in both rats and mice) and reduced ingestion of food in rats;
- Since no direct exposure data is available, an additional indirect evaluation of the level of exposure of rats given mexiletine in food consisted in a comparison of its effects on mortality, food intake and body weight gain between the 107-week carcinogenicity study and the 26- week and the 78-week repeat-dose toxicity studies (Studies U76-0256 and U76-0242, respectively), and since no clear information on exposure is available this is not considered as reliable information for assessment;
- absence of historical data from the laboratory to validate the findings of neoplastic changes.

The applicant acknowledged also that the reports of the 2-year carcinogenicity studies in mice (Study U82-0381) and in rats (Study U83-0309), presented in the initial submission of the MAA, were incomplete. Over the course of the evaluation procedure, missing Parts 2 and 3 of the rat Study U83-0309 have been made available and include: fate of individual animals, haematological individual values, individual macroscopic examinations (for males and females killed or dying during the treatment) as well as: Curriculum vitae, protocol and amendments, analysis certificate, technique for formulation analysis (concentration, homogeneity and stability), chemical analysis of the diet, water and sawdust, collation of data, recording, delivery and preparation of the test substance, techniques.

However no additional information on the exposure of animals to the test substance was presented in the study report U83-0309, and additionally the applicant acknowledged the lack of toxicokinetic data to support the animal's exposure during the carcinogenicity studies U82-0381 and U82-0309.

To address the genotoxic and carcinogenic potential of mexiletine, the applicant performed and provided a complete genotoxic assessment including an Ames test, an *in vitro* cytogenetic test and an *in vivo* cytogenetic test. This programme included a bacterial reverse mutation test (Study 46107 MMT), an *in vitro* micronucleus test in cultured human lymphocytes (Study 46109 MNH) and an *in vivo* bone marrow micronucleus test by oral route (gavage) in rats (Study 46108 MAR). The Final Study Reports were provided and assessed.

Mexiletine did not show any mutagenic activity in the bacterial reverse mutation test with *Salmonella typhimurium* and *Escherichia coli* strains, either in the presence or absence of metabolic activation. In the in vivo testing, no statistically significant or any increase in the frequency of micronucleated polychromatic erythrocytes (MPE) cells was noted in any of the test item-treated groups relative to the vehicle control group and no dose-response relationship was brought to evidence. The toxicokinetic measurements performed 0.5 h and 2 h after the last treatment at the high dose showed that the bone marrow of animals was adequately exposed to mexiletine. Based on the overall data provided by the applicant regarding these studies, it was agreed that the test item did not induce damage to the chromosomes or the mitotic apparatus of bone marrow cells. In conclusion, mexiletine did not exhibit any

mutagenic or chromosomal damage effects under the conditions of the genotoxicity testing of this programme.

According to the applicant, the absence of carcinogenic effects of mexiletine is also supported by the previous clinical experience.

Information that carcinogenicity studies were of unclear clinical relevance was also reflected in the Section 5.3 of the SmPC.

2.3.5. Ecotoxicity/environmental risk assessment

The starting posology comprises one tablet (167 mg mexiletine, corresponding to 200 mg mexiletine hydrochloride) to be taken daily and the recommended maximal dose is 500 mg (mexiletine, corresponding to 600 mg mexiletine hydrochloride).

The applicant prepared an environmental risk assessment. Following a thorough assessment, no risk was identified as summarised in the tables below.

Table 3: Physicochemical properties of mexiletine

Parameter	Method	Results	Conclusion
Water solubility		⩾300 g/L – 20ºC	Freely soluble in water
Dissociation constant		pKa= 8.4	Ionisable
Molecular weight		215.73 g/mol	
CAS Number		5370-01-4	

Table 4: Summary of environmental fate/effects

Substance (INN/Invented Name): mexiletine / Namuscla			
CAS-number (if available): 1210344-57-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	-1.24 (pH 5.05) 0.05 (pH 6.94) 2.28 (pH 9.75)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{OW}	-1.24 (pH 5.05) 0.05 (pH 6.94) 2.28 (pH 9.75)	Not B.
	BCF	NA	B/not B

Persistence	DT_{50} or ready biodegradability	$DT_{50, water}$ = ~4-7d $DT_{50, whole\ system}$ = ~29-59d	Overall, unlikely to be persistent.
Toxicity			Not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	3.0	µg/L	> 0.01 threshold (Y). Triggers Phase IIA.
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	K_{oc} sludge 1 = 34 L/kg K_{oc} sludge 2 = 53 L/kg	K_{oc} sludge < 10 000 L/kg. Adsorption data for at least 3 soils/sediments for equilibrium partitioning calculations in sediment risk assessment will be provided by the applicant as a PAM
Biodegradability	OECD 301	No biodegradation within 28 days	Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50, water}$ = ~4 - 7d $DT_{50, whole\ system}$ = ~29 - 59d % shifting to sediment = 50-58% AR after 14d.	Triggers an OECD TG218 test.

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition	OECD TG201	NOEC	4600	µg/L	*S.subspicatus*

Algae, Growth Inhibition	OECD TG201	NOEC	1540	µg/L	*P. subcapitata*
Daphnia sp. Reproduction Test	OECD TG211	NOEC	286	µg/L	*D. magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	1000	µg/L	*D. rerio*
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	100-131	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD TG218	$NOEC_{OC10}$	77000	µg/ kg	*C. riparius*

In Phase I, a PEC surfacewater 3.0 µg/L was calculated for mexiletine hydrochloride. As it exceeds the action limit of 0.01 µg/L, a Phase II fate and effects assessment were performed.

Groundwater exposure estimation

The exposure of groundwater from mexiletine was calculated as 3.0X 0.25 = 0.75 µg/L

Predicted no effect concentrations (PNECs) and Risk characterisation

PNEC	PEC/PNEC ratio	RisK characterisation
PNEC surfacewater = 28.6 µg/L	0.10	<1 No risk
PNEC groundwater = 28.6 µg/L	0.026	<0.1 No risk
PNEC microorganism = 10 000 µg/L	0.0003	<1 No risk

No risk was identified

Phase II, Tier B

Environmental assessment in the sediment compartment

Sediment Dwelling Organism (OECD 218 - Study S18-00275)

The study was performed under static conditions in artificial sediment for a period of 28 days. Nominal mexiletine concentrations were 6.25, 12.5, 25.0, 50.0 and 100 mg/kg.

The maturation of larvae to adults midges were similar to the control. Based on the initial measured sediment concentrations of applied test substance, midge development rate (male/female combined) and percent emergence, the No-Observed-Effect Concentration (NOEC) was determined to be 100 mg/kg. No effects were observed in the nominal concentrations tested. However, the measured content of mexiletine was more than 20% deviated of nominal concentration at the end of exposure period, thus a geometric mean was calculated and a NOEC of 77 mg/kg determined.

Calculation of the Predicted Environmental Concentration in sediment (PECsediment)

The PECsediment was calculated following the methodology provided in ECA – 2016. In this approach are considered the following parameters:

$$\text{Ksusp-water} = F_{watersusp} + F_{solidsusp} \cdot \frac{Kp_{susp}}{1000} \cdot RHO_{solid} = 0.9 + 0.1 \cdot \frac{7.1}{1000} \cdot 2500 = 2.7$$

Fwatersusp = 0.9	:	fraction water in compartment suspended matter (default)	[m^3 m^{-3}]
FSolidsusp = 0.1	:	fraction solids in compartment suspended matter (default)	[m^3 m^{-3}]
RHOsolid = 2500	:	density of solid phase (default)	[kg m^{-3}]

The maximum Kd: 7.1

Factor of 2.6 = conversion from wet to dry sediment

PEC sediment = 0.021 mg/kg dry sediment

The maximum sediment Kd at an equilibrium period of 14 days after application, was calculated from the results of the OECD 308 study. Therefore, the Kd value was used for the calculation of PEC sediment. This approach was accepted.

Sediment risk characterisation

PEC/PNEC = 0.021/1.0 <1 No risk identified

2.3.6. Discussion on non-clinical aspects

The assessment of the pharmacological, PK, and toxicological properties of mexiletine for the indication of the treatment of myotonic disorders relies on studies performed between 1968 and 1992 and covering the secondary PD and toxicological aspects of the dossier. Other information, the primary PD and PK, rely on the scientific literature. The studies conducted were performed before regulatory guidance came into force, or at their early beginning. They were, however, conducted according to standards which make them consistent with most recommendations of the actual guidelines, the most important caveats being the absence of GLP compliance for the earliest studies and the absence of toxicokinetic studies. For this latter reason, the safety margins of mexiletine could not be estimated based on the drug exposures and are only based on allometric scaling of the NOAELs determined across studies.

The potential adverse effects identified in the non-clinical programme of mexiletine may be classified in 3 groups, and compared to the ADRs listed from the clinical experience with mexiletine, arising from the MYOMEX clinical study and post-marketing data covering several millions patient-years of exposure (SmPC Section 4.8):

- Adverse effects arising from the safety pharmacology evaluation, expected to occur at the single therapeutic doses of 167 mg. These include:
  - Possible changes in the QRS, QTc and PR intervals, tachycardia: the potential effects of tachycardia and ECG alterations are well known pharmacological effects of mexiletine and are taken into account in the labelling of mexiletine.

- Motor incoordination, ataxia: these effects have been evidenced in healthy animals and their relevance to the patient population is uncertain, since mexiletine alleviates the motor symptoms of this population.
- Mydriasis and salivation: salivation was identified as an increase in the effect of carbachol-induced salivation in mice. This effect was observed in toxicology studies at doses where mexiletine induced clinical signs of convulsive state in dogs, which are not expected to be reached in the therapeutic population and is considered unlikely. Mydriasis may be related to blurred vision reported and is thus taken into account in the labelling of mexiletine.

- Adverse effects arising from the toxicology studies and corresponding to exaggerated pharmacological effects. These include:
  - Ataxia, tremor, convulsions: these effects are well known effects of mexiletine and are taken into account in the labelling of mexiletine.
  - Possibly increased heart rate and QRS: as mentioned above, these effects are well known pharmacological effects of mexiletine and are taken into account in the labelling of mexiletine.
  - Diarrhoea and emesis: nausea has been reported as a common adverse reaction and is taken into account in the labelling of mexiletine. Diarrhoea has not been reported as an adverse reaction. Of note it was observed only in dogs, and since this symptom is obvious, it may be expected to be species specific and not to occur in patients.

- Adverse effects arising from the toxicology studies and corresponding to toxic effects. These include:
  - Increased biochemical liver parameters: this is reflected in the labelling of mexiletine.
  - Changes in weight and fatty liver degeneration: Contrary to the SmPC, mentioning "Unknown: asymptomatic increase of hepatic enzymes", fatty liver degeneration was consistently observed in several studies in rats and dogs with low incidence and severity, for the longest durations tested, up to 26 weeks by gavage and 78 weeks in rats and 52 weeks and was reversible. The incidence in the therapeutic population is unknown.
  - Fatty degeneration of myocardial fibres: This effect was observed in dogs with a significant incidence (from 1/6 to 4/6 animals) and a low severity, while it was only observed in rats dying prematurely and at higher doses than dogs. The incidence in the therapeutic population is unknown and the labelling will take this potential adverse reaction into account.
  - Body weight, food consumption: The observed changes in body weight are not reported in the SmPC as an adverse reaction. Since this symptom is obvious, it may be expected to have been readily detected in patients if it occurred in humans.

The studies in rats on carcinogenic potential were negative, but not performed in accordance with current standards and therefore of unclear clinical relevance. The negative genotoxicity potential does not indicate an increased carcinogenic risk of treatment with mexiletine. Nevertheless, there will be a remaining uncertainty due to the lack of complete carcinogenicity testing, which will be considered in the benefit/risk discussion. Additional risk-minimization has been proposed, such as a reminder not to continue long-term treatment in a patient not responding or experience benefit of the treatment. In addition, section 5.3 of the SmPC was updated with information that carcinogenicity studies are insufficient.

Most of the potential adverse reactions identified in the preclinical evaluation of mexiletine have been reported in the labelling of mexiletine. Only diarrhoea and body weight changes were identified in animals and are not reported in the SmPC. Since both signs are very obvious, they may be expected to not have occurred in patients despite forty years of use of mexiletine covering several million patient-years.

Two signs of fatty degeneration of liver cells and myocardial fibres have been identified and are not reported in the Tabulated list of ADRs of the SmPC. Both signs have not been identified in the latest PSUR covering the period from October 2005 to October 2008. This PSUR concerns 486,077 patient years (marketed product) and approx. 7,740 patient years (clinical trials) for this period. The following occurrences were reported using the SOCs of Cardiac Disorders (no AE related to fatty degeneration of myocardial fibres), Hepatobiliary Disorders (Hepatic lesion, 1 SAE), Investigations (no AE of fatty degeneration of liver cells and myocardial fibres) and Metabolic disorders (Hypercholesterolaemia, 1 SAE). Therefore, these findings may be expected to be of very low expectancy and no specific measures are envisaged.

The ecotoxicity/environmental risk assessment is acceptable. The applicant has agreed to perform after approval adsorption data on preferable 3 soils in accordance with OECD 106.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers the following measures necessary to address the non clinical issues:

To provide adsorption data for at least 3 soils/sediments for equilibrium partitioning calculations in sediment risk assessment by one year at the latest after the Commission Decision.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study No, Phase,	Design Control Type	Study & Control Drugs: Dose, Route, Regimen	Study Objectives	No. Subjects per Arm Entered/ Completed	Diagnosis Inclusion Criteria	Primary Endpoint(s)
MYOMEX Phase III	Randomised, cross-over, double-blind, placebo-controlled	Mexiletine hydrochloride 200 mg tid, per os. Placebo	Efficacy and safety	25 (Cross-over study) 26/24	Subjects with MC or PC	Score of stiffness severity as self-reported by the patient on a VAS.
Statland *et al.* (2012) Phase II	Randomised, cross-over, double-blind, placebo-controlled	Mexiletine hydrochloride 200 mg tid, per os. Placebo	Efficacy and safety	59 (Cross-over study) 59/52	Subjects with NDM	Severity score of stiffness reported by participants during the 3rd

Study No, Phase,	Design Control Type	Study & Control Drugs: Dose, Route, Regimen	Study Objectives	No. Subjects per Arm Entered/ Completed	Diagnosis Inclusion Criteria	Primary Endpoint(s)
						and 4th week of each treatment period via IVR diary
Logigian *et al.* (2010) Phase II	Randomised, cross-over, double-blind, placebo-controlled (two studies)	Mexiletine hydrochloride 150 mg (Trial 1) or 200 mg (Trial 1) tid, per os. Placebo	Efficacy and safety	30 (Cross-over study) [10 participants enrolled in both trials] Trial 1 (150 mg): 20/18 Trial 2 (200 mg): 20/18	Subjects with DM1	Average RT (time to decline in force from 90% to 5% of PF).
Kwiecinski *et al.* (1992) Phase II	Randomised, single-blind, placebo-controlled	Mexiletine hydrochloride 400 mg/day for 2 wk and 600 mg/day for 2 wk, per os. Placebo	Efficacy and safety	24	Subjects with myotonic disorders	Eye opening, hand opening, stair test, EMG RT
Suetterlin *et al.* (2015)	Retrospective review of a patient cohort	Mexiletine hydrochloride until symptoms resolved or up to 600 mg/day	Efficacy and safety	63	Subjects with genetically confirmed NDM or hyperkalemic periodic paralysis	Efficacy determined by patient report
Lo Monaco *et al.* (2015)	Prospective, open-label, uncontrolled study	Mexiletine hydrochloride, individual dosage	Efficacy and safety	21	Subjects with genetic diagnosis of recessive myotonia congenita	Maximal CMAP amplitude depression using 3 Hz repetitive nerve stimulation
Contardi *et*	Prospective,	Mexiletine	Efficacy and	18	Subjects	Muscular

Study No, Phase,	Design Control Type	Study & Control Drugs: Dose, Route, Regimen	Study Objectives	No. Subjects per Arm Entered/ Completed	Diagnosis Inclusion Criteria	Primary Endpoint(s)
al. (2012) 1 centre EU (Italy)	open-label, uncontrolled study	hydrochloride, 400 mg/day	safety		with DM1	strength, determined by a dynamometer

§ harmonic mean; # hospitalised patients without cardiac, renal or hepatic disease; * [median (range)]

AUC_{inf} – area under the plasma concentration-time curve extrapolated to infinite time; C_{max} – maximum observed plasma concentration; CL/F – apparent clearance; d – days; F – bioavailability; N – number of subjects; NCA – non-compartmental analysis; tid – three times a day; T_{max} – time to reach maximum plasma concentration; $t_{1/2}$ – Elimination half-life; V_z/F – apparent volume of distribution during terminal elimination phase

2.4.2. Pharmacokinetics

Key PK parameters for mexiletine from single and multiple dose studies conducted by the applicant are summarised in the **Table 9** below.

Table 5: Summary of Mexiletine Pharmacokinetic Parameters from the Applicant's Studies and Published Population Pharmacokinetic Analyses

Study	N Healthy/Condition	PK analysis method	Oral dose (as mexiletine hydrocloride)	C_{max} (µg/mL)	T_{max} (h)	AUC_{inf} (µg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
U82-0399	4 Healthy	NCA	100 mg	0.30	4.4§	AUC_{0-48}: 3.69	-	-	-
			200 mg	0.46	2.2§	AUC_{0-48}: 5.10	-	-	-
			400 mg	0.92	2.4§	AUC_{0-48}: 10.25	-	-	-
U94-0146	7 Healthy	NCA	100 mg	0.21 ± 0.03	3.14 ± 0.69	2.96 ± 0.63	9.4 ± 2.1	-	-
			150 mg	0.35 ± 0.02	2.86 ± 0.69	5.80 ± 1.52	10.8 ± 2.2	-	-
			200 mg	0.45 ± 0.05	3.71 ± 0.49	7.76 ± 1.50	11.1 ± 2.5	-	-
U91-0879 *R*− *S*+	12 Healthy	CA	200 mg	0.22 ± 0.07 0.20 ± 0.06	2.0 ± 1.2 2.2 ± 1.4	2.8 ± 0.94 2.6 ± 0.93	8.0 ± 2.5 8.3 ± 2.7	33.2 ± 11.8 36.5 ± 13.2	370 ± 123 420 ± 168
U77-0298	10#	NCA WinNonLin	300 mg	0.46 ± 0.16	3.8 ± 1.1	6.7 ± 2.7	10.0 ± 3.3	52.3 ± 20.7	681 ± 158
U79-0321	6 Healthy	NCA WinNonLin	400 mg	0.81 ± 0.14	2.1 ± 0.9	8.3 ± 3.8	7.0 ± 1.5	55.5 ± 22.0	523 ± 112
U94-0147	6 Healthy	NCA	150 mg tid × 7d	0.91	-	-	-	-	-
MYOMEX	24 Myotonia	-	200 mg tid × 18d	C_{2h} 1.14 ± 0.41	-	-	-	-	-
U96-0077	11 Ventricular arrhythmias	NCA WinNonLin	200 mg tid × 4d	1.2 ± 0.9	-	22.0 ± 27.1	9.9 ± 4.8	42 ± 24	498 ± 279
U94-0148	6 Diabetic neuropathy	NCA	100 mg tid × 6d	0.59 ± 0.10	-	3.70 ± 0.65	14.1 ± 7.3	27.7 ± 5.1	-

§ harmonic mean; # hospitalised patients without cardiac, renal or hepatic disease; * [median (range)]

AUC_{inf} – area under the plasma concentration-time curve extrapolated to infinite time; C_{max} – maximum observed plasma concentration; CL/F – apparent clearance; d – days; F – bioavailability; N – number of subjects; NCA – non-compartmental analysis; tid – three times a day; T_{max} – time to reach maximum plasma concentration; $t_{1/2}$ – Elimination half-life; V_z/F – apparent volume of distribution during terminal elimination phase

Absorption

Mexiletine has an absolute oral bioavailability exceeding 80%. As mexiletine is a weak base (pK_a ~9.1), it is completely ionised in the acidic environment of the stomach where absorption is negligible. Gastrointestinal absorption, therefore, begins to occur in the upper part of the intestine as pH and the fraction of unionised drug increase, with peak plasma concentrations occurring 1 to 4 hours post-administration.

Although the bioavailability of mexiletine has not been investigated in patients with myotonic disorders, the range of pre- and post-dose plasma concentrations reported in the MYOMEX Study is consistent with corresponding values reported at similar dosing schedules in healthy subjects and patient populations with cardiac diseases, suggesting that the absorption and elimination of mexiletine in patients with myotonic disorders are comparable.

Distribution

Mexiletine is a lipid soluble molecule (log P ~2), which is extensively and rapidly distributed, as reflected by a large but variable volume of distribution with mean values ranging from 370 to 520 L (~5 to 8 L/kg) in the Applicant's studies. Protein binding of mexiletine is 60%. Mexiletine freely penetrates erythrocytes; as a result, blood concentrations are reported to be 12-15% higher than corresponding serum levels. Salivary concentrations of mexiletine also tend to be higher than serum concentrations, offering the possibility of non-invasive therapeutic drug monitoring.

Mexiletine is known to cross the placenta and is readily transferred into human breast milk, where it can be present at higher concentrations than in maternal plasma at corresponding time-points. However, assuming an infant's daily milk intake of 500 ml and a maternal plasma concentration of 2 µg/ml, it is unlikely that an infant would have an ingestion of more than 1.25 mg of mexiletine in any 24 hour period. This information was included in the SPC and, as a precautionary measure, it was considered that is preferable to avoid the use of Namuscla during pregnancy

Elimination

Metabolism

Mexiletine undergoes extensive hepatic metabolism; only 10-15% of the drug is eliminated as the parent molecule. The major metabolic pathways are aliphatic and aromatic hydroxylation, leading to the formation of hydroxymethyl-mexiletine (HMM), *N*-hydroxymexiletine (NHM), *m*-hydroxymexiletine (MHM) and *p*-hydroxymexiletine (PHM), most of which are eliminated as glucuronide conjugates. The majority of these metabolites do not appear to be pharmacologically active, although MHM (urinary excretion: < 2% of the administered dose) was recently found to be ~2-fold more potent than the parent molecule in *in vitro* assays. HMM and NHM, have plasma exposures close to 25% of the mexiletine exposure. Their plasma profiles seem to be similar to the Mexiletine profile.

In vitro studies with human liver microsomes indicate that the formation of HMM and PHM is catalysed principally by the cytochrome P450 2D6 (CYP2D6) enzyme and to a minor extent by CYP1A2. The formation of NHM is catalysed mainly by CYP1A2, and to a lesser extent by CYP2E1 and CYP2B6.

The significant genetic polymorphism of CYP2D6 results in individuals who are poor (PMs), extensive (EMs), or ultrarapid metabolisers of CYP2D6 substrates, including mexiletine. *In vitro* and/or *in vivo* studies have demonstrated that the enzymatic conversion of mexiletine to HMM, PHM, and MHM is genetically determined and coincides with the sparteine/ debrisoquine polymorphism and is similarly inhibited by the co-administration of CYP2D6 inhibitors such as quinidine in EMs. In PMs, mexiletine PK is characterised by significantly lower total and renal clearance resulting in prolonged elimination $t_{1/2}$, higher areas under the curve (AUCs), and lower volume of distribution compared to EMs. Furthermore, urinary recoveries of unchanged mexiletine are higher in PMs, while those of HMM, PHM & MHM are lower in PMs with concomitantly decreased partial clearances of these metabolites. In contrast, urinary excretion of NHM, which is not genetically determined by CYP2D6, tends to be higher in PMs. Due to these marked differences between the elimination process between CYP2D6 PM and EM, recommendations exist about the dose uptitration administration of the drug in the SPC.

Excretion

Mexiletine and its metabolites are excreted almost exclusively via the kidneys; faecal excretion represents less than 5% of the dose. However, the urinary excretion of mexiletine is very sensitive to urinary pH. At acidic pH, mexiletine is almost entirely ionised and there is little renal reabsorption; as pH increases and mexiletine becomes unionised, there is more renal reabsorption and decreased urinary excretion of unchanged mexiletine (30-50%). It is agreed that no SmPC recommendation due to urine pH is necessary, since the impact on the overall exposure is relatively low. However, the relevant information should be summarised and included in SmPC in section 5.2 as this is a part of the characterisation of PK properties

Impact of Stereoselectivity on Mexiletine Pharmacokinetics

Mexiletine is administered as a 50:50 racemic mixture of the *R*− and *S*+ enantiomers. Despite conflicting reports, the overall disposition of mexiletine does not appear to be enantioselective.

Dose proportionality and time dependencies

Despite considerable interindividual variability, mexiletine exposure is dose proportional following single doses (100 to 600 mg of mexiletine hydrochloride) in healthy subjects and multiple doses (up to ~14 mg/kg) in arrhythmic patients without evidence of drug accumulation. With the available data, there is no indication that a significant time dependency is expected.

Pharmacokinetics using human biomaterials

Comparison of Pharmacokinetics in Healthy Subjects and Patients

PK data for mexiletine have been principally derived from healthy subjects and patients with cardiac disease, in view of the original indication for which mexiletine was approved. Although no formal PK studies have been conducted in patients with myotonic disorders, serum mexiletine concentrations were measured in the pivotal MYOMEX Study before [C_{min}] and 2 hours after [C_{2h}] mexiletine intake at steady-state at the end of each 18 day treatment period The mean (± SD) C_{min} and C_{2h} concentrations were 0.66 ± 0.32 µg/mL and 1.10 ± 0.42 µg/mL, respectively.

A comparison of individual steady-state serum mexiletine levels from the MYOMEX Study with those from multiple dose studies indicates that the concentrations observed in the MYOMEX Study are in the same

range as those reported in patients with ventricular arrhythmias and diabetic neuropathy. Furthermore, serum levels observed in the MYOMEX Study are consistent with those reported in published studies in patients with myotonia using similar dosing schedules. Taken together, these data also indicate that the PK of mexiletine are unchanged in MC and PC patients relative to other patient populations in whom the PK of mexiletine are well established.

Effect of Intrinsic Factors

No Age or gender effects were observed in the PK of mexeletine

Body Weight

Oral mexiletine is usually administered as a fixed dose regimen. However, a negative correlation between plasma mexiletine concentrations and body weight is generally observed. A similar observation has been made during the MYOMEX Study, where mexiletine concentrations were slightly higher in PC patients, who had a lower body weight at baseline than MC patients. This information is reflected in the SmPC.

Race

There have been no formal studies to investigate the influence of race on mexiletine PK. Studies conducted in Japan have reported comparable magnitudes of PK parameters to those performed in Caucasian subjects. However, given that the metabolism of mexiletine is governed by the CYP2D6 phenotype, and the worldwide distribution of the PM phenotype varies considerably regionally, racial differences in mexiletine metabolism cannot be precluded, although dose adjustment is not warranted on the basis of the information currently available.

Renal Impairment

Studies have generally not found a statistically significant correlation between creatinine clearance and plasma clearance or elimination $t_{1/2}$ after intravenous (IV) or oral administration of mexiletine in renally impaired patients, including dialysis-dependent patients. Haemodialysis, haemofiltration, peritoneal dialysis and plasmapheresis do not appear to affect the clearance of mexiletine. Routine dose adjustment is therefore not required in patients with mild and moderate renal failure and those receiving dialysis; as data in patients with severe renal disease are limited, mexiletine is not recommended in this case.

Hepatic impairment

Hepatic function has a significant influence on mexiletine PK given that mexiletine is primarily eliminated via hepatic metabolism. In the Applicant's studies (Studies U88-0397 and U84-0946), the elimination of mexiletine was markedly retarded in patients with hepatic impairment as reflected by a prolonged elimination $t_{1/2}$ (2 to 3-fold) and decreased clearance (30-60%) compared to healthy subjects. SPC indicates that mexiletine should therefore be used with caution in patients with mild or moderate hepatic impairment and not be used in patients with severe hepatic impairment. However, since the elimination t1/2 for CYP2D6 PM could be even higher and the proposed dose escalation period of 7 days may not be sufficient, patients with HI might require further caution and a dose escalation for 14 days could be considered.

Effect of Extrinsic Factors

Effect of Food

Food does not affect the rate or extent of absorption of mexiletine. Therefore, mexiletine can be taken with or without food.

The co-administration of mexiletine (a potent CYP1A2 inhibitor) and caffeine (a CYP1A2 substrate) can result in increased plasma concentrations of caffeine.

Effect of Cigarette Smoking

Cigarette smoking increases the clearance and shortens the elimination $t_{1/2}$ of mexiletine although the precise mechanism of this interaction is unclear. This information is included in the SPC.

Drug-Drug Interactions

Drugs which are substrates, inhibitors or inducers of the CYP450 enzymes implicated in the metabolism of mexiletine (specifically, CYP2D6 and CYP1A2), have the potential to interact with mexiletine. No in vitro data predicting in vivo DDI potential of mexiletine was, however, provided. Increased plasma mexiletine levels have been reported with CYP2D6/CYP1A2 inhibitors (quinidine, propafenone, fluvoxamine and ciprofloxacin). Decreased plasma mexiletine levels have been reported with CYP2D6 inducers (rifampicin, phenytoin).

Genetic polymorphism in mexiletine metabolism plays an important role in the predisposition to drug-drug interactions, such that extensive metabolisers (EMs; the majority of Europeans) are more susceptible to certain drug-drug interactions (e.g., with propafenone and quinidine) compared to PMs.

As mexiletine is principally absorbed in the small intestine, drugs affecting the rate of gastric emptying can modify the rate of mexiletine absorption (C_{max} and/or t_{max}). Narcotic analgesics, atropine and antacids, which delay gastric emptying, can reduce C_{max} and/or prolong t_{max}, while metoclopramide, which increases gastric emptying, significantly reduces the time to peak mexiletine levels. Overall, these interactions are unlikely to be clinically significant unless C_{max} and/or t_{max} are critical to the therapeutic effect.

Drugs that acidify or alkalinise the urine are likely to, respectively, enhance or reduce the rate of elimination of mexiletine.

The concomitant administration of mexiletine with theophylline, caffeine, lidocaine and tizanidine can decrease their elimination resulting in increased plasma levels of these substrates, which can potentially lead to toxicity. The metabolism of propafenone and digoxin does not appear to be affected by mexiletine.

The applicant provided some reports with in vitro data, but there are shortcomings in the response provided. First, in vitro data required according to DDI guideline is missing; CYP induction and potential of inhibition of the transporters OATP1B1, OATP1B3, BCRP, OAT1 and OAT3. Additionally, a study provided showed that mexiletine is an *in vitro* inhibitor of OCT2, thus an *in vivo* study is warranted. Lastly, the CYP inhibition data provided did not cover clinically relevant concentrations (up to 50 µM was studied, but cut offs are 135 µM and 447 µM in liver and intestine (CYP3A4), respectively.

In conclusion, the *in vitro* data provided was not in accordance with EMA DDI guideline. It is foreseen that the study reports will be available within 8 months from the Commission decision. As soon as available, they will be submitted to the CHMP. Until then, sections 4.3 (Contraindications) and 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC have been updated to restrict the concomitant use of mexiletine with drugs with narrow therapeutic index.

2.4.3. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

Data from several clinical pharmacology studies (conducted to support the antiarrhythmic indication), together with bibliographical references (including three controlled clinical studies).

No formal clinical pharmacodynamic (PD) studies have been conducted in patients with myotonic disorders. The pharmacodynamics effects of mexiletine have been supported in the studies conducted to support the antiarrhythmic indication, and that is considered applicable to the myotonia indication. Exploratory pharmacodynamic biomarkers have been included in the pivotal study justifying the lack of established PD markers for measuring clinical outcomes in NDMs. In terms of clinical pharmacodynamics the absence of PD data is considered satisfactory given the hybrid nature of submission.

The proposed mechanism of action is plausible. There is an important body of non-clinical evidence and some clinical data to corroborate the pharmacodynamics action of mexiletine (reduction in the fast sodium influx), in relation to the clinically desired effect (reduction in muscle hyperexcitability).

Although there are no established PD endpoints for the non-dystrophic myotonias, electrophysiological evaluation of the effect of these channelopathies on muscle membrane excitability after functional triggers such as exercise provides a useful tool for the diagnosis and clinical evaluation of both MC and PC phenotypes.

Primary PD exploratory parameters were measured in several clinical studies. In clinical series/cohort studies, clinical studies and also case reports, mexiletine was shown to reduce mean hand grip relaxation time in patients with DM1; reduce the severity score of muscle stiffness (patient-reported outcome); decreased handgrip myotonia on clinical examination and resulted in a less marked decrease in amplitude of the evoked motor response (CMAP amplitude) to repetitive nerve stimulation in NDM patients. The pharmacodynamics data is convincing regarding the MoA, and the applicant has further discussed the relationship between dose, exposure and PD endpoint in the proposed indication.

In line with the non-clinical and clinical observations, unwanted effects related to the mode of action of mexiletine are likely to occur on the cardiovascular and CNS systems upon administration of therapeutic doses.

Substantial reduction of the QTc prolongation associated with hERG potassium channel block and congenital type 3 long QT syndrome was also found to be associated with mexiletine and these effects are included in the product information.

No formal drug combination studies were conducted by the applicant. PD drug interaction with mexiletine has been included in the SmPC for Antiarrhythmic agent separating the effect between medicines inducing/not inducing lethal ventricular arrhythmias (Torsade de pointes). Other mexiletine-antiarrhythmic drug combinations have been investigated and this information is properly included in the SmPC. No clinical significant PD interactions with antiepileptic medicines have been demonstrated. An important set of data could support PK/PD relationship in the intended indication, despite considerable inter individual variability. Mexiletine treatment started at 200 mg/day, and was up-titrated by 200 mg increments every 3 days to reach a maximum dose of 600 mg/day (200 mg tid) in one week. As stiffness (based on the VAS) was determined each time the dose of mexiletine was increased, it was possible to determine a potential dose-response relationship.

It is acknowledged that the applicant has made an effort collecting data to support PK/PD relationship in the intended indication, despite considerable inter-individual variability. There was no clear relationship between mexiletine plasma levels and treatment effect as measured by stiffness score on the VAS even though the mexiletine concentration was within expected therapeutic window for all patients. However, based on the large previous safety experience with mexiletine, on the results of the study of Logigian et al. (2010) and on the existing EU guidelines, the recommended dose of Namuscla for the antimyotonic management of subjects with myotonic disorders has been established.

In summary, the PK/PD relationship and the optimal dose regimen in the target population is considered satisfactory.

2.4.4. Discussion on clinical pharmacology

A discussion on the clinical pharmacology is presented above. No formal clinical pharmacology studies have been conducted in patients with myotonic disorders. However, given the previous approval history the pharmacokinetics (PK) of mexiletine have been extensively studied.

Additionally, it is considered that the primary pharmacology of mexiletine is reasonably described and evidence to support the clinical pharmacodynamic of mexiletine for the treatment of myotonic disorders have been satisfactorily justified.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of the product is deemed satisfactory.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

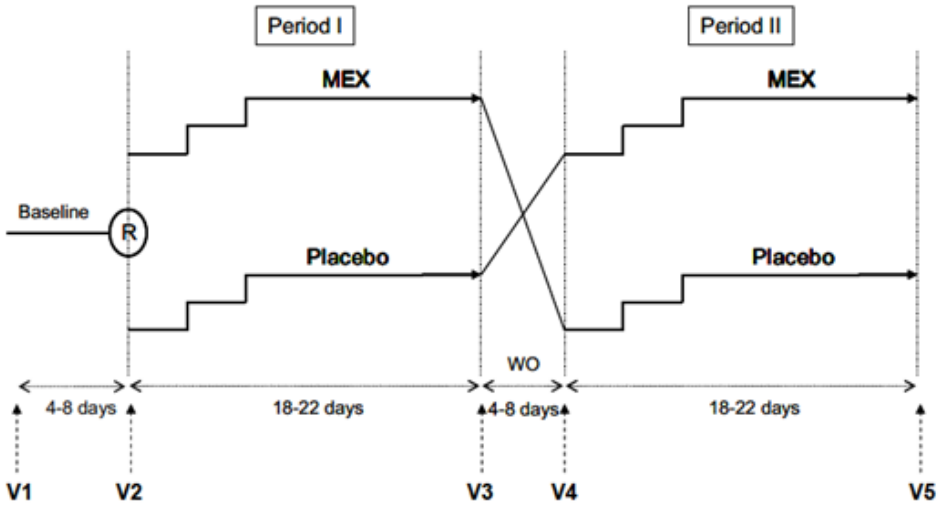
There was no specific dose-response study. The choice of dose is discussed in the main study which is considered acceptable by the CHMP.

2.5.2. Main study(ies)

This was a multi-centre, double-blind, placebo-controlled; cross-over (2 treatment periods of 18 days) study with a 4-day wash-out period, to compare the effects of mexiletine versus placebo in patients with MC and PC – both NDMs.

Treatment was administered according to routine practice, started at 200 mg/day (as mexiletine hydrochloride), and up-titrated by 200 mg increment each 3 days to reach a maximum dose of 600 mg/day in one week. After a baseline period (4-8 days) to eliminate residual mexiletine from a previous treatment, patients were randomised and received either mexiletine or a placebo for 18 days (maximum 22 days; period I). After a wash-out period of minimum 4 days (maximum 8 days), they received the study product they did not receive during period I for 18 days (maximum 22 days; period II).

Study diagram:



V1: screening visit (day -4); V2: baseline visit (day 1), start of period I; V3: visit 3 (day 18), end of period I; V4: visit 4 (day 22), start of period II; V5: visit 5 (day 39), end of period II.

MEX: mexiletine; R: randomisation.

Methods

- **Study participants**

A total of 26 patients were recruited. One patient withdrew his consent before study start; one patient was prematurely discontinued due to an adverse event (AE).

Eligible subjects were male and female participants, aged between 18 and 65 years, with genetically definite MC and PC, who experienced myotonic symptoms severe enough to justify treatment (based on clinical and disabling criteria), and who were drug-naïve or were receiving mexiletine at effective dosage and agreed to stop treatment at least 4 days before inclusion.

Inclusion criteria:

Genetically definite MC and PC.

Male and female patients, aged between 18 and 65 years, who were able to comply with the study conditions.

Patients who experienced myotonic symptoms severe enough to justify treatment. The severity was based on:

- Clinical criteria: myotonia was considered severe if it involved at least 2 segments (upper limb, lower limb or face).
- Disabling criteria: myotonia was considered severe if patients noticed impacts on at least 3 of the 7 daily activities listed in the disabling section of the CMS (talking, writing, feeding, hygiene, getting dressed, waling, climbing stairs

Thus, patients who experienced myotonic symptoms severe enough to justify treatment were those with myotonia that involved at least 2 segments and that had an impact on at least 3 daily activities.

Patients who were drug-naïve or those who were receiving mexiletine at an effective dosage and who agreed to stop treatment at least 4 days before inclusion.

Pregnancy: non-childbearing potential women (i.e. postmenopausal or surgically sterile) or using a medically-accepted contraceptive regimen.

Normal cardiac exam performed by a cardiologist including electrocardiogram (ECG) and cardiac ultrasound (if not done within 3 months before trial).

Exclusion criteria

Intercurrent event which could interfere with the muscle function (infection, trauma, fracture, etc.).

Coincidental renal, hepatic, respiratory, thyroid, other neuromuscular disease or heart disease that contraindicated mexiletine or interfered with clinical evaluation.

Use of any of the following medications that could interfere with muscle function: diuretics, anti-epileptics (sodium channel blockers), anti-arrhythmics, corticosteroids, and beta-blockers

Allergy to mexiletine.

- **Treatments**

Test product: Mexiletine hydrochloride 200 mg capsules (equivalent to 167 mg mexiletine) or matching placebo.

Dosage regimen: Treatment started at 200 mg/day and was titrated upward by 200 mg increment each 3 days to reach a maximum dose of 600 mg/day in one week. Patients took one mexiletine capsule once a day (200 mg) for 3 days (day 1 to day 3 or day 22 to day 24, depending on the treatment sequence), then one capsule twice a day (400 mg) for 3 days (day 4 to day 6 or day 25 to day 27) and finally one capsule three times a day (tid) (600 mg) until the end of the period (day 7 to day 17 or day 28 to day 38).

Prior and concomitant therapy:

Any concomitant therapy or medication given at baseline visit, or during study drug administration, was indicated in the CRF. Generic or trade name, and dosage were indicated. All medications were coded according to WHO-DRUG medical codes. At the screening visit, the investigator asked the patient about the current use of medications, including over-thecounter medications, vitamins, and herbals. At each clinic visit thereafter, the investigator inquired about use of medications since the previous visit, and recorded any additions, discontinuations, and/or changes on the CRF.

- **Objectives**

Primary:

- To evaluate the efficacy of mexiletine for the symptomatic treatment of NDMs based upon several criteria including stiffness assessment (using visual analogue self-assessment scale [VAS]), quality of life, chair test results, and clinical global impression (CGI) of efficacy.
- To evaluate the safety of mexiletine for the symptomatic treatment of NDMs.

Secondary:

- To evaluate electromyographic (EMG) tests as a standardised outcome measure of myotonia and of treatment efficacy.

- To assess the reliability and validity of a new clinical myotonia rating scale (CMS) to evaluate myotonia severity.
- Outcomes/endpoints

Primary efficacy measure:

- Score of stiffness severity as self-reported by the patient on a VAS.

Secondary efficacy measures:

- The time needed to stand up from a chair, walk around the chair and sit down again (chair test).
- Changes in health-related quality-of-life as measured by individualised neuromuscular quality of life (INQoL) scale.
- CGI Efficacy index.
- Preference between the 2 treatment periods.
- Number of intolerable increase in myotonia severity necessitating withdrawal.
- Measure of the compound muscle action potential (CMAP) amplitude decline recorded from the abductor digiti minimi (ADM) muscle after repeated short exercise test at room temperature and after cooling.
- Score of a CMS. This scale comprises 2 sections: a myotonia severity scale based on examination of the patient and a disability scale based on the patient's view of disability in activities of daily living.
- Mexiletine plasma concentrations.

Safety:

- AE frequency and severity
- Changes in clinical laboratory values
- Changes in vital signs
- Electrocardiogram (ECG)
- CGI Tolerability index
- • Sample size

At the time of protocol writing (2010), 200 patients (114 MC and 86 PC) were identified by molecular analysis in the 7 study centres selected for the study. From clinical experience, 40 to 50% of patients require symptomatic treatment for myotonia. Considering the expected number of recruited patients, 24 patients (12 of each diagnosis) represent 25% of the overall population. It was postulated that a 50% reduction of the primary outcome (stiffness VAS score) would be a clinically significant goal. In order to obtain 24 patients with 2 analysable periods of treatment, it was estimated that up to 40 patients had to be screened. Patients withdrawn from the study during the first period were to be replaced if they refused to complete the second period.

- **Randomisation**

Patients were randomly assigned to a sequence of treatment (mexiletine-placebo or placebo mexiletine), i.e. half of the patients were randomly assigned to receive mexiletine during period I and placebo during period II and the other half were randomly assigned to receive placebo during period I and mexiletine during period II. Diagnoses were balanced by stratification within both sequences.

- **Blinding (masking)**

Patients, sponsor, and study personnel were blinded to the treatment (mexiletine or placebo).

The randomization list was prepared by an Hôpital and a copy was kept by the poison control center from another Hospital . The phone number of this poison control center was mentioned on the treatment boxes and on the patient card. If a patient experienced an AE for which it was necessary to break the blind during the study to determine the appropriate treatment for the event, the investigator or his/her designee had to call the poison control center before unblinding. The reason for unblinding had to be documented in the CRF. Unblinded patients were not to be replaced.

- **Statistical methods**

The statistical analysis was performed according to the protocol version 1.3, dated 22 November 2010 and statistical analysis plan (SAP) version 5.1, dated 27 July 2015.

Study populations

Population of included patients: All patients who signed an informed consent form.

Intention-to-treat population (ITT): All randomized patients (patients having received a randomization number at V2).

Modified intention-to-treat population (mITT): All randomized patients with at least one available evaluation pertaining to the primary criterion or with a VAS value at V3 or V5.

Per protocol population (PP): All randomized patients who did not have any major protocol deviation, who had no intercurrent event which could interfere with the evaluation of the primary criterion and who completed the 2 study periods. Note that in the original protocol the PP had been defined as "all randomized patients who did not have any major protocol deviation and who completed the 2 study periods"; this was subsequently revised after unblinding. In the original protocol, the PP had been defined as "all randomized patients who did not have any major protocol deviation and who completed the 2 study periods". After revision of the definition, the PP population included "all randomized patients who did not have any major protocol deviation, who had no intercurrent event which could interfere with the evaluation of the primary criterion and who completed the 2 study periods".

Safety population (SAF): All included patients who received at least one study treatment dose (number of capsules taken the day before > 0, time of treatment intake).

Analysis of demographic and baseline data

Baseline data are defined as the last observation collected before randomization.

Demographic were analyzed for the mITT and the PP populations. All variables were described globally, by treatment sequence and by diagnosis. Medical history was listed and vital signs were described. Previous and concomitant treatments, including mexiletine, were coded using the WHO Drug Dictionary and described.

Compliance analysis was performed in the SAF population by actual treatment received.

Analysis of efficacy data

Primary criterion

The primary criterion was the score of stiffness severity as self-reported by the patients on a VAS (0-100 mm). The primary analysis was performed in the mITT and PP populations. Absolute changes from baseline (V2 or V4) at end of period (V3 or V5) were assessed for each period by treatment and by diagnosis.

Difference between treatments was evaluated using a mixed effect linear model on ranks including:

- Diagnosis, treatment, study period and treatment sequence as fixed effects and the diagnosis-treatment interaction.
- Patient as random effect.
- Baseline value as covariate.

This model allowed testing if a carry-over effect was present:

1. If the p-value associated with the sequence fixed effect was > 0.05, the carry-over effect was to be ruled out and the final model was to be the one which included:
   - Diagnosis, treatment, and study period as fixed effects and the diagnosis-treatment interaction.
   - Patient as random effect.
   - Baseline value as covariate.
2. If the p-value associated with the sequence fixed effect was ≤ 0.05, the carry-over effect was not ruled out and the data were described and analyzed by period. Treatments were compared using a Wilcoxon test independently for each diagnosis.

Secondary criteria

Analyses were performed in the mITT and PP populations and described by treatment and diagnosis as follows,

Mexiletine plasma concentrations

Mexiletine plasma concentrations were assessed at the beginning and at the end of each treatment period.

Analysis of safety data

Safety analysis was performed in the SAF population.

AEs were coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT).

Other safety parameters included patients with abnormal laboratory values postrandomization, weight, blood pressure, CGI-tolerability index and ECG data.

CGI collected data were transformed as binary variables (good tolerability [very good, good, moderate] vs. poor tolerability) and tolerability between treatments was compared using the McNemar test.

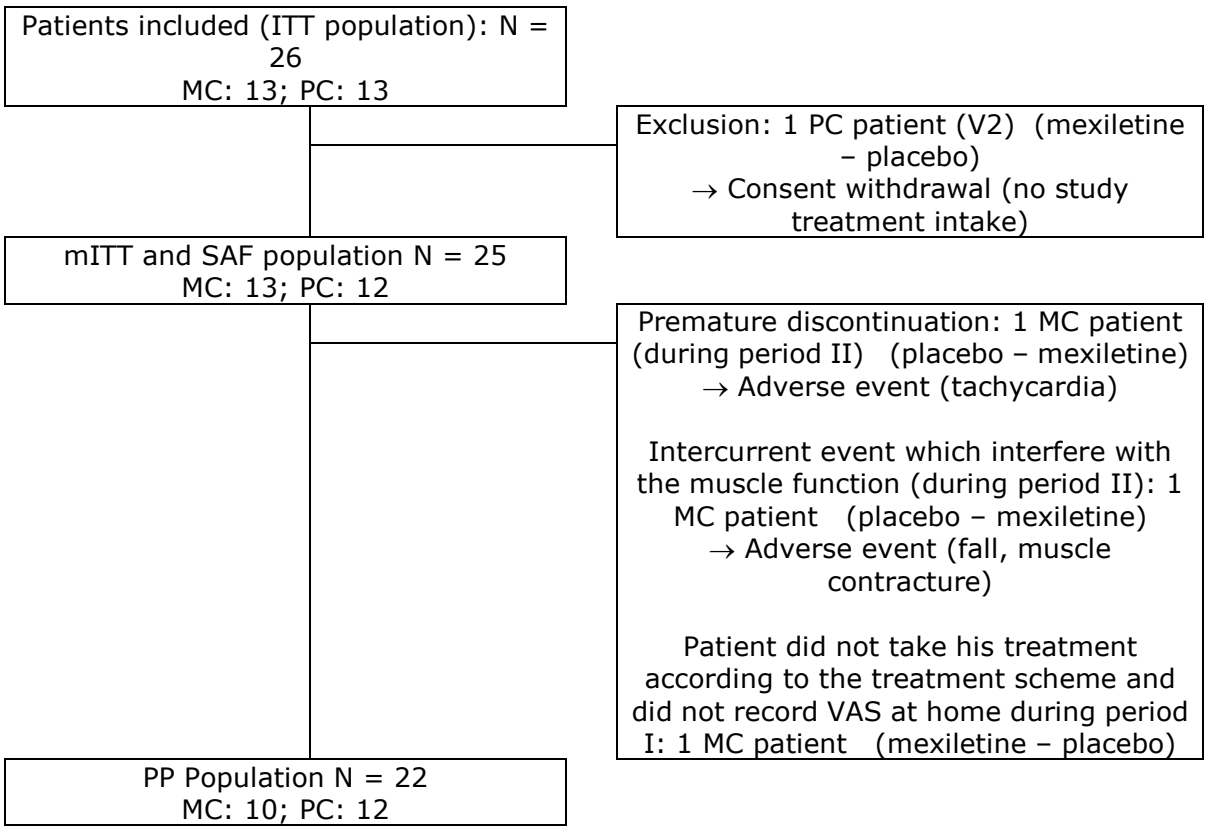
Changes from baseline in ECG parameters were described for each visit and the treatment effect was assessed using a mixed effect linear model which included treatment, study period, and treatment sequence as mixed effects, patient as random effect, and baseline value as covariate. Baseline values

were compared using the Wilcoxon rank-sum test. Correlations between ECG parameters and mexiletine plasma concentrations were assessed using the Spearman coefficient.

Results

- **Participant flow**

The participant flow is provided in Figure below:



Of the 26 patients enrolled in the study, one withdrew his consent prior to treatment period I (he did not receive any study treatment and was not included in the modified intention-to-treat (mITT) and Safety populations).

In addition, one subject did not complete the study due to occurrence of an AE (tachycardia in a context of anxiety), one had intercurrent event unrelated to treatment which interfered with the muscle function and one did not take his treatment according to the treatment scheme. These 3 subjects were excluded from the Per Protocol (PP) population.Efficacy analyses were performed on the mITT population.

- **Recruitment**

A total of 26 patients, 13 diagnosed with MC and 13 diagnosed with PC, were recruited by 6 centres of which 2 only recruited patients with MC. All patients were randomised in a 1:1 ratio to one of the treatment sequences (placebo-mexiletine or mexiletine-placebo).

- **Conduct of the study**

Protocol versions and dates	Ethics committee / Competent Authorities	Date of approvals	Reasons for notification
1.1 dated 27 July 2010	CPP Ile de France I	24 August 2010	-
1.2 dated 18 October 2010	Afssaps	27 October 2010	-
Amendment 1 1.3 dated 22 November 2010	CPP Ile de France I	06 December 2010	Update of study procedure to answer Afssaps request for addition of ECG after study treatment initiation
Amendment 2*	CPP Ile de France I	06 September 2011	Patient's information sheet update
Amendment 3*	CPP Ile de France I	24 October 2011	New principal investigator in one of the participating center (Nice)
Amendment 4 2.0 dated 24 June 2013	CPP Ile de France I	09 July 2013	Prolongation of the recruitment period and study duration

* No substantial changes were made to the protocol and therefore no new version of the protocol was developed.
CPP: Comité de Protection des Personnes (Ethics Committee); ECG: electrocardiogram.

- **Baseline data**

There were 13 patients with MC and 12 with PC. Age of the overall study population ranged from 20 to 66 years and about 2/3 of the patients were male. While the male/female ratio was 1/1 in the patients with PC, about 85% of the patients with MC were male (Table below).

Table 6: Demography – mITT Population (Study MYOMEX)

Parameter	Diagnosis		Treatment sequence		
			Placebo-mexiletine	Mexiletine-placebo	Total
Age (years)	MC	N	6	7	**13**
		Mean (SD)	34.9 (8.3)	44.8 (13.6)	**40.3 (12.2)**
		Med [range]	34.8 [23.7;48.4]	44.9 [20.2;66.0]	**40.9 [20.2;66.0]**
	PC	N	7	5	**12**
		Mean (SD)	45.6 (12.9)	46.46 (6.2)	**46.0 (10.2)**
		Med [range]	49.2 [21.8;59.6]	45.5 [39.0;52.9]	**48.9 [21.8;59.6]**
	Total	**N**	**13**	**12**	**25**
		Mean (SD)	**40.7 (12.0)**	**45.5 (10.8)**	**43.0 (11.4)**
		Med [range]	**37.3 [21.8;59.6]**	**45.2 [20.2;66.0]**	**44.9 [20.2;66.0]**
Gender	MC	N	6	7	**13**
		Male, n (%)	5 (83.3%)	6 (85.7%)	**11 (84.6%)**
		Female, n (%)	1 (16.7%)	1 (14.3%)	**2 (15.4%)**
	PC	N	7	5	**12**
		Male, n (%)	4 (57.1%)	2 (40.0%)	**6 (50.0%)**
		Female, n (%)	3 (42.9%)	3 (60.0%)	**6 (50.0%)**
	Total	**N**	**13**	**12**	**25**
		Male, n (%)	**9 (69.2%)**	**8 (66.7%)**	**17 (68.0%)**
		Female, n(%)	**4 (30.8%)**	**4 (33.3%)**	**8 (32.0%)**
Weight (kg)	MC	N	6	7	**13**
		Mean (SD)	78.8 (21.6)	77.4 (15.3)	**78.0 (17.7)**
		Med [range]	74.0 [59.0;118.0]	76.0 [64.0;109.0]	**76.0 [59.0;118.0]**
	PC	N	7	5	**12**
		Mean (SD)	67.3 (12.3)	71.1 (13.8)	**68.9 (12.4)**
		Med [range]	66.0 [50.0;90.0]	71.0 [55.5;93.0]	**68.0 [50.0;93.0]**
	Total	**N**	**13**	**12**	**25**
		Mean (SD)	**72.6 (17.5)**	**74.8 (14.4)**	**73.6 (15.8)**
		Med [range]	**68.0 [50.0;118.0]**	**71.0 [55.5;109.0]**	**70.0 [50;118.0]**
Height (cm)	MC	N	6	7	**13**
		Mean (SD)	174.2 (9.4)	170.0 (11.1)	**171.9 (10.2)**
		Med [range]	177.0 [156;183]	167 [160;191]	**174 [156;191]**
	PC	N	7	5	**12**
		Mean (SD)	170.6 [13.0]	169.2 (7.2)	**170 (10.5)**
		Med [range]	166.0 [156;194]	170.0 [160;179]	**168.0 [156;194]**
	Total	**N**	**13**	**12**	**25**

Parameter	Diagnosis		Treatment sequence		
			Placebo-mexiletine	Mexiletine-placebo	Total
		Mean (SD)	**172.2 (11.1)**	**169.7 (9.3)**	**171.0 (10.2)**
		Med [range]	**174.0 [156;194]**	**168.5 [160;191]**	**172.0 [156;194]**
BMI (kg/m²)	MC	N	6	7	**13**
		Mean (SD)	25.8 (5.5)	26.6 (2.5)	**26.2 (4.0)**
		Median [range]	25.6 [19.5;35.2]	26.4 [22.9;29.9]	**25.9 [19.5;35.2]**
	PC	N	7	5	**12**
		Mean (SD)	23.2 (4.0)	24.7 (2.9)	**23.8 (3.6)**
		Median [range]	23.5 [18.1; 29.7]	24.0 [21.7;29.0]	**23.8 [18.1;29.7]**
	Total	**N**	**13**	**12**	**25**
		Mean (SD)	**24.4 (4.7)**	**25.8 (2.8)**	**25.1 (3.9)**
		Med [range]	**24.7 [18.1;35.2]**	**25.6 [21.7;29.9]**	**25.2 [18.1;35.2]**
SBP (mmHg)	MC	N	6	7	**13**
		Mean (SD)	131.0 (12.6)	128.0 (12.1)	**129.4 (11.9)**
		Median [range]	135.5 [110.0;142.0]	127.0 [110.0;143.0]	**131.0 [110.0;143.0]**
	PC	N	7	5	**12**
		Mean (SD)	121.6 (14.8)	111.4 (16.3)	**117.3 (15.6)**
		Median [range]	126.0 [101.0;138.0]	102.0 [98.0;135.0]	**118.5 [98.0;138.0]**
	Total	**N**	**13**	**12**	**25**
		Mean (SD)	**125.9 (14.1)**	**121.1 (15.8)**	**123.6 (14.8)**
		Med [range]	**130.0 [101.0;142.0]**	**121.5 [98.0;143.0]**	**126.0 [98.0;143.0]**
DBP(mmHg)	MC	N	6	7	**13**
		Mean (SD)	76.5 (8.0)	77.6 (7.3)	**77.1 (7.4)**
		Median [range]	79.5 [63.0;85.0]	80.0 [64.0;84.0]	**80.0 [63.0;85.0]**
	PC	N	7	5	**12**
		Mean (SD)	67.3 (15.8)	66.6 (14.1)	**67.0 (14.4)**
		Median [range]	63.0 [44.0;89.0]	61.0 [50.0;85.0]	**62.5 [44.0;89.0]**
	Total	**N**	**13**	**12**	**25**
		Mean (SD)	**71.5 (13.2)**	**73.0 (11.6)**	**72.2 (12.2)**
		Med [range]	**71.0 [44.0;89.0]**	**78.5 [50.0;85.0]**	**77.0 [44.0;89.0]**

Overall, the compliance was high and only 3 patients did not take their medications according to schedule (all in the mexiletine treatment period). Poor compliance as a result of AEs was reported for only two patients.

At screening, patients currently treated with mexiletine had to stop mexiletine at least 4 days before the baseline visit (V2). Regarding previous mexiletine intake, the situation at screening was as follows:

- 11 patients were currently treated with mexiletine at screening: 9 patients with MC (4 in the placebo-mexiletine sequence and 5 in the mexiletine-placebo sequence) and 2 patients with PC (one in each treatment sequence).
- Among the 14 patients (4 MC and 10 PC) who were not taking mexiletine at screening, one patient with MC had been treated with mexiletine 600 mg/day and discontinued his treatment 5 days before V1. Similarly, 2 patients with PC had been treated with 200 and 400 mg/day of mexiletine and had discontinued their treatment 0.2 months and 44.6 months before study start, respectively.
- Overall, 11 patients were completely naïve to mexiletine.
- • Numbers analysed

The study was analysed on a mITT basis for primary efficacy. 13 MC and 12 MC pts have been studied.

- **Outcomes and estimation**

Primary efficacy analysis: Stiffness score

The individual stiffness VAS scores before treatment (V2 or V4) and at the end of the treatment period (V3 or V5) in the mITT population are presented by diagnosis and by treatment sequence in Figure below for the mITT population and in Figure 2.7.3 3 for the PP population.

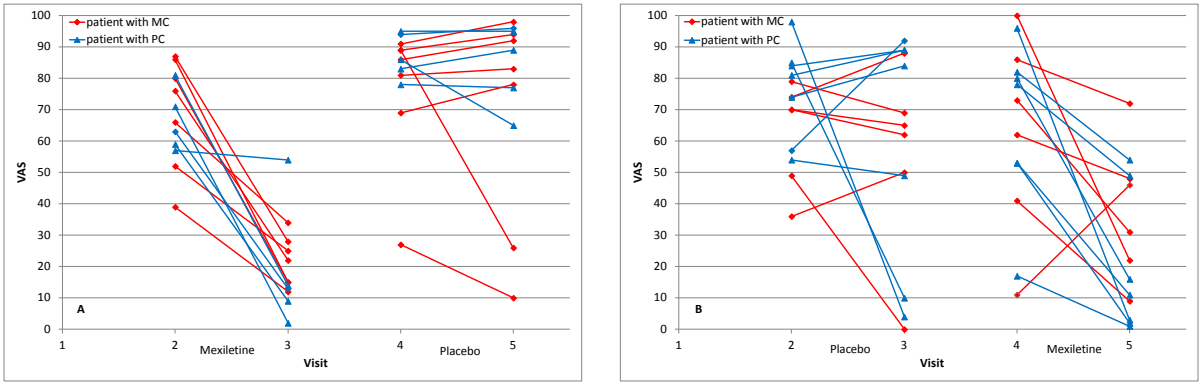


Figure 2: Stiffness VAS Score by Treatment Sequence: A: Mexiletine → Placebo, B: Placebo → Mexiletine – mITT Population (Study MYOMEX)

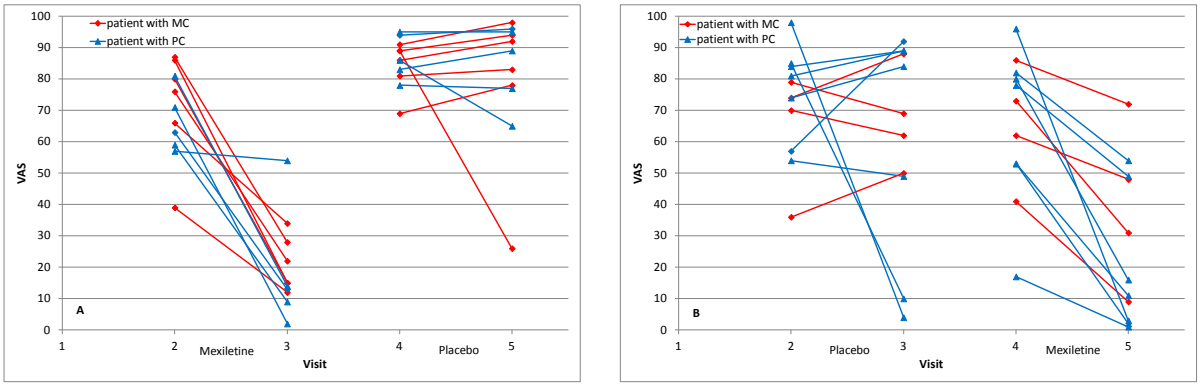


Figure 3: Stiffness VAS Score by Treatment Sequence: A: Mexiletine → Placebo, B: Placebo → Mexiletine – PP Population (Study MYOMEX)

In period I, before treatment, median stiffness score was slightly lower for patients with MC about to receive placebo compared to patients with MC about to receive mexiletine (70 versus 76). The opposite trend was observed for patients with PC (median: 81 for patients about to receive placebo versus 63 for patients about to receive mexiletine). In period II, before treatment, median stiffness score was slightly lower for patients about to receive mexiletine in each diagnosis (patients with MC: 68 vs. 86, respectively; patients with PC: 78 vs. 86). Of note, the difference observed for the overall population between V2 (start of period I) and V4 (start of period 2) was not significant (71 versus 81; Wilcoxon-signed rank test, p=0.242).

Figure above clearly shows that mexiletine led to a significant improvement of stiffness regardless of diagnostic and treatment sequence. The individual stiffness VAS score for patients receiving placebo generally remained stable. Of note, the patient who had back muscle contracture secondary to a fall during Period II (0110704MC), under mexiletine treatment, had an increase of VAS from 11 to 46. This patient was not included in the PP population.

As the hypothesis of a carry-over effect was rejected, consequently the data from the two periods were combined. The stiffness VAS scores before treatment (V2 or V4) and at the last visit (V3 or V5) in the mITT population are summarised in Table below. The median stiffness VAS scores for patients receiving mexiletine were of 71 at baseline and decreased to 16 at the end of the treatment period while those on placebo did not change (81 vs. 78 at baseline and end of treatment, respectively). This represents a median change of -78% of the stiffness VAS score compared to baseline for subjects under mexiletine (vs. a +2% median change for placebo). In MC subjects, the median stiffness VAS scores under mexiletine were of 73 at baseline and decreased to 25 at the end of the treatment period (-68% median change) while those on placebo did not change (74 vs. 69 at baseline and end of treatment). Similarly, in PC subjects, the median stiffness VAS scores under mexiletine were of 67 at baseline and decreased to 12 at the end of the treatment period (-81% median change) while those on placebo did not change (83.5 vs. 86.5 at baseline and end of treatment).

Table 7: Evolution of Stiffness VAS Score Before Treatment (V2 or V4) and at the Last Visit (V3 or V5) – mITT Population (Study MYOMEX)

		Placebo		Mexiletine	
		Before treatment	**End of treatment**	**Before treatment**	**End of treatment**
VAS (mm)					
MC	N	13	13	13	13
	Mean (SD) Med [range]	70.0 (20.6) 74.0 [27;91]	62.7 (32.4) 69.0 [0;98]	66.1 (24.7) 73.0 [11;100]	29.2 (17.6) 25.0 [9;72]
PC	N Mean (SD) Med [range]	12 80.8 (13.7) 83.5 [54;98]	12 69.9 (32.4) 86.5 [4;96]	12 65.8 (20.5) 67.0 [17;96]	12 19.0 (20.8) 12.0 [1;54]
Total	**N** **Mean (SD)** **Med [range]**	**25** **75.2 (18.1)** **81.0 [27;98]**	**25** **66.2 (31.9)** **78.0 [0;98]**	**25** **66.0 (22.3)** **71.0 [11;100]**	**25** **24.3 (19.5)** **16.0 [1;72]**
VAS (mm) Absolute change from reference value (V2 or V4)					
MC	N Mean (SD) Med [range]	 - -	13 -7.3 (23.7) 2.0 [-63;14]	 - -	13 -36.9 (30.2) -32.0 [-78;35]*
PC	N Mean (SD) Med [range]	 - -	12 -10.8 (36.9) 1.0 [-94;35]	 - -	12 -46.8 (25.1) -50.0 [-93;-3]
Total	**N** **Mean (SD)** **Med [range]**	 **-** **-**	**25** **-9.0 (30.1)** **2.0 [-94;35]**	 **-** **-**	**25** **-41.7 (27.7)*** **-42.0 [-93;35]**

*Patient 0110704MC with MC presented a high stiffness score compared to the baseline value, which increased the mean value.

The difference between the two treatments regarding the stiffness VAS absolute change from baseline was estimated using a linear mixed model on ranks with the following parameters:

- Diagnosis, treatment, and period as fixed effect and interaction diagnosis-treatment
- The subject as random factor
- The baseline value as fixed covariate

The model showed a significant effect of the treatment ($p < 0.001$) and baseline value ($p = 0.002$) in the mITT population (Table below). As the diagnosis-treatment interaction effect was not significant ($p=0.357$), the linear model was not computed by diagnosis.

Table 8: Mixed Effect Linear Model for the Stiffness VAS Absolute Change from Baseline – mITT Population (Study MYOMEX)

Diagnosis	Parameter	p-value
Total population	Diagnosis	0.716
	Treatment	**< 0.001**
	Period	0.133
	Treatment-diagnosis interaction	0.357
	Baseline value	**0.002**

Bold: Significant values

Stiffness score as a function of time

The stiffness VAS scores, evaluated at baseline, at Day 4 and Day 7 before each dose increase, and at Day 18, are depicted in Figure 2.7.3 4 by treatment and treatment sequence in the mITT population. For patients receiving mexiletine, the stiffness VAS scores decreased as a function of time, while the stiffness VAS scores remained generally stable for patients receiving placebo.

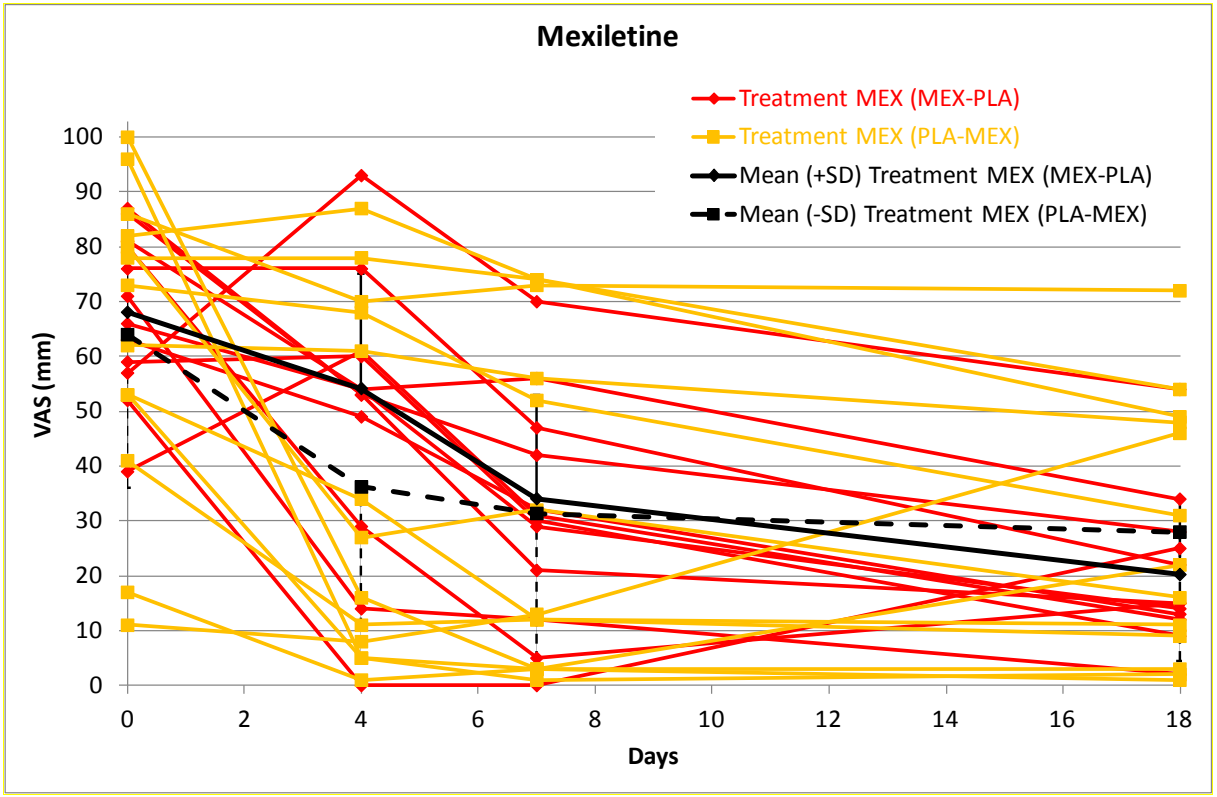


Figure 4: Stiffness VAS Score as a Function of Time by Treatment and Treatment Sequence – mITT Population (Study MYOMEX)

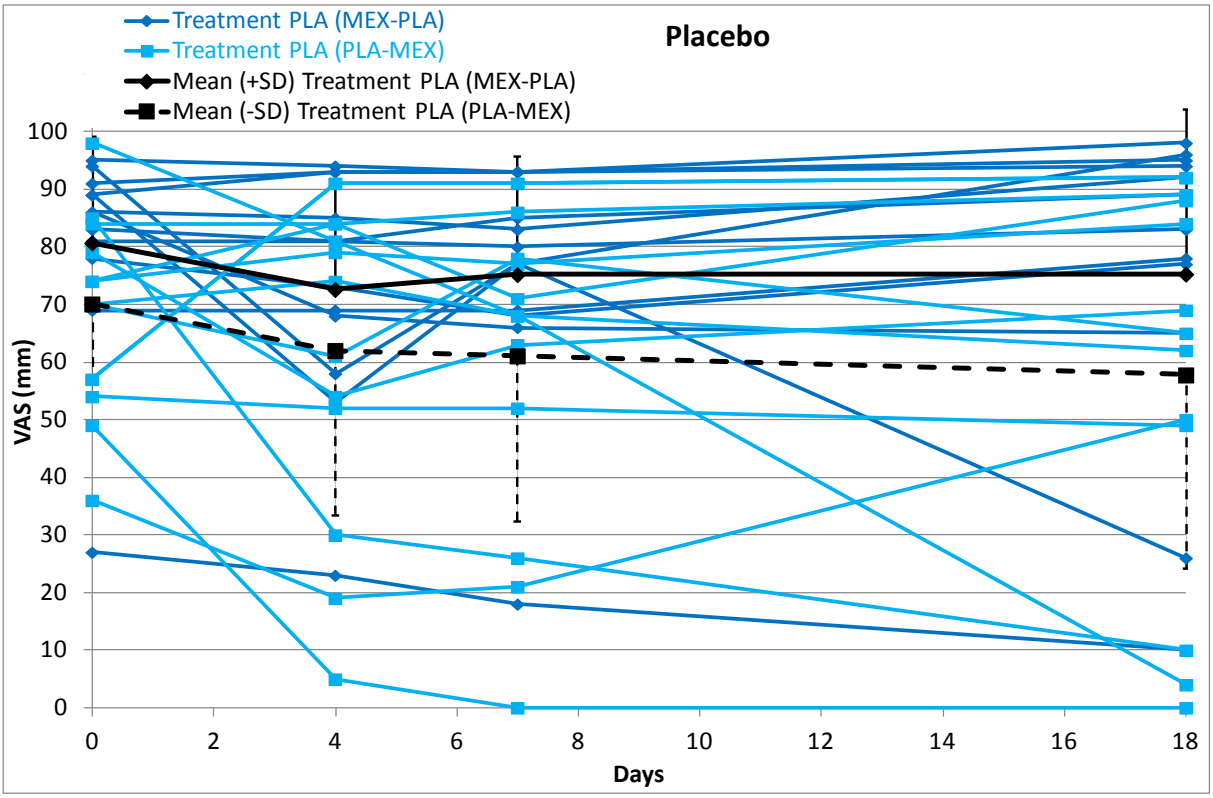


Figure 5: MEX-PLA: sequence mexiletine-placebo; PLA-MEX: sequence placebo-mexiletine

Percentage of patients with an absolute VAS change from baseline ≥ 50 mm

The percentages of patients with an absolute VAS change from baseline ≥ 50 mm at Day 4, Day 7 and Day 18 in the mITT population are summarised in Table 2.7.3 6. At each time point, the percentage of patients with an absolute VAS change from baseline ≥ 50 mm was greater in subjects receiving mexiletine than those receiving placebo. On Day 18, 57% and 14% of the patients had an absolute VAS change from baseline ≥ 50 mm in the mexiletine and placebo treatments, respectively.

Table 9: Percentage of Patients with an Absolute VAS Change from Baseline ≥ 50 mm – mITT Population (Study MYOMEX)

	Number of patients with VAS score at baseline ≥ 50 mm		Patients with an absolute VAS change from baseline ≥ 50 mm N (%)	
	Placebo	**Mexiletine**	**Placebo**	**Mexiletine**
Day 4				
MC (N=13)	10	9*	0 (0.0)	2 (22.2)
PC (N=12)	12	11	1 (8.3)	3 (27.3)
Total (N=25)	**22**	**20***	**1 (4.5)**	**5 (25.0)**
Day 7				
MC (N=13)	10	9*	0 (0.0)	3 (33.3)
PC (N=12)	12	11	1 (8.3)	4 (36.4)
Total (N=25)	**22**	**20***	**1 (4.5)**	**7 (35.0)**
Day 18				
MC (N=13)	10	10	1 (10.0)	5 (50.0)
PC (N=12)	12	11	2 (16.7)	7 (63.6)
Total (N=25)	**22**	**21**	**3 (13.6)**	**12 (57.1)**

*Patient 0410106GM did not report VAS data on Day 4 and Day 7 after treatment with mexiletine

Chair test

Overall, at baseline, the mean time required to stand up from a chair, walk around and sit down again was longer for the patients with MC compared to patients with PC (9.1 ± 3.7 seconds for patients with MC versus 5.3 ± 1.9 seconds for patients with PC) in the mITT population. In each diagnostic group, no marked differences were observed between treatment sequences (Table 2.7.3 7).

Table 10: Chair Test Results at Baseline – mITT Population (Study MYOMEX)

Diagnosis		**Chair test (seconds)**		
		Placebo-mexiletine	**Mexiletine-placebo**	**Total**
MC	N Mean (SD) Median [range]	6 9.7 (2.8) 9.0 [7;15]	7 8.6 (4.4) 7.0 [4;16]	**13** **9.1 (3.7)** **9.0 [4;16]**
PC	N Mean (SD) Median [range]	7 5.0 (1.4) 5.0 [3;7]	5 5.8 (2.6) 5.0 [3;10]	**12** **5.3 (1.9)** **5.0 [3;10]**
Total	**N** **Mean (SD)** **Median [range]**	**13** **7.2 (3.2)** **7.0 [3;15]**	**12** **7.4 (3.9)** **6.0 [3;16]**	**25** **7.3 (3.5)** **6.0 [3;16]**

The absolute values and the absolute change from baseline values of the chair test before and after treatment in the mITT population are presented in Table 2.7.3 8. Median duration to stand up, turn around the chair and sit down was around 6.0 seconds after placebo and around 5.0 seconds after mexiletine, with longer times observed in patients with MC compared to patients with PC (median after placebo: 9.0 versus 6.0 seconds; median after mexiletine: 6.0 versus 5.0 seconds, respectively).

Table 11: Chair Test Before and After Treatment – mITT Population (Study MYOMEX)

Diagnosis		Chair test (seconds): Absolute values			Chair test (seconds): Absolute changes from V2	
		Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
MC (N=13)	Mean (SD) Med [range] p*	9.1 (3.7) 9.0 [4;16]	9.5 (4.8) 9.0 [4;20]	5.7 (1.8) 6.0 [3;10]	0.5 (1.9) 0.0 [-2;4]	-3.4 (3.3) -3.0 [-11;0] 0.008
PC (N=12)	Mean (SD) Med [range] p*	5.3 (1.9) 5.0 [3;10]	5.3 (1.5) 6.0 [3;7]	4.6 (1.0) 5.0 [3;6]	0.0 (1.3) 0.0 [-3;2]	-0.8 (1.5) 0.0 [-5;0] 0.021
Total (N=25)	**Mean (SD)** **Med [range]** **p***	**7.3 (3.5)** **6.0 [3;16]**	**7.5 (4.1)** **6.0 [3;20]**	**5.2 (1.6)** **5.0 [3;10]**	**0.2 (1.6)** **0.0 [-3;4]**	**-2.1 (2.9)** **-1.0 [-11;0]** **0.0007**

* Wilcoxon signed-rank test p value

Overall, the change in the time recorded for the chair test at the end of the treatment period was significantly higher after mexiletine treatment (p (Wilcoxon signed-rank test) = 0.0007; Table above). Changes from baseline indicated an improvement after mexiletine treatment mainly for patients with MC (median improvement of 3.0 seconds) while no marked changes were observed for patients with PC. Indeed, the time required to stand up from a chair, walk around and sit down again for patients with PC was already short at baseline and could not be further improved. Of note, the MC patient who misunderstood the treatment schedule (0410106GM) and did not achieve the dose of 600 mg/day was one of the 2 patients who did not show any improvement with the chair test.

Health-related quality of life

The number of patients with symptoms (weakness, muscular locking, pain, and fatigue) before and after treatment are presented for the mITT population; the health-related quality of life scores (measured using the INQoL scale) before and after treatment are presented for the mITT population in Table below.

Number of Subjects with Symptoms (subdomains: weakness, locking, pain, and fatigue)

Prior to treatment, almost all patients reported weakness and muscular locking. Pain was reported by 60% of the patients; fatigue was also reported by 80% of the patients.

After treatment with placebo, the percentage of patients with symptoms was similar to baseline values for both diagnoses. After treatment with mexiletine, the percentage of patients with symptoms was lower compared to baseline values for both diagnoses for all subdomains at the exception of muscular locking.

When looking at each symptom (Table below):

- Symptoms of muscular locking were reported for almost all patients, whether treated by placebo or mexiletine.
- Symptoms of weakness were less frequently reported after mexiletine treatment compared to placebo (19 out of 25 patients with mexiletine [76%] versus 23 out of 25 patients with placebo [92%]).

- Symptoms of pain were also less frequently reported after mexiletine treatment compared to placebo (8 out of 25 patients with mexiletine [32%] versus 18 out of 25 patients with placebo [72%]).
- Similar observations were made for the fatigue symptoms (13 out of 25 patients with mexiletine [52%] versus 20 out of 25 patients with placebo [80%]).

Table 12: Number of Patients with Symptoms Before and After Treatment – mITT Population (Study MYOMEX)

Symptom	Diagnosis	Number of patients with symptoms (%)		
		Before treatment	**Placebo**	**Mexiletine**
Weakness	MC (N=13)	13 (100.0%)	12 (92.3%)	11 (84.6%)
	PC (N=12)	11 (91.7%)	11 (91.7%)	8 (66.7%)
	Total (N=25)	**24 (96.0%)**	**23 (92.0)**	**19 (76.0%)**
Locking	MC (N=13)	12 (92.3%)	11 (84.6%)	13 (100%)
	PC (N=12)	12 (100.0%)	12 (100.0%)	11 (91.7%)
	Total (N=25)	**24 (96.0%)**	**23 (92.0%)**	**24 (96.0%)**
Pain	MC (N=13)	8 (61.5%)	9 (69.2%)	4 (30.8%)
	PC (N=12)	7 (58.3%)	9 (75.0%)	4 (33.3%)
	Total (N=25)	**15 (60.0%)**	**18 (72.0%)**	**8 (32.0%)**
Fatigue	MC (N=13)	12 (92.3%)	12 (92.3%)	8 (66.7%)
	PC (N=12)	8 (66.7%)	8 (66.7%)	5 (41.7%)
	Total (N=25)	**20 (80.0%)**	**20 (80.0%)**	**13 (52.0%)**

Table 13: Individualised Neuromuscular Quality of Life Before and After Treatment – mITT Population (Study MYOMEX)

Domain	Diagnosis		Absolute values			Absolute changes from V2	
			Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
Weakness	MC (N=13)	Mean (SD)	61.9 (27.1)	62.8 (32.1)	35.6 (24.1)	0.8 (20.0)	-26.3 (28.1)
		Med [range]	68.4 [11;95]	68.4 [0;10]	31.6 [0;74]	0.0 [-53;32]	-26.3 [-84;26]
	PC (N=12)	Mean (SD)	64.9 (28.2)	60.5 (26.1)	25.0 (24.3)	-4.4 (26.9)	-39.9 (30.6)
		Med [range]	65.8 [0;95]	65.8 [0;90]	21.1 [0;79]	-5.3 [-53;37]	-42.1 [-95;26]
	Total (N=25)	**Mean (SD)**	**63.4 (27.1)**	**61.7 (28.8)**	**30.5 (24.3)**	**-1.7 (23.2)**	**-32.8 (29.6)**
		Med [range]	**68.4 [0;95]**	**68.4 [0;10]**	**31.6 [0;79]**	**0.0 [-53;37]**	**-36.8 [-95;26]**
Locking	MC (N=13)	Mean (SD)	65.2 (25.8)	63.2 (38.1)	37.3 (21.3)	-2.0 (38.0)	-27.9 (31.8)
		Med [range]	68.4 [0;95]	79.0 [0;10]	31.6 [16;79]	0.0 [-58;84]	-26.3 [-74;37]
	PC (N=12)	Mean (SD)	73.3 (19.4)	69.3 (21.6)	23.3 (17.0)	-4.0 (22.1)	-50.0 (21.9)
		Med [range]	81.6 [37;95]	81.6 [21;90]	21.1 [0;58]	0.0 [-58;21]	-47.4 [-84;-11]
	Total (N=25)	**Mean (SD)**	**69.1 (22.9)**	**66.1 (30.8)**	**30.5 (20.3)**	**-3.0 (30.8)**	**-38.5 (29.2)**
		Med [range]	**73.7 [0;95]**	**79.0 [0;10]**	**21.1 [0;79]**	**0.0 [-58;84]**	**-36.8 [-84;37]**
Pain	MC (N=13)	Mean (SD)	34.0 (31.4)	41.3 (34.5)	16.2 (28.0)	7.3 (18.1)	-17.8 (39.6)
		Med [range]	42.1 [0;79]	52.6 [0;84]	0.0 [0;74]	5.3 [-21;47]	0.0 [-79;68]
	PC (N=12)	Mean (SD)	43.4 (32.3)	51.8 (34.7)	9.2 (15.9)	8.3 (21.6)	-34.2 (26.6)
		Med [range]	52.6 [0;84]	63.2 [0;84]	0.0 [0;47]	2.6 [-37;47]	-39.5 [-84;0]
	Total (N=25)	**Mean (SD)**	**38.5 (31.5)**	**46.3 (34.3)**	**12.8 (23.0)**	**7.8 (19.4)**	**-25.7 (34.3)**
		Med [range]	**52.6 [0;84]**	**57.9 [0;84]**	**0.0 [0;74]**	**5.3 [-37;47]**	**-26.3 [-84;68]**
Fatigue	MC (N=13)	Mean (SD)	58.7 (25.5)	61.9 (34.3)	33.6 (35.3)	3.2 (25.7)	-25.1 (33.2)
		Med [range]	57.9 [0;95]	68.4 [0;10]	26.3 [0;10]	10.5 [-53;37]	-21.0 [-79;26]
	PC (N=12)	Mean (SD)	49.1 (38.6)	49.1 (38.3)	13.2 (20.0)	0.0 (14.0)	-36.0 (29.9)
		Med [range]	57.9 [0;95]	68.4 [0;95]	0.0 [0;63]	0.0 [-26;26]	-42.1 [-84;0]
	Total (N=25)	**Mean (SD)**	**54.1 (32.1)**	**55.8 (36.1)**	**23.8 (30.2)**	**1.7 (20.6)**	**-30.2 (31.5)**
		Med [range]	**57.9 [0;95]**	**68.4 [0;10]**	**15.8 [0;10]**	**0.0 [-53;37]**	**-31.6 [-84;26]**

Domain	Diagnosis		Absolute values			Absolute changes from V2	
			Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
Activities	MC (N=13)	Mean (SD)	56.6 (24.2)	59.5 (28.5)	35.6 (26.2)	2.9 (20.4)	-21.0 (28.2)
		Med [range]	52.8 [17;86]	66.7 [0;93]	23.2 [10;89]	0.0 [-30;50]	-13.9 [-64;20]
	PC (N=12)	Mean (SD)	65.8 (11.6)	62.0 (21.0)	20.0 (18.8)	-3.8 (16.0)	-45.8 (16.2)
		Med [range]	69.4 [44;80]	68.0 [20;83]	14.4 [0;68]	0.0 [-39;14]	-54.7 [-62;-10]
	Total (N=25)	**Mean (SD)**	**61.0 (19.4)**	**60.7 (24.7)**	**28.1 (23.9)**	**-0.3 (18.4)**	**-32.9 (26.0)**
		Med [range]	**69.4 [17;86]**	**67.6 [0;93]**	**17.6 [0;89]**	**0.0 [-39;50]**	**-34.3 [-64;20]**
Indepen-dence	MC (N=13)	Mean (SD)	25.2 (25.3)*	29.1 (21.6)	20.5 (26.3)	3.0 (19.8)*	-3.9 (30.0)*
		Med [range]	13.9 [0;75]*	33.3 [0;61]	11.1 [0;83]	0.0 [-25;39]*	0.0 [-58;72]*
	PC (N=12)	Mean (SD)	41.2 (20.7)	40.3 (23.7)	11.6 (12.8)	-0.9 (12.4)	-29.6 (19.4)
		Med [range]	44.4 [6;83]	44.4 [11;83]	5.6 [0;36]	0.0 [-22;19]	-33.3 [-58;11]
	Total (N=25)	**Mean (SD)**	**33.2 (24.0)**	**34.4 (22.9)**	**16.2 (21.0)**	**1.0 (16.3)**	**-16.8 (28.0)**
		Med [range]	**36.1 [0;83]**	**36.1 [0;83]**	**5.6 [0;83]**	**0.0 [-25;39]**	**-16.7 [-58;72]**
Social relation-ship	MC (N=13)	Mean (SD)	24.2 (23.5)	31.2 (27.5)	20.2 (22.7)	7.0 (16.0)	-4.1 (21.7)
		Med [range]	16.7 [0;67]	29.6 [0;89]	11.1 [0;62]	0.0 [-19;31]	0.0 [-48;30]
	PC (N=12)	Mean (SD)	38.4 (23.8)	40.4 (27.9)	14.0 (10.8)	1.9 (15.5)	-24.4 (23.7)
		Med [range]	40.3 [0;81]	42.1 [0;79]	13.9 [0;38]	1.4 [-19;28]	-22.7 [-72;17]
	Total (N=25)	**Mean (SD)**	**31.0 (24.2)**	**35.6 (27.5)**	**17.2 (17.9)**	**4.6 (15.6)**	**-13.8 (24.5)**
		Med [range]	**25.9 [0;81]**	**32.4 [0;89]**	**13.9 [0;62]**	**0.0 [-19;31]**	**-12.0 [-72;30]**
Emotions	MC (N=13)	Mean (SD)	46.8 (26.1)	46.4 (25.7)	26.7 (23.4)	-0.4 (29.5)	-20.1 (28.1)
		Med [range]	38.9 [17;92]	52.8 [0;78]	16.7 [0;72]	5.6 [-61;44]	-11.1 [-89;11]
	PC (N=12)	Mean (SD)	56.5 (26.1)	53.9 (30.9)	18.1 (12.6)	-2.6 (15.7)	-38.4 (25.9)
		Med [range]	61.1 [0;86]	59.7 [0;89]	20.8 [0;39]	0.0 [-39;19]	-38.9 [-78;0]
	Total (N=25)	**Mean (SD)**	**51.4 (26.0)**	**50.0 (28.0)**	**22.6 (19.1)**	**-1.4 (23.4)**	**-28.9 (28.1)**
		Med [range]	**52.8 [0;92]**	**52.8 [0;89]**	**19.4 [0;72]**	**0.0 [-61;44]**	**-16.7 [-89;11]**
Body image	MC (N=13)	Mean (SD)	49.8 (30.0)	48.3 (27.6)	34.8 (26.0)	-1.5 (30.2)	-15.0 (33.8)
		Med [range]	47.2 [0;97]	50.0 [0;81]	25.0 [0;89]	0.0 [-67;50]	-11.1 [-86;50]
	PC (N=12)	Mean (SD)	53.5 (21.5)	52.3 (26.0)	19.4 (16.0)	-1.2 (33.1)	-34.0 (29.0)
		Med [range]	51.4 [28;10]	51.4 [0;89]	16.7 [0;44]	0.0 [-67;44]	-33.3 [-83;17]

Domain	Diagnosis		Absolute values			Absolute changes from V2	
			Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
	Total (N=25)	**Mean (SD)**	**51.6 (25.8)**	**50.2 (26.3)**	**27.4 (22.7)**	**-1.3 (31.0)**	**-24.1 (32.4)**
		Med [range]	**50.0 [0;10]**	**50.0 [0;89]**	**19.4 [0;89]**	**0.0 [-67;50]**	**-22.2 [-86;50]**
Overall quality of life	MC (N=13)	Mean (SD)	43.3 (22.2)*	45.9 (22.4)	31.0 (25.7)	3.1 (17.4)*	-11.9 (25.8)*
		Med [range]	49.4 [8.;73]*	47.8 [0;82]	23.3 [5;81]	-2.2 [-28;36]*	-5.3 [-65;32]*
	PC (N=12)	Mean (SD)	52.2 (18.2)	54.4 (23.2)	22.8 (16.0)	2.1 (12.8)	-29.4 (20.7)
		Med [range]	54.2 [25;76]	59.4 [18;83]	22.8 [0;46]	2.8 [-22;25]	-28.1 [-63;4]
	Total (N=25)	**Mean (SD)**	**47.8 (20.4)**	**49.9 (22.7)**	**27.1 (21.6)**	**2.6 (15.0)**	**-20.7 (24.6)**
		Med [range]	**51.1 [8;76]**	**48.3 [0;82]**	**23.3 [0;81]**	**1.1 [-28;36]**	**-25.0 [-65;32]**
Perceived treatment effects	MC (N=13)	Mean (SD)	15.4 (22.5)	27.6 (32.2)	43.0 (44.7)	12.2 (40.3)	27.6 (48.6)
		Med [range]	0.0 [0;67]	25.0 [-8;10]	58.3 [-58;10]	0.0 [-42;10]	33.3 [-58;10]
	PC (N=12)	Mean (SD)	11.8 (16.1)	24.2 (22.2)	51.4 (33.1)	12.4 (23.0)	39.6 (34.5)
		Med [range]	4.2 [-8;42]	20.8 [0;67]	66.7 [-8;92]	8.3 [-17;58]	45.8 [-25;92]
	Total (N=25)	**Mean (SD)**	**13.7 (19.4)**	**26.0 (27.3)**	**47.0 (39.0)**	**12.3 (32.5)**	**33.3 (42.0)**
		Med [range]	**0.0 [-8;67]**	**25.0 [-8;10]**	**58.0 [-58;10]**	**0.0 [-42;10]**	**41.7 [-58;10]**
Expected treatment effects	MC (N=13)	Mean (SD)	18.6 (29.9)	28.9 (34.0)	35.3 (53.8)	10.3 (47.9)	16.7 (61.0)
		Med [range]	0.0 [-8;83]	16.7 [0;10]	50.0 [-10;10]	0.0 [-67;10]	33.3 [-10;10]
	PC (N=12)	Mean (SD)	18.8 (27.6)	36.1 (29.4)	51.4 (31.4)	17.4 (32.5)	32.6 (35.3)
		Med [range]	4.2 [-8;75]	29.2 [0;92]	62.5 [-8;92]	12.5 [-25;92]	25.0 [-8;92]
	Total (N=25)	**Mean (SD)**	**18.7 (28.2)**	**32.3 (31.4)**	**43.0 (44.3)**	**13.7 (40.5)**	**24.3 (49.9)**
		Med [range]	**0.0 [-8;83]**	**25.0 [0;10]**	**50.0 [-10;10]**	**8.3 [-67;10]**	**25.0 [-10;10]**

End of treatment period values were collected at V3 and V5.
The 4 main domains of the INQoL include symptoms (subdomains: weakness, locking, pain, and fatigue); life domains (subdomains: activities, independence, social relationships, emotions, and body image); treatment effects (subdomains: perceived treatment effects and expected treatment effects); and overall quality of life, an aggregation of parts of the 5 subdomains (activities, independence, social relationships, emotions, and body image). A score for "weakness, locking, pain and fatigue" was defined only if the patient reported this feeling in relation to his/her myotonia.
* N=12.

Symptoms (subdomains: weakness, locking, pain, and fatigue)

Looking at the score of each symptoms item before treatment, median scores were above 50, with the highest (i.e., worse) median score reported for locking (median score of 73.7 overall, 68.4 for patients with MC and 81.6 for patients with PC). The median absolute change from baseline remained stable

(varied between 0 and 5) after the administration of placebo but decreased after the administration of mexiletine (varied between – 26 and -37).

Life (subdomains: activities, independence, social relationships, emotions, and body image)

The greatest impact of pathology prior to treatment was on the subdomain "activities" for both pathologies (median score of 69.4 overall, 52.8 for patients with MC and of 69.4 for patients with PC). The median absolute change from baseline was 0 for each subdomain after the administration of placebo and decreased after the administration of mexiletine from -12 to -34.

Overall quality of life (aggregation of the 5 life subdomains)

The median overall quality of life prior to treatment was rated at 51.1 overall, 49.4 for patients with MC and 54.2 for patients with PC. In patient with MC, the median absolute change from baseline was slightly larger after mexiletine treatment compared to placebo treatment (-5.3 vs. -2.2, respectively). The difference was more pronounced in patient with PC (-28.1 vs. 2.8, respectively).

Treatment effects (subdomains: perceived treatment effects and expected treatment effects)

The median perceived treatment effect and expected treatment effect were rated at 0 prior to treatment. The median absolute changes from baseline were higher after mexiletine treatment compared to placebo treatment for the two subdomains for the overall population (perceived treatment effect: 42 vs. 0; expected treatment effect 25 vs. 8, respectively).

Difference between treatments

The difference between the two treatments regarding the absolute change from baseline for each domain was estimated using a linear mixed model on ranks with the following parameters:

- Treatment, period and sequence as fixed effect
- The subject as random factor
- The baseline value as fixed covariate

The mixed effect linear model showed no significant effect of the treatment sequence for the mITT and PP populations ($p > 0.05$). The results of the linear mixed model for the mITT population are presented in Table below.

Table 14: Mixed Effect Linear Model for Each Domain of the Individualised Neuromuscular Quality of Life Questionnaire – mITT Population (Study MYOMEX)

Domain	Parameter	p-value
Weakness	Treatment	**<0.001**
	Period	0.184
	Baseline value	**<0.001**
Locking	Treatment	**<0.001**
	Period	0.408
	Baseline value	0.116
Pain	Treatment	**<0.001**
	Period	0.863
	Baseline value	**<0.001**
Fatigue	Treatment	**<0.001**
	Period	**0.001**
	Baseline value	**<0.001**
Activities	Treatment	**<0.001**
	Period	**0.024**
	Baseline value	**<0.001**
Independence	Treatment	**<0.001**
	Period	**0.023**
	Baseline value	**<0.001**
Social relationship	Treatment	**<0.001**
	Period	**0.002**
	Baseline value	**<0.001**
Emotions	Treatment	**<0.001**
	Period	**0.023**
	Baseline value	**0.002**
Body image	Treatment	**<0.001**
	Period	0.193
	Baseline value	0.240
Overall quality of life	Treatment	**<0.001**
	Period	**0.002**
	Baseline value	**<0.001**
Perceived treatment effect	Treatment	**0.002**
	Period	0.190
	Baseline value	0.681
Expected treatment effect	Treatment	0.077
	Period	0.377
	Baseline value	0.611

Bold: Significant values

The mixed effect linear models showed, for the mITT population:

- A treatment effect for each domain of the INQoL questionnaire ($p < 0.01$) except for the expected treatment effect ($p=0.077$)
- An effect of baseline values for all domains ($p \leq 0.02$) except for muscular locking, body image, perceived treatment effect and expected treatment effect
- A period effect for fatigue, overall quality of life, social relationship, current feeling, independence, and activities ($p < 0.03$)

These results suggest that mexiletine significantly improved the quality of life of the patients.

Clinical global impression of efficacy

CGI of efficacy as assessed by the patients and the investigators in the mITT population are provided in Table below.

Investigators reported the mexiletine treatment as efficient for all but 2 patients with MC (92% of the total population) while they considered the placebo as poorly efficient for most patients (80% of the total population, 11/13 patients with MC and 9/12 patients with PC; p<0.001; Table 2.7.3 12).

Similarly, all but 2 patients with MC (92% of the total population) reported the mexiletine treatment as efficient (11 patients with MC and 12 patients with PC) while most patients (76% of the total population, 10 patients with MC and 9 with PC) considered the placebo as poorly efficient (p<0.001; Table below).

Table 15: Clinical Global Impression of Efficacy – mITT Population (Study MYOMEX)

Diagnostic		Placebo	Mexiletine	MacNemar, p-value
CGI as judged by the investigators				
MC		N=13	N=12*	
	Efficient	2 (15.4%)	10 (83.3%)	
	Not efficient	11 (84.6%)	2 (16.7%)	
PC		N=12	N=12	
	Efficient	3 (25.0%)	12 (100.0%)	
	Not efficient	9 (75.0%)	0 (0.0%)	
Total		**N=25**	**N=24**	**p ≤ 0.001**
	Efficient	**5 (20.0%)**	**22 (91.7%)**	
	Not efficient	**20 (80.0%)**	**2 (8.3%)**	
CGI as judged by the patients				
MC		N=13	N=13	
	Efficient	3 (23.1%)	11 (84.6%)	
	Not efficient	10 (76.9%)	2 (15.4%)	
PC		N=12	N=12	
	Efficient	3 (25.0%)	12 (100.0%)	
	Not efficient	9 (75.0%)	0 (0.0%)	
Total		**N=25**	**N=25**	**p ≤ 0.001**
	Efficient	**6 (24.0%)**	**23 (92.0%)**	
	Not efficient	**19 (76.0%)**	**2 (8.0%)**	

* The data for Patient 0410211PM is missing. Efficient = good or fair reported in the case report form; Not efficient = poor or none reported in the case report form

Patient's preference and willingness to continue treatment

Overall, the patients significantly preferred the mexiletine treatment period (20 patients [80%]; binomial test p=0.0041). Placebo was considered as the preferred treatment by one patient with PC (8.3%) and by 4 patients with MC (31%) including the one who did not have any preference and the one who prematurely discontinued study treatment due to AE.

All but 2 patients with MC (92%) were willing to continue taking mexiletine after the study:

- The patient who prematurely discontinued the study after having experienced an AE (excluded from the PP population).
- The patient who had no preference for one or the other period and for whom mexiletine treatment was considered as poorly efficient by both the patient and the investigator (stiffness VAS absolute change from baseline was only of -14 after mexiletine treatment; 86 at baseline vs. 72 after treatment). This patient also experienced fatigue considered as possibly related to mexiletine (concomitantly, the patient restarted a professional activity).

Number of intolerable increase in myotonia severity necessitating patient's withdrawal

No patient withdrew due to intolerable increase in myotonia severity. Only one patient with MC (4.0% of the total population) prematurely discontinued the study medication following occurrence of an AE (for further details see Module 2.7.4).

Electromyography

Short exercise tests (3 tests, lasting 10 seconds each, with 50-second intervals) were performed on the left hand at room temperature and on the right hand after cooling (7-minute cold exposure) at each study visit. Overall, large inter- and intra-individual variations were observed from one visit to the other. The data are presented for the mITT population only, and separately for patients with MC and PC as distinct electrophysiological patterns are recognised for each of the non-dystrophic subgroups (Matthews et al., 2010).

Patients with MC:

The CMAP amplitudes reported as the percent of pre-first exercise values for patients with MC are summarised in Table 2.7.3 13 for repeated exercises at room temperature. The CMAP amplitudes after cold exposure (% pre-test) and for repeated exercises after cold exposure (% pre-first exercise values) are summarised in Table 2.7.3 14. Graphical representations are given in Figure 2.7.3 5 for exercises at room temperature and Figure 2.7.3 6 for exercises after cold exposure.

At room temperature, the mean CMAP amplitude decreased after the first short exercise and returned to normal values after exercise cessation (i.e. before short exercise 2). When reported as the percent of pre-first exercise values, the mean (± SD) % values post-first exercise were: 60 ± 25% before treatment initiation (V2), 73 ± 28% after mexiletine treatment and 64 ± 37% after placebo treatment (Table 2.7.3 13). The decrease in CMAP amplitude (compared to pre-first exercise values) was more pronounced prior to treatment initiation (60%) and in subjects receiving placebo (64%) compared to subjects receiving mexiletine (73%).

The CMAP amplitude recovered with repeated exercise and approached the pre-first exercise value. After the second short exercise, the mean ± SD values were 97 ± 20%, 95 ± 13% and 90% ± 31% before treatment, after mexiletine and after placebo treatments, respectively. After the third exercise, the mean ± SD values were 93 ± 26%, 99 ± 13% and 90 ± 30%, respectively (Table 2.7.3 13). As changes in CMAP amplitude between -10 to +20% of the pre-exercise value are considered normal (Fournier et al., 2004), these changes may be considered to be within the normal range.

Table 16: Percent of Pre-Exercise CMAP Amplitude After Repeated Exercises at Room Temperature in Patients with MC Before any Treatment (V2) and at the End of each Treatment Period (V3 or V5) – mITT Population (Study MYOMEX)

Exercise		Before*	Placebo**	Mexiletine**
		% of pre-exercise value ***	% of pre-exercise value ***	% of pre-exercise value ***
Short exercise 1 After test		N=12	N=13	N=12
	Mean (SD)	59.8 (25.1)	63.8 (37.0)	73.1 (28.4)
	Med [range]	62.6 [12.4;88.0]	64.8 [0.0;122.6]	82.0 [8.6;102.5]
Short exercise 2 Before test		N=12	N=13	N=12
	Mean (SD)	96.3 (18.8)	96.6 (22.8)	103.5 (14.5)
	Med [range]	98.7 [63.7;132.7]	98.0 [43.0;125.0]	107.7 [66.8;120.0]
Short exercise 2 After test		N=12	N=13	N=12
	Mean (SD)	97.1 (20.1)	89.6 (31.2)	94.9 (13.1)
	Med [range]	96.0 [65.6;131.6]	83.8 [1.5;123.7]	98.0 [70.3;110.1]
Short exercise 3 Before test		N=12	N=13	N=11
	Mean (SD)	105.4 (12.08)	102.7 (17.8)	107.8 (11.5)
	Med [range]	105.5 [92.0;135.7]	100.0 [63.1;127.2]	109.1 [88.1;125.7]
Short exercise 3 After test		N=13	N=13	N=11
	Mean (SD)	92.8 (25.9)	90.1 (29.8)	98.6 (13.2)
	Med [range]	101.2 [46.9;129.6]	100.0 [9.2;124.6]	101.3 [70.8;112.6]

* Tests were performed at V2 on the left hand
** Tests were performed on the left hand, either at V3 or V5 according to the treatment period.
*** Value relative to value recorded before short exercise test 1.

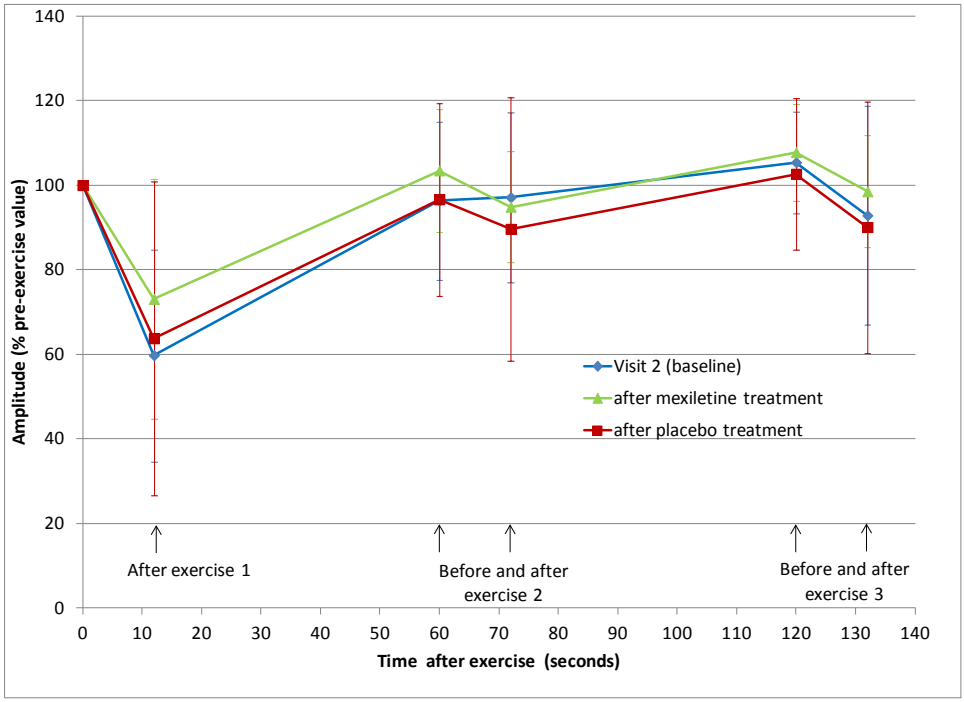


Figure 6: CMAP Amplitude (% Pre-First Exercise Value) After Repeated Exercises at Room Temperature in Patients with MC – mITT Population (Study MYOMEX)

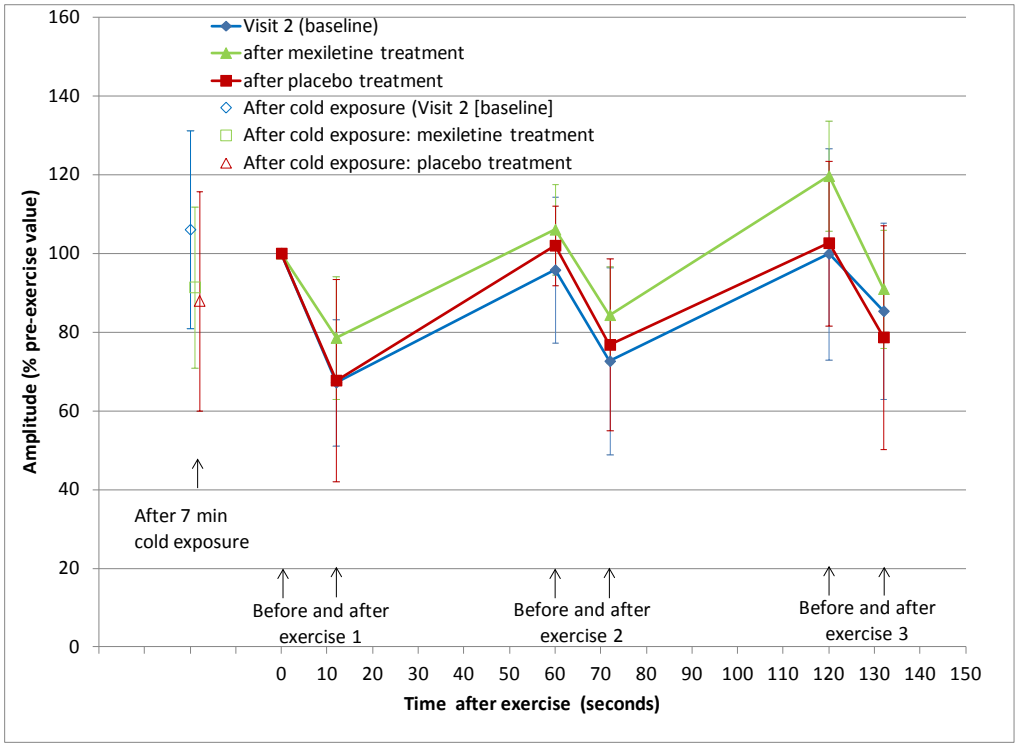
Values shown as mean ± SD. CMAPs were first monitored before exercises for 1-2 minutes to enable baseline stabilisation. Short exercises lasted 10 seconds each with 50-second interval.

After cold exposure, the mean CMAP amplitude decreased after the first short exercise and returned to normal values after exercise cessation (i.e. before short exercise 2). When reported as the percent of pre-first exercise values, the mean (± SD) % values post-first exercise were: 67 ± 16% before treatment initiation (V2), 79 ± 16% after mexiletine treatment and 68 ± 26% after placebo treatment (Table below). The decrease in CMAP amplitude (compared to pre-first exercise values) was more pronounced prior to treatment initiation (67%) and in subjects receiving placebo (68%) compared to subjects receiving mexiletine (79%). Similar trends were observed after the second and the third short exercises.

Table 17: CMAP Amplitude after Cold Exposure (% Pre-Test) and Repeated Exercises (% Pre-First Exercise) in Patients with MC Before any Treatment (V2) and at the End of each Treatment Period (V3 or V5) – mITT Population (Study MYOMEX)

Treatment		Before (V2)*	Placebo**	Mexiletine**
		% of pre-exercise value ***	% of pre-exercise value ***	% of pre-exercise value ***
After cold exposure[$] (no test)		N=11	N=13	N=13
	Mean (SD)	106.1 (25.1)	88.0 (27.9)	91.4 (20.5)
	Med [range]	103.8 [68.7;159.8]	94.0 [42.2;138.0]	86.9 [62.7;143.8]
Short exercise 1 after cold exposure After test		N=13	N=13	N=12
	Mean (SD)	67.2 (15.9)	67.7 (25.7)	78.6 (15.5)
	Med [range]	72.4 [27.2;90.0]	63.0 [18.2;105.2]	79.8 [47.7;103.9]
Short exercise 2 after cold exposure Before test		N=13	N=13	N=12
	Mean (SD)	95.8 (18.5)	102.0 (10.2)	106.1 (11.5)
	Med [range]	100.0 [63.2;130.3]	103.4 [85.6;116.1]	106.9 [80.8;126.0]
Short exercise 2 after cold exposure After test		N=13	N=13	N=12
	Mean (SD)	72.6 (23.7)	76.8 (21.8)	84.4 (12.3)
	Med [range]	79.2 [27.9;104.5]	79.3 [41.3;103.2]	83.9 [59.9;107.0]
Short exercise 3 after cold exposure Before test		N=13	N=13	N=12
	Mean (SD)	99.9 (26.8)	102.6 (20.9)	119.7 (14.0)
	Med [range]	103.9 [36.8;149.4]	103.4 [59.7;136.4]	117.8 [104.5;145.0]
Short exercise 3 after cold exposure After test		N=13	N=13	N=12
	Mean (SD)	85.3 (22.4)	78.7 (28.4)	91.0 (15.0)
	Med [range]	89.6 [38.2;129.2]	91.0 [9.1;110.3]	93.7 [49.6;113.0]

* Tests were performed at V2 on the right hand.
** Tests were performed on the right hand, either at V3 or V5 according to the treatment period.
*** Value relative to value recorded before short exercise test 1 except for "After cold exposure", for which the value is relative to value before cold exposure.
$ 5-7 minutes of cold exposure



Values shown as mean ± SD. After repeated exercises, CMAP amplitudes are expressed as a % of the value prior to the first exercise ("pre-first exercise"). Short exercises lasted 10 seconds each with 50-second interval.

Figure 7: CMAP Amplitude After Repeated Exercise (% Pre-First Exercise Value) After Cold Exposure in Patients with MC – mITT Population (Study MYOMEX)

Patients with PC:

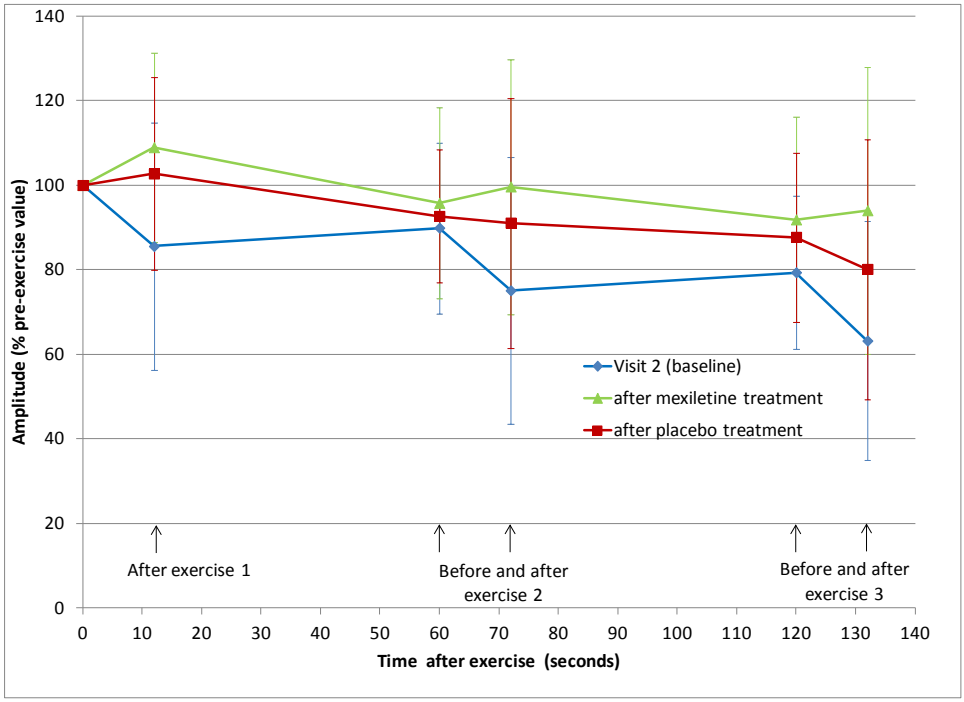
The CMAP amplitudes reported as the percent of pre-first exercise values for patients with PC are summarised in Table 22 for repeated exercises at room temperature. The CMAP amplitudes after cold exposure (% pre-test) and for repeated exercises after cold exposure (% pre-first exercise values) are summarised in Table 23. Graphical representations are given in Figure 8 for exercises at room temperature and Figure 9 for exercises after cold exposure.

Overall, at room temperature, repeated short exercise induced a decrease in CMAP amplitude in patients with PC. However, the mean values post-first exercise were > 100% after placebo and mexiletine treatments (103% and 109%, respectively). During the treatment periods (placebo or mexiletine), the change in mean amplitude followed the same pattern as prior to treatment but the decrease was generally less pronounced. The decrease in amplitude seemed partially prevented by mexiletine (94%) after the third short exercise compared to placebo (80%).

Table 18: Percent of Pre-Exercise CMAP Amplitude after Repeated Exercises at Room Temperature in Patients with PC Before any Treatment (V2) and at the End of each Treatment Period (V3 or V5) – mITT Population (Study MYOMEX)

Exercise		Before*	Placebo**	Mexiletine**
		% of pre-exercise value (%)***	% of pre-exercise value (%)***	% of pre-exercise value (%)***
Short exercise 1 After test	Mean (SD) Med [range]	N=12 85.6 (29.3) 92.0 [21.4;116.9]	N=12 102.7 (22.7) 98.9 [69.2;152.0]	N=12 108.9 (22.4) 114.2 [57.9;136.0]
Short exercise 2 Before test	Mean (SD) Med [range]	N=12 89.9 (20.2) 95.5 [30.6;106.9]	N=12 92.7 (15.7) 95.6 [61.5;117.5]	N=12 95.8 (22.6) 102.6 [39.6;124.7]
Short exercise 2 After test	Mean (SD) Med [range]	N=12 75.1 (31.6) 84.9 [17.4;126.2]	N=12 91.1 (29.5) 99.2 [33.9;137.0]	N=12 99.7 (30.2) 102.4 [29.0;150.3]
Short exercise 3 Before test	Mean (SD) Med [range]	N=12 79.4 (18.1) 84.7 [40.9;102.4]	N=12 87.7 (20.0) 89.4 [45.5;119.8]	N=12 91.9 (24.3) 97.5 [29.2;128.9]
Short exercise 3 After test	Mean (SD) Med [range]	N=12 63.2 (28.2) 56.8 [24.9;107.6]	N=12 80.2 (30.7) 72.7 [21.9;140.6]	N=12 94.0 (34.0) 95.2 [15.1;149.1]

* Tests were performed at V2 on the left hand
** Tests were performed on the left hand, either at V3 or V5 according to the treatment period.
*** Value relative to value recorded before short exercise 1.



Values shown as mean ± SD.

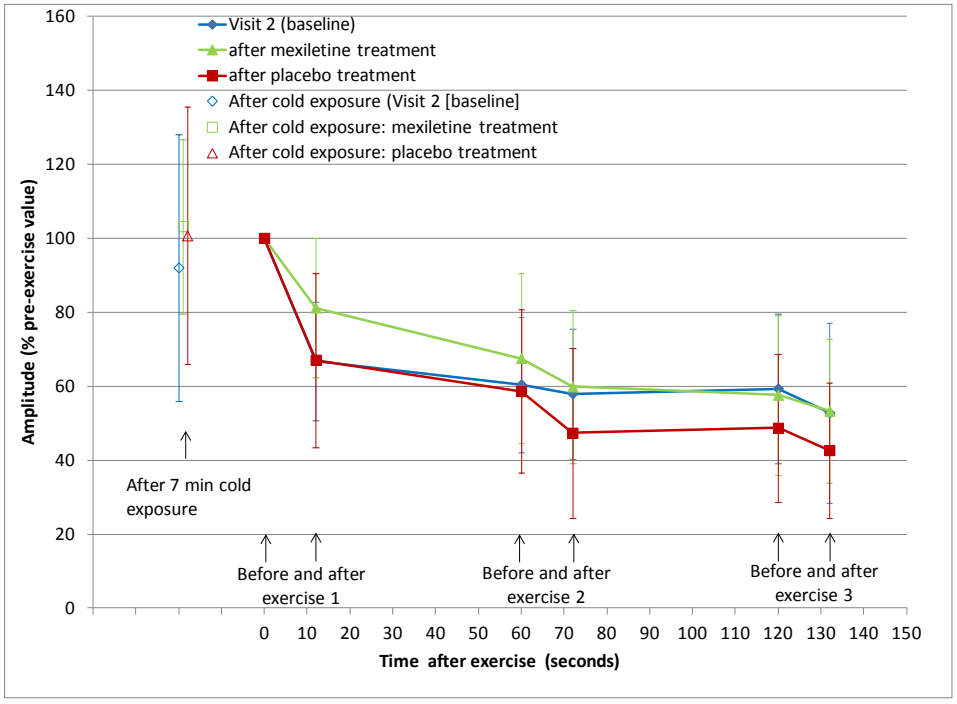
Figure 8: CMAP Amplitude (% Pre-First Exercise Value) After Repeated Exercises at Room Temperature in Patients with PC – mITT Population (Study MYOMEX)

Cold exposure aggravated the decrease in amplitude after short exercises prior to treatment initiation and after mexiletine and placebo treatment. Results suggested a protective effect of the mexiletine treatment after the first short exercise where the decrease in CMAP amplitude was less pronounced (81%) compared to prior to treatment initiation and after placebo treatment (67% each) (Table 2.7.3 16). After the second and third short exercise, the mean decrease in CMAP amplitude (compared to pre-first exercise values) was similar prior to treatment initiation (58% and 53%, respectively) and in subjects receiving mexiletine (60% and 53%) but less pronounced than in subjects receiving placebo (47% and 43%).

Table 19: CMAP Amplitude after Cold Exposure (% Pre-Test) and Repeated Exercises (% Pre-Exercise) in Patients with PC Before any Treatment (V2) and at the End of each Treatment Period (V3 or V5) – mITT Population (Study MYOMEX)

Treatment		Before*	Placebo**	Mexiletine**
		% of pre-exercise (%)***	% of pre-exercise (%)***	% of pre-exercise (%)***
After cold exposure$ (no test)	Mean (SD) Med [range]	N=11 92.0 (36.0) 91.4 [37.2;174.1]	N=12 100.7 (34.8) 103.6 [4.9;149.5]	N=11 103.2 (23.6) 101.5 [66.3;133.9]
Short exercise 1 after cold exposure After test	Mean (SD) Med [range]	N=12 66.7 (16.10) 68.4 [31.3;93.5]	N=12 67.1 (23.5) 61.8 [35.3;103.4]	N=12 81.2 (18.8) 84.6 [54.2;113.1]
Short exercise 2 after cold exposure Before test	Mean (SD) Med [range]	N=12 60.4 (18.3) 64.0 [34.0;86.0]	N=12 58.6 (22.0) 59.7 [16.3;89.2]	N=12 67.5 (23.0) 59.9 [25.4;106.0]
Short exercise 2 after cold exposure After test	Mean (SD) Med [range]	N=12 57.9 (17.7) 59.9 [27.9;94.4]	N=12 47.3 (22.9) 44.1 [5.1;80.3]	N=12 59.8 (20.7) 53.6 [27.1;94.0]
Short exercise 3 after cold exposure Before test	Mean (SD) Med [range]	N=12 59.3 (20.12) 60.5 [27.7;100.0]	N=12 48.7 (20.1) 47.9 [14.3;85.5]	N=12 57.6 (21.6) 57.9 [22.0;103.8]
Short exercise 3 after cold exposure After test	Mean (SD) Med [range]	N=12 52.8 (24.3) 44.9 [25.3;102.8]	N=12 42.6 (18.3) 38.4 [16.3;72.2]	N=12 53.3 (19.45) 54.2 [18.6;92.0]

* Tests were performed at V2 on the right hand
** Tests were performed on the right hand either at V3 or V5 according to the treatment period.
*** Value relative to value recorded before short exercise test 1 except for "After cold exposure", for which the value is relative to value before cold exposure.
$ 5-7 minutes of cold exposure
CMAP: compound muscle action potential; Med: median; mITT: modified intention-to-treat; PC: paramyotonia congenita; SD: standard deviation.



Values shown as mean ± SD. After repeated exercises, CMAP amplitudes are expressed as a % of the value prior to the first exercise ("pre-first exercise"). Short exercises lasted 10 seconds each with 50-second interval.
CMAP: compound muscle action potential; mITT: modified intention-to-treat; PC: paramyotonia congenita.

Figure 9: CMAP Amplitude After Repeated Exercise (% Pre-First Exercise) After Cold Exposure in Patients with PC – mITT Population (Study MYOMEX)

Clinical myotonia rating scale

The severity and disability global scores before and after treatment are presented in Table below. Note that the range for the global severity scores range between 0 and 104, with 0 corresponding to a normal situation in all items while the global disability scores range between 0 and 27, with 0 corresponding to a normal situation in all items.

At baseline, the severity global scores and the disability global scores were similar for patients with MC and PC.

Although some patients presented an improvement in their global severity score after placebo treatment, overall the severity score did not really improve or worsen (median absolute change from baseline: 0, range: -46; 35). On the other hand, all patients treated with mexiletine showed an improvement in their severity score (median absolute change from baseline: -27, range: -57; -2). Overall, the improvement was generally greater in patients with PC compared to patients with MC (median absolute change from baseline: -41 versus -22, respectively; Table below).

Table 20: Severity and Disability Global Scores Before and After Treatment – mITT Population (Study MYOMEX)

Items	Diagnosis		Absolute values			Absolute changes from V2	
			Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
Severity global score*	MC N=13	Mean (SD)	53.4 (9.4)	46.0 (26.1)	31.0 (16.2)	-7.4 (21.7)	-22.4 (14.9)
		Med [range]	51.5 [41;74]	54.0 [0;81]	32.0 [1;56]	0.0 [-46;35]	-22.0 [-50;-2]
	PC N=12	Mean (SD)	54.2 (11.0)	49.38 (20.8)	16.5 (15.3)	-4.8 (16.4)	-37.7 (13.7)
		Med [range]	57.5 [27;70]	59.0 [9.0;67.0]	12.5 [1;47]	1.8 [-43;10]	-40.5 [-57;-19]
	Total N=25	**Mean (SD)**	**53.8 (10.0)**	**47.6 (23.3)**	**24.0 (17.1)**	**-6.2 (19.0)**	**-29.8 (16.0)**
		Med [range]	**54.0 [27;74]**	**56.0 [0;81]**	**20.0 [1;56]**	**0.0 [-46;35]**	**-27.0 [-57;-2]**
Disability global score**	MC N=13	Mean (SD)	8.2 (2.8)	7.54 (4.4)	3.9 (2.5)	-0.7 (3.3)	-4.4 (2.8)
		Med [range]	7.0 [4;14]	8.0 [0;13]	3.0 [0;9]	0.0 [-7;3]	-5.0 [-9;-1]
	PC N=12	Mean (SD)	7.3 (2.8)	6.5 (3.2)	1.5 (2.1)	-0.8 (3.6)	-5.8 (3.4)
		Med [range]	7.5 [3;14]	7.5 [1;11]	0.5 [0;7]	-0.5 [-8;6]	-6.0 [-11;1]
	Total N=25	**Mean (SD)**	**7.8 (2.8)**	**7.0 (3.8)**	**2.7 (2.6)**	**-0.8 (3.4)**	**-5.1 (3.1)**
		Med [range]	**7.0 [3;14]**	**8.0 [0;13]**	**2.0 [0;9]**	**0.0 [-8;6]**	**-5.0 [-11;1]**

* Min-max range for global severity score is 0-104, with 0 corresponding to a normal situation in all items
** Min-max range for global disability score is 0-27, with 0 corresponding to a normal situation in all items

Similar observations can be made for the disability global score:

- After treatment with placebo, median absolute change from baseline showed no improvement of the disability score (0, range: -8; 6) for the total population.
- After treatment with mexiletine, the median absolute improvement was -5 (range: 11; 1) for the total population.

The improvement in the disability score was similar in PC and MC patients (median absolute change from V2: -6 versus -5, respectively; Table below).

The mixed effect linear model showed a significant effect of the treatment, period, baseline value, and diagnosis-treatment interaction on the severity score for the total population (Table below). As the

diagnosis-treatment interaction factor had a significant effect (p=0.013), a mixed effect linear model was computed by diagnosis. A significant effect of the treatment was observed in patients with PC (p<0.001) but not in patients with MC (p=0.069). In both pathologies, mexiletine tended to decrease the severity score but this effect was significant only for patients with PC.

Table 21: Mixed Effect Linear Model for the Severity Global Score – mITT Population (Study MYOMEX)

Diagnosis	Parameter	p-value
MC	Treatment	0.069
	Period	0.167
	Baseline value	**0.007**
PC	Treatment	**<0.001**
	Period	0.073
	Baseline value	**0.015**
Total population	Diagnosis	0.381
	Treatment	**<0.001**
	Period	**0.025**
	Treatment-diagnosis interaction	**0.013**
	Baseline value	**<0.001**

Bold: significant values

The mixed effect linear model showed a significant effect of the treatment and baseline value on the disability score for the total population (Table below). Therefore, mexiletine significantly decreased the disability score in the overall population. However, the diagnosis-treatment interaction effect was not significant (p=0.143) and the linear model was not computed by diagnosis (Table below).

Table 22: Mixed Effect Linear Model for the Disability Global Score – mITT Population (Study MYOMEX)

Diagnosis	Parameter	p-value
Total population	Diagnosis	0.159
	Treatment	**<0.001**
	Period	0.155
	Treatment-diagnosis interaction	0.143
	Baseline value	**0.008**

Bold: significant values

- **Ancillary analyses**

Correlations between CMS, INQoL, and stiffness VAS scores assessed using the Spearman coefficient are provided in Table below.

Table 23: Correlations between Clinical Myotonia Scale, Quality of Life, and Stiffness Scores assessed using the Spearman Coefficient– mITT Population (Study MYOMEX)

	Clinical Myotonia Scale		INQoL			Stiffness score (VAS)
	Severity global score	**Disability global score**	**Quality of life**	**Perceived treatment effect**	**Expected treatment effect**	
Severity global score	1	0.73 ($p \leqslant 0.001$)	0.67 ($p \leqslant 0.001$)	-0.44 ($p \leqslant 0.001$)	-0.32 (p=0.006)	0.70 ($p \leqslant 0.001$)
Disability global score	0.73 ($p \leqslant 0.001$)	1	0.47 ($p \leqslant 0.001$)	-0.42 ($p \leqslant 0.001$)	-0.28 (p=0.015)	0.69 ($p \leqslant 0.001$)

The global score of severity was strongly correlated with the disability score (0.73, p ≤ 0.001), the stiffness score (0.70, p ≤ 0.001) and the quality of life (0.67, p ≤ 0.001). It was also inversely related to the perceived and expected treatment effects (-0.44, p ≤ 0.001 and -0.32, p=0.006 respectively).

Similarly, the global score of disability was strongly correlated with the severity score (0.73, p ≤ 0.001), the stiffness score (0.69, p ≤ 0.001) and moderately correlated with the quality of life (0.47, p ≤ 0.001). It was also inversely related to the perceived and expected treatment effects (-0.42, p ≤ 0.001 and -0.28, p=0.015 respectively).

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of Efficacy for trial MYOMEX

Title: Efficacy and safety of mexiletine in non-dystrophic myotonias			
Study identifier	MYOMEX		
Design	Multi-centre, double-blind, placebo-controlled, cross-over Phase III study		
Hypothesis	Exploratory: Comparative analysis		
Treatments groups	Mexiletine		Double-blind, cross-over mexiletine Duration: 18 days, 25 randomised
	Placebo		Double-blind, cross-over placebo. Duration: 18 days, 25 randomised
Endpoints and definitions	Primary endpoint	Stiffness score	Score of stiffness severity as self-reported by the patient on a VAS at baseline and Day 18 Analysis done for the mITT and PP populations
	Secondary endpoint	Chair test	Time needed to stand up from a chair, walk around the chair and sit down again at baseline and Day 18
	Secondary endpoint	Individualised neuromuscular quality of life (INQoL)	Health-related quality-of-life as measured by INQoL scale at baseline and Day 18
	Secondary endpoint	CGI Efficacy index	Clinical global impression of efficacy determined by the patient and by the investigator at baseline and Day 18
	Secondary endpoint	Preference between the 2 treatment periods	Preference between the 2 treatment periods determined by the patient at Day 18
	Secondary exploratory endpoint	Clinical Myotonia Scale	Scale comprised of 2 sections: a myotonia severity scale based on examination of the patient and a disability scale based on the patient's view of disability in activities of daily living. Determined at baseline and Day 18
Results and Analysis			
Analysis description	**Primary Analysis: Stiffness score (VAS) (mm)**		
Analysis population and time point description	Intent to treat Analysis at Day 18 (end of treatment period)		

Descriptive statistics and estimate variability	Treatment group	Mexiletine	Placebo
	Number of subjects	25	25
	Mean (SD) VAS value at Baseline	66.0 (22.3)	75.2 (18.1)
	Mean (SD) VAS value at Day 18	24.3 (19.5)	66.2 (31.9)
	Mean (SD) VAS absolute change from baseline	-41.7 (27.7)	-9.0 (30.1)
	Percentage of Patients with an Absolute VAS Change from Baseline ⩾ 50 mm at Day 18	12/21 (57.1%)	3/22 (13.6%)
Effect estimate per comparison	VAS Absolute Change from Baseline	Comparison groups	Mexiletine vs. Placebo
		Mixed Effect Linear Model	
		P-value	p < 0.001
Analysis description	**Primary Analysis: Stiffness score (VAS) (mm)**		
Analysis population and time point description	Per protocol Analysis at Day 18 (end of treatment period)		
Descriptive statistics and estimate variability	Treatment group	Mexiletine	Placebo
	Number of subjects	22	22
	Mean (SD) VAS value at Baseline	67.5 (18.9)	78.8 (14.7)
	Mean (SD) VAS value at Day 18	23.4 (20.3)	71.8 (27.8)
	Mean (SD) VAS absolute change from baseline	-44.2 (22.8)	-7.0 (30.9)
	Percentage of Patients with an Absolute VAS Change from Baseline ⩾ 50 mm at Day 18	11/19 (57.9%)	3/21 (14.3%)
Effect estimate per comparison	VAS Absolute Change from Baseline	Comparison groups	Mexiletine vs. Placebo
		Mixed Effect Linear Model	
		P-value	p < 0.001

Analysis description	**Secondary analysis Chair test (s)**		
Analysis population and time point description	Intent to treat Analysis at Day 18 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	25	25
	Mean (SD) value at Baseline	7.3 (3.5)	
	Mean (SD) value at Day 18	5.2 (1.6)	7.5 (4.1)
	Mean (SD) absolute change from baseline	-2.1 (2.9)	0.2 (1.6)
Effect estimate per comparison	Chair test time Change from Baseline	Comparison groups	Mexiletine vs. Placebo
		Wilcoxon signed-rank test	
		Effect of treatment	p = 0.0007
Analysis description	**Secondary analysis Individualised Neuromuscular Quality of Life**		
Analysis population and time point description	Intent to treat Analysis at Day 18 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	25	25
Weakness	Mean (SD) value at Baseline	63.4 (27.1)	
	Mean (SD) value at Day 18	30.5 (24.3)	61.7 (28.8)
	Mean (SD) absolute change from baseline	-32.8 (29.5)	-1.7 (23.2)
Locking	Mean (SD) value at Baseline	69.1 (22.9)	
	Mean (SD) value at Day 18	30.5 (20.3)	66.1 (30.8)
	Mean (SD) absolute change from baseline	-38.5 (29.2)	-3.0 (30.8)
Pain	Mean (SD) value at Baseline	38.5 (31.5)	
	Mean (SD) value at Day 18	12.9 (22.8)	46.3 (34.3)
	Mean (SD) absolute change from baseline	-25.7 (34.3)	7.8 (19.4)
Fatigue	Mean (SD) value at Baseline	54.1 (32.1)	
	Mean (SD) value at Day 18	23.8 (30.2)	55.8 (36.1)
	Mean (SD) absolute change from baseline	-30.3 (31.5)	1.7 (20.6)
Activities	Mean (SD) value at Baseline	61.0 (19.4)	
	Mean (SD) value at Day 18	28.1 (23.9)	60.7 (24.7)

	Mean (SD) absolute change from baseline	-32.9 (26.0)	-0.3 (18.4)
Independence	Mean (SD) value at Baseline	33.2 (24.0)	
	Mean (SD) value at Day 18	16.2 (21.0)	34.4 (22.9)
	Mean (SD) absolute change from baseline	-16.8 (28.0)	1.0 (16.3)
Social relationships	Mean (SD) value at Baseline	31.0 (24.3)	
	Mean (SD) value at Day 18	17.2 (17.9)	35.6 (27.5)
	Mean (SD) absolute change from baseline	-13.9 (24.5)	4.6 (15.6)
Emotions	Mean (SD) value at Baseline	51.4 (26.0)	
	Mean (SD) value at Day 18	22.6 (19.1)	50.0 (28.0)
	Mean (SD) absolute change from baseline	-28.9 (28.1)	-1.4 (23.4)
Body image	Mean (SD) value at Baseline	51.6 (25.8)	
	Mean (SD) value at Day 18	27.4 (22.7)	50.2 (26.3)
	Mean (SD) absolute change from baseline	-24.1 (32.4)	-1.3 (31.0)
Overall quality of life	Mean (SD) value at Baseline	47.8 (20.4)	
	Mean (SD) value at Day 18	27.1 (21.6)	49.9 (22.7)
	Mean (SD) absolute change from baseline	-20.7 (24.6)	2.6 (15.0)
Perceived treatment effects	Mean (SD) value at Baseline	13.7 (19.4)	
	Mean (SD) value at Day 18	47.0 (39.0)	26.0 (27.3)
	Mean (SD) absolute change from baseline	33.3 (42.0)	12.3 (32.5)
Expected treatment effects	Mean (SD) value at Baseline	18.7 (28.2)	
	Mean (SD) value at Day 18	43.0 (44.3)	32.3 (31.4)
	Mean (SD) absolute change from baseline	24.3 (49.9)	13.7 (40.5)

Effect estimate per comparison	Effect of treatment Change from Baseline	Comparison groups	Mexiletine vs. Placebo
		Linear mixed model	
		Weakness	p < 0.001
		Locking	p < 0.001
		Pain	p < 0.001
		Fatigue	p < 0.001
		Activities	p < 0.001
		Independence	p < 0.001

		Social relationships	p < 0.001
		Emotions	p < 0.001
		Body image	p < 0.001
		Overall quality of life	p < 0.001
		Perceived treatment effects	p = 0.002
		Expected treatment effects	p = 0.077
Analysis description	**Secondary analysis** **CGI Efficacy Index**		
Analysis population and time point description	Intent to treat Analysis at Day 18 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	25	25
	CGI as judged efficient by the investigators	(n=24)	
	n (%)at Day 18	22 (91.7%)	5 (20.0%)
	CGI as judged efficient by the patients		
	n (%)at Day 18	23 (92.0%)	6 (24.0%)
Effect estimate per comparison	CGI as judged efficient by the investigators	Comparison groups	Mexiletine vs. Placebo
		Mc Nemar test	
		Effect of treatment	p <0.0001
	CGI as judged efficient by the patients	Comparison groups	Mexiletine vs. Placebo
		Mc Nemar test	
		Effect of treatment	p <0.0001
Analysis description	**Secondary analysis** **Patient's preference over the two treatment periods**		
Analysis population and time point description	Intent to treat Analysis at Day 18 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	25	25
	n (%)at Day 18	20 (80.0%)	5 (20.0%)
Effect estimate per comparison	CGI as judged efficient by the investigators	Comparison groups	Mexiletine vs. Placebo
		Binomial test	
		Effect of treatment	p = 0.0041
Analysis description	**Secondary analysis** **Clinical myotonia rating scale**		
Analysis population and time point description	Intent to treat Analysis at Day 18 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**

	Number of subjects	25	25
Severity global score	Mean (SD) value at Baseline	53.8 (10.0)	
	Mean (SD) value at Day 18	24.0 (17.1)	47.6 (23.3)
	Mean (SD) absolute change from baseline	-29.8 (16.0)	-6.2 (19.0)
Disability global score	Mean (SD) value at Baseline	7.8 (2.8)	
	Mean (SD) value at Day 18	2.7 (2.6)	7.0 (3.8)
	Mean (SD) absolute change from baseline	-5.1 (3.1)	-0.8 (3.4)
Effect estimate per comparison	Effect of treatment Change from Baseline	Comparison groups	Mexiletine vs. Placebo
		Linear mixed model	
		Severity global score	p < 0.001
		Disability global score	p < 0.001

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

There was only one main study. No pooled analysis or meta-analysis was performed. Instead, a comparison of effect on several studies (Myomex + published studies) was performed.

Clinical studies in special populations

The efficacy of mexiletine has been investigated in the elderly as indicated in the table below.

Table 25: Clinical Studies in Special Populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	1/25 (MYOMEX Study)		
Non Controlled Trials	2/21 (Lo Monaco et al., 2015)		

Of note, the controlled study reported by Statland et al. (2012) included 59 subjects aged 16-68 years, however the number of patients older than 65 years is not reported. In the studies reported by Logigian et al. (2010), the age range of enrolled subjects is not detailed (mean ± SD = 46.2 ± 9.0 years in the 150 mg trial; 42.6 ± 8.6 years in the 200 mg trial).

Regarding uncontrolled studies, the trial reported by Contardi et al. (2012) included 33 subjects aged 17-71 years, 18 of which received mexiletine; however the number of patients older than 65 years is not reported. In the study published by Suetterlin et al. (2015), the age of enrolled subjects was not reported.

In all other studies, subjects were below 65 years old. Case reports were not included in the analysis.The applicant has presented their known available data regarding the patient elder age groups. No patient 75

or above has been studied with mexiletine, and only 3 known pts have been treated between 65 and 74 years of age.

Supportive study(ies)

Following an extended literature search, 29 publications were identified as of interest, including 3 controlled trials of mexiletine (Kwiecinski *et al.*, 1992; Logigian *et al.*, 2010; Statland *et al.*, 2012) and 3 prospective or retrospective uncontrolled studies (Contardi *et al.*, 2012; Lo Monaco *et al.*, 2015; Suetterlin *et al.*, 2015). In addition, several case reports in adults and in children were identified that support the claim of efficacy of mexiletine.

The most compelling evidence is provided by three recent randomised clinical trials: two trials in patients with DM1 reported in the publication by Logigian *et al.* (2010) and one trial in patients with NDM (Statland *et al.*, 2012).

Controlled Studies

Statland et al. (2012)

Table 26: Statland *et al.* (2012): Study Design

• **Study objective**	• To determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDMs.
• **Design**	• A randomised, double-blind, placebo-controlled 2-period crossover Phase 2 study.
• **Study location**	• United States, Canada, England, Italy (7 centres)
• **Number of subjects/ Inclusion criteria**	• A total of 62 eligible patients were recruited, of which 3 were ineligible at screening. • Eligible participants were aged at least 16 years, had clinical symptoms or signs of NDMs, and had myotonic potentials on EMG. Patients taking antimyotonic agents were required to discontinue medications for a washout period equal to 7 times the half-life of elimination before their baseline visit.
• **Test product** • **Dosage regimen**	• 200 mg mexiletine (as mexiletine hydrochloride) (TEVA Pharmaceutical) or placebo (microcrystalline cellulose [Avicel PH 102]) capsules 3 times daily for 4 weeks, followed by the opposite intervention for 4 weeks, with 1-week washout in between.
• **Route of administration**	• Oral administration
• **Duration of treatment**	• Treatment periods were 4 weeks in duration, separated by a 1-week washout period.
• **Criteria for evaluation**	• **Efficacy:** The primary end point was defined as the severity score of stiffness reported by participants during the third and fourth week of each treatment period via the interactive voice response (IVR) diary. Participants called in to report symptom severity on a scale of 1 to 9, with 1 being minimal and 9 being the worst ever experienced (no symptom = 0 for analysis) (Statland *et al.*, 2011).

	Secondary end points included: • Participant-assessed pain, weakness, and tiredness as measured by the IVR diary from daily telephone calls made over the last 2 weeks of each period. • Clinical myotonia bedside assessment (participants were asked to squeeze their eyes closed for 5 seconds, then rapidly open them, and make a tight fist for 5 seconds, then rapidly open them). Five trials of each manoeuvre were performed in sequence at each visit and the time was measured by a stopwatch. • A quantitative measure of handgrip myotonia was obtained using a commercially available grip dynamometer and computerised capture system. Maximum voluntary contractions (MVC) following forced right-hand grip were recorded and the time to relax from 90% to 5% of maximal force was determined using automated analysis software (Logigian *et al.,* 2005*;* Moxley *et al.,* 2007. • The maximal post-exercise decrement in CMAP after short and long exercise was determined (Fournier *et al.,* 2004; Tan *et al.,* 2011). • Myotonia on needle EMG was graded on a 1+ to 3+ scale in the right abductor digiti minimi (RADM) and right tibialis anterior (RTA) (Streib, 1987). • Patients filled out the 36-Item Short-Form Health Survey (SF-36) and the INQoL (Ware *et al.,* 1992; McHorney *et al.,* 2007). The INQoL is composed of 10 sections (muscle locking, weakness, pain, fatigue, activities, social relationships, independence, emotions, body image, and effects of treatment) and a summary quality of life score.
• **Sample size**	• The sample size goal was set to 54 participants with available primary end point measurements for both treatment periods. This sample size, determined by computer simulation, provided at least 93% power to detect an effect size of one-quarter of an SD (within-participant) in the primary end point with a 2-sided hypothesis test and an $\alpha = .05$. The variation in power was due to varying the degree of between-participant SD; larger SDs lowered the power since the effect in the active treatment period for low-severity scores cannot be less than 0. The simulations were based on 500 Monte Carlo realisations, a mean for the placebo group of 3, a within-participant SD of 1.5, and a between-participant SD ranging from 1.5 to 3.0. The effect size of one-quarter of an SD was chosen to be conservative given the tentative assumptions in the simulation, to compensate for the unknown degree of participant adherence to treatment, and to have a sufficient sample size available for the secondary IVR diary end points for which some participants do not have the symptom.

• **Randomisation and blinding**	• Participants were randomly assigned the order of the 2 treatments in a 1:1 ratio, stratified by institution. Randomisation was performed centrally at the data management coordinating centre (University of South Florida, Tampa) using a computer-generated permuted block structure, initially with a block size of 4 then, toward the end of the trial, switching to a block size of 2. Each participant was assigned a "kit" number. In this kit, there were only 2 bottles of medication ("A" for period 1 and "B" for period 2). Only 1 bottle was dispensed at a time. Participants, physicians, and evaluators were blinded to medication assignment.
• **Statistical analysis**	• This study used the intention-to-treat principle modified to remove missing values that were assumed to be missing at random. All treatment effect analyses used the linear mixed-effects model (random effect for participant, independent and identically distributed random errors within participant) to adjust for any period effect and include data from dropouts. One assumption required to produce valid Wald tests is that the residuals be normally distributed. To fulfil this assumption, the daily reported IVR severity scores (involving the 4 end points of stiffness, pain, tiredness, and weakness) were replaced with the weekly means, and quantile-quantile plots confirmed that this assumption was satisfied. Another assumption when modelling crossover study data and including only the main effects for period and treatment is that the treatment effect is the same across periods. The lack of consistency is often referred to as a "carryover" effect, although this term can be a misnomer. • For the primary end point, the Wald test of the treatment-sequence group variable (treatment group) was significant (estimate, 0.997; P = 0.04). This result does not necessarily indicate that the second period data are invalid and should be ignored. However, it may indicate that the treatment effect in period 2 is biased and that the additive model may yield biased estimates. A fair presentation of the results is to include an interaction term for period 2 and treatment, in order to present the treatment effect estimates separately by period. The test for "carryover" effect was considered significant if P < 0.10 (Grizzle, 1965). Significance was detected for 4 of the subscales of the SF-36: vitality, emotional role, mental health, and mental composite. Thus, these results and stiffness are displayed by period. The significance level displayed for period 2 is from the Wald test associated with the interaction term of period 2 and mexiletine and not the entire treatment effect, and the significance level displayed for period 1 is from the test of the main effect term for treatment variable. Most of the confidence intervals (CIs) were computed in the usual way using the SE of the estimate taken from the model results; the exceptions were the end points requiring a log transformation for which a bootstrap CI was computed. The effect size was the treatment effect estimate divided by the within-participant SD. • To test whether the overall treatment effect varies within mutation class, the log likelihood test was used, contrasting the model with vs. without the treatment and mutation class interaction terms as a homogeneity test.

	• For the electrographic myotonia assessment, the score was converted to a numeric value (absent = 0, 1+ = 1, 2+ = 2, and 3+ = 3). The end point was the sum of the numerical scores of the 2 muscles. Although the mixed model was used to provide mean estimates, the paired Wilcoxon test was used to test the treatment effect hypothesis. To fulfil the normality assumption for the clinical handgrip and eye closure times, the following transformation was applied: $log(t_i + 0.1)$. Similarly, quantitative handgrip myometry required a $log(t_i)$ transformation; the model included a linear term for grip sequence number and a nested random effect for trial number. • All P values were 2-sided and 0.05 was considered the threshold of statistical significance for all tests except for the carryover effect. Because this trial identified a primary end point, all other P values presented were for secondary end points and are not adjusted for multiple testing. Analysis was performed using TIBCO Spotfire S+ version 8.1 (TIBCO Software Inc).
• **Additional available details**	• Study conducted between December 23, 2008, and March 30, 2011, as part of the National Institutes of Health–funded Rare Disease Clinical Research Network.

Results

Patient Population

Out of the 59 subjects randomised, there were 33 men and 26 women, with mean age of 42.9 years (range, 16-68 years). Participants were predominantly white (57/59 [96.6%]) and non-Hispanic (46/59 [78.0%]). Thirty-four participants had chloride channel mutations, 21 had sodium channel mutations, and 4 had no mutation identified. Seventeen participants were taking medications for myotonia before the start of the study, including 13 (22.0%) taking mexiletine. Randomisation between groups was balanced, with the exception of more men in the placebo followed by mexiletine group.

Efficacy Results

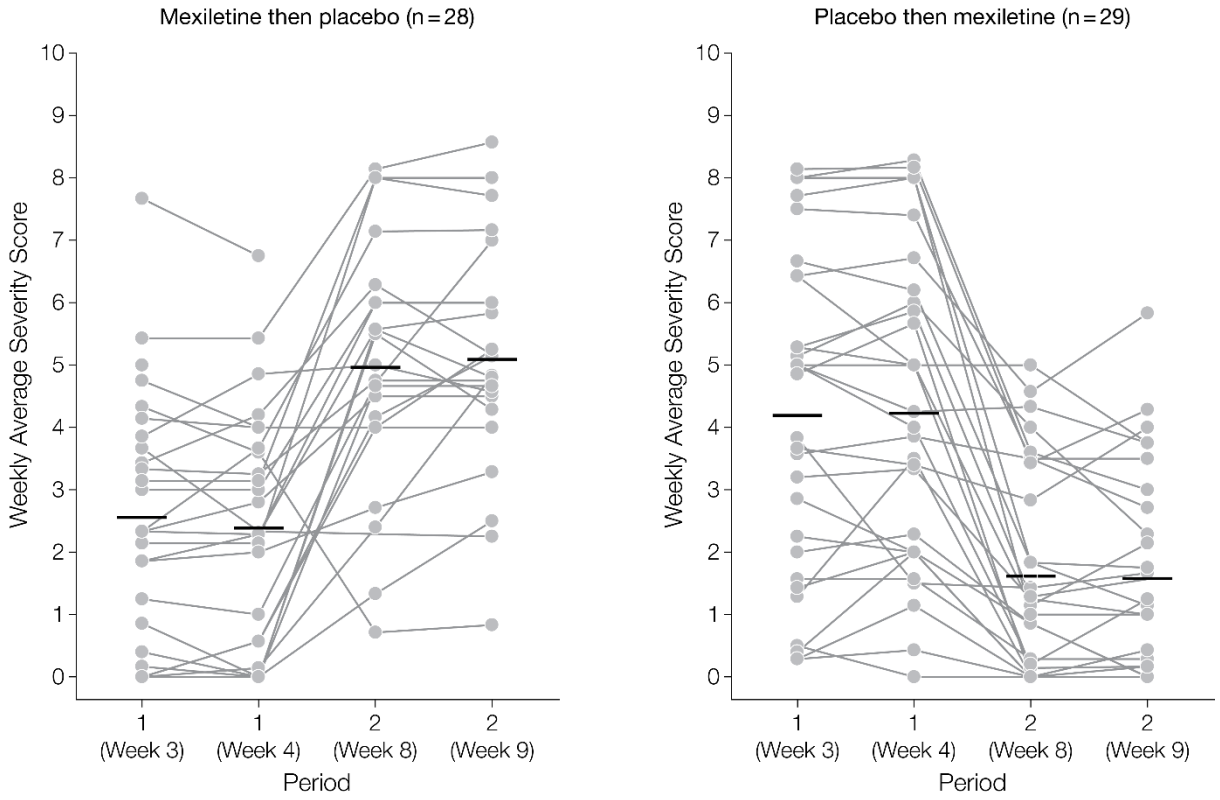


Figure 10: Weekly Stiffness Severity Scores by Treatment Sequence (Statland *et al.*, 2012)

There were significant improvements with mexiletine in most other outcomes in the study, including patient-reported outcomes (PRO), quality of life scales, and quantitative measures of myotonia. Mexiletine improved the SF-36 physical composite score (mexiletine, 44.8 vs. placebo, 39.2; difference, 5.58; 95% CI, 3.44-7.72; P < 0.001) and INQoL summary quality of life score (mexiletine, 14.0 vs. placebo, 16.7; difference, −2.69; 95% CI, −4.07 to −1.30; P < 0.001).

Mexiletine improved myotonia as measured on clinical examination by overall handgrip times in seconds (mexiletine, 0.164 seconds vs. placebo, 0.494 seconds; difference, −0.330; 95% CI, −0.633 to −0.142; P < 0.001) and overall quantitative myotonia assessment handgrip 90% to 5% RTs (mexiletine, 0.321 seconds vs. placebo, 0.429 seconds; difference, −0.109; 95% CI, −0.177 to −0.0560; P < 0.001). Electrophysiological measures of myotonia showed a mixed response. Mexiletine significantly improved the severity of graded myotonia on EMG (RADM: difference, −0.568; 95% CI, −0.812 to −0.325; P < 0.001). There was no statistically significant association with mexiletine and electrophysiological exercise testing.

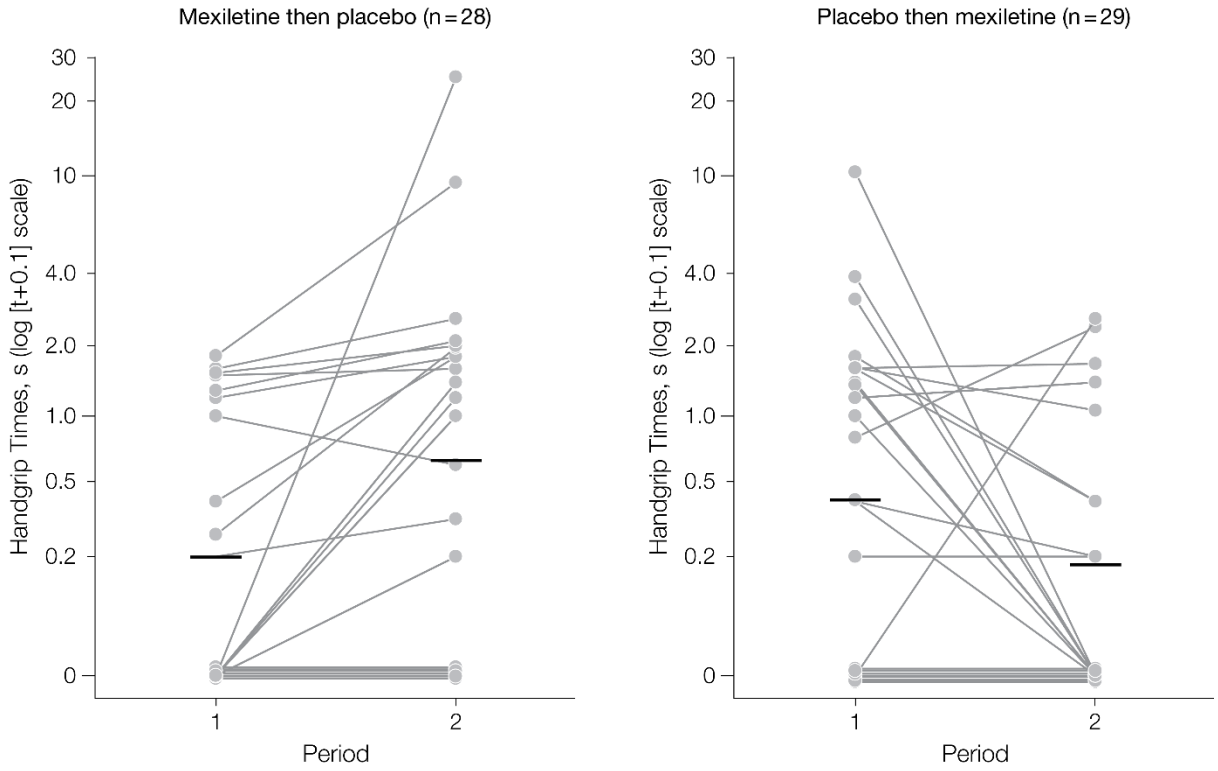


Figure 11: Clinical Evaluation of Handgrip Myotonia Times by Treatment Sequence (Statland *et al.*, 2012)

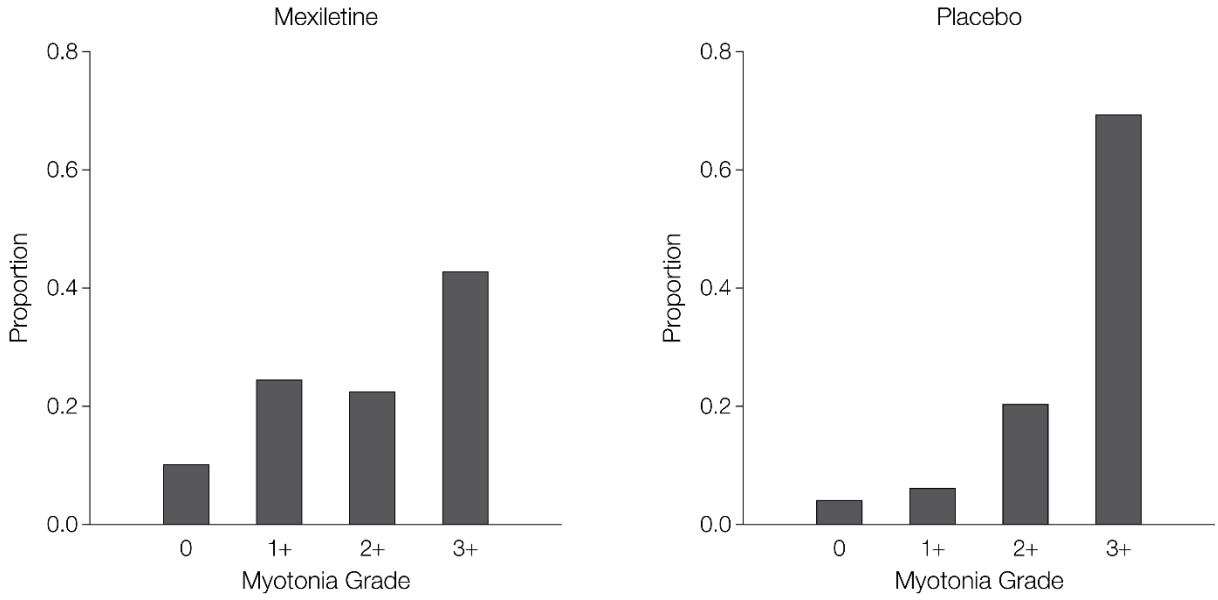


Figure 12: Graded Myotonia on Electromyography for Right Abductor Digiti Minimi (n = 56) in Placebo and Mexiletine Treatment Groups (Statland *et al.*, 2012)

The reduction in the severity of stiffness score was more pronounced for participants with chloride mutations than sodium mutations in period 2 (chloride, −4.18; 95% CI, −5.25 to −3.12; vs. sodium, −2.67; 95% CI, −3.84 to −1.51; P = 0.003), but showed to be the reverse in period 1 (chloride, −1.67; 95% CI, −2.73 to −0.614; vs. sodium, −2.11; 95% CI, −3.28 to −0.933). In addition, the decrease in the

clinical quantitative myotonia assessment handgrip times was greater for participants with chloride mutations than sodium mutations (chloride, −1.24 seconds; 95% CI, −1.77 to −0.711 seconds; vs. sodium, −0.355 seconds; 95% CI, −1.03 to 0.316 seconds; P = 0.04).

Mexiletine levels at baseline, the end of washout, and the end of both placebo groups were not detectible. The mean (SD) mexiletine level at the end of mexiletine treatment periods was 0.54 (0.35) µg/mL (reference antiarrhythmic therapeutic range for 600-1200 mg/day, 0.5 2.0 µg/mL).

Table 27: Summary of Efficacy for Trial Statland *et al.* (2012)

Title: Phase II Therapeutic Trial of Mexiletine in Non-Dystrophic Myotonia			
Study identifier	Statland *et al.* (2012)		
Design	Multi-centre, double-blind, placebo-controlled, cross-over Phase II study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 months (23 December 2008-30 March 2011) Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Mexiletine		Double-blind, cross-over mexiletine. Duration: 4 weeks, 59 randomised
	Placebo		Double-blind, cross-over placebo. Duration: 4 weeks, 59 randomised
Endpoints and definitions	Primary endpoint	Stiffness on the IVR	Patient-reported stiffness on the IVR (scale of 1-9) at weeks 3-4
	Secondary endpoint	Pain on the IVR	Patient-reported pain on the IVR at weeks 3-4
	Secondary endpoint	Weakness on the IVR	Patient-reported weakness on the IVR at weeks 3-4
	Secondary endpoint	Tiredness on the IVR	Patient-reported tiredness on the IVR at weeks 3-4
	Secondary endpoint	Handgrip myotonia	After MVCs following forced right hand grip, measure of time to relax from 90% to 5% of average maximal force, at week 4
	Secondary endpoint	Clinical Hand Grip Myotonia	Time to open the fist after a forced handgrip, at week 4

	Secondary endpoint	Clinical Eye Closure Myotonia	Time to open the eyes after forced eye closure, at week 4
	Secondary endpoint	CMAP After Short Exercise Test	Maximal post-exercise CMAP after short periods of exercise as a percent of the baseline measurement, at week 4
	Secondary endpoint	CMAP After Long Exercise Test	Maximal post-exercise CMAP after long periods of exercise as a percent of the baseline measurement, at week 4
	Secondary endpoint	Myotonia by EMG (RADM)	Amount of myotonia present on needle exam (right abductor digiti minimi [RADM]), at week 4
	Secondary endpoint	Myotonia by EMG (RTA)	Amount of myotonia present on needle exam (right tibialis anterior [RTA]), at week 4
	Secondary endpoint	Individualised neuromuscular quality of life (INQoL)	Health-related quality-of-life as measured by INQoL scale at week 4
	Secondary endpoint	Short Form 36 - Physical Composite Score	Physical burden on quality of life [summary of questions related to physical impact of a disease or condition (physical function, role physical, bodily pain, and general health)]. For participants who experienced weakness in either period.
	Secondary endpoint	Short Form 36 - Mental Composite Score	Mental burden on quality of life [summary of questions related to mental impact of a disease or condition (mental function, role emotional, vitality, and mental health)] at week 4.
Database lock	Unknown		
Results and Analysis			
Analysis description	**Primary Analysis** **Stiffness score (IVR)**		
Analysis population and time point description	Modified intent to treat (n=57) Analysis at Weeks 3-4 (end of treatment period)		
Descriptive statistics and estimate	**Treatment group**	**Mexiletine**	**Placebo**
	Period 1		

variability	Number of subjects	28	29
	Mean (95% CI) stiffness	2.53 (1.80 to 3.17)	4.21 (3.40 to 5.20)
	Difference (95% CI)	-1.68 (-2.66 to -0.706)	
	Period 2		
	Number of subjects	29	25
	Mean (95% CI) stiffness	1.60 (1.04 to 2.20)	5.27 (4.44 to 6.27)
	Difference (95% CI)	-3.68 (-3.85 to -0.139)	

Effect estimate per comparison	Stiffness score (IVR) for Period 1	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p < 0.001
	Stiffness score (IVR) for Period 2	Comparison groups	Mexiletine vs. Placebo
		Mixed Effect Linear Model	
		Effect of treatment	p = 0.04

Analysis description	**Secondary Analysis** **Pain score (IVR)**
Analysis population and time point description	Modified intent to treat (n=48 patients experiencing pain) Analysis at Weeks 3-4 (end of treatment period)

Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	48	48
	Mean (95% CI) stiffness	1.54 (0.924 to 2.13)	3.17 (2.43 to 3.93)
	Mean difference (95% CI)	-1.63 (-2.00 to -1.26)	

Effect estimate per comparison	Pain score (IVR)	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p < 0.001

Analysis description	**Secondary Analysis** **Weakness score (IVR)**
Analysis population and time point description	Modified intent to treat (n=44 patients experiencing weakness) Analysis at Weeks 3-4 (end of treatment period)

Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	44	44
	Mean (95% CI) stiffness	1.96 (1.42 to 2.63)	3.22 (2.52 to 3.98)
	Mean difference (95% CI)	-1.26 (-1.67 to -0.861)	
Effect estimate per comparison	Weakness score (IVR)	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p < 0.001
Analysis description	**Secondary Analysis** **Tiredness score (IVR)**		
Analysis population and time point description	Modified intent to treat (n=49 patients experiencing tiredness) Analysis at Weeks 3-4 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	49	49
	Mean (95% CI) stiffness	2.90 (2.12 to 3.68)	3.82 (3.03 to 4.53)
	Mean difference (95% CI)	-0.918 (-1.30 to -0.532)	
Effect estimate per comparison	Tiredness score (IVR)	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p < 0.001
Analysis description	**Secondary analysis** **Quantitative measure of handgrip myotonia (s)**		
Analysis population and time point description	Modified intent to treat (n=54) Analysis at Week 4 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	54	54
	Mean (95% CI) relaxation time	0.321 (0.274 to 0.370)	0.429 (0.365 to 0.517)
	Mean difference (95% CI)	-0.109 (-0.177 to -0.056)	
Effect estimate per	Relaxation time	Comparison groups	Mexiletine vs. Placebo

comparison	(hand grip myotonia)	Wald test	
		Effect of treatment	p < 0.001
Analysis description	**Secondary analysis** **Clinical handgrip myotonia (s)**		
Analysis population and time point description	Modified intent to treat (n=57) Analysis at Week 4 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	57	57
	Mean (95% CI) time to open the fist	0.164 (0.0858 to 0.294)	0.494 (0.281 to 0.872)
	Mean difference (95% CI)	-0.330 (-0.633 to -0.142)	
Effect estimate per comparison	Clinical hand grip myotonia	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p < 0.001
Analysis description	**Secondary analysis** **Clinical eye closure myotonia (s)**		
Analysis population and time point description	Modified intent to treat (n=57) Analysis at Week 4 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	57	57
	Mean (95% CI) time to open the eye	0.161 (0.0704 to 0.314)	0.474 (0.261 to 0.871)
	Mean difference (95% CI)	-0.313 (-0.602 to -0.149)	
Effect estimate per comparison	Clinical eye closure myotonia	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p < 0.001
Analysis description	**Secondary analysis** **CMAP after short exercise test (% of baseline measurement)**		

Analysis population and time point description	Modified intent to treat (n=56) Analysis at Week 4 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	56	56
	Mean (95% CI) % of baseline CMAP amplitude	83.1 (77.5 to 88.4)	78.6 (71.9 to 84.7)
	Mean difference (95% CI)	4.54 (-0.680 to 9.75)	

Effect estimate per comparison	CMAP after short exercise test	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p = 0.09

Analysis description	**Secondary analysis** **CMAP after long exercise test (% of baseline measurement)**		
Analysis population and time point description	Modified intent to treat (n=56) Analysis at Week 4 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	56	56
	Mean (95% CI) % of baseline CMAP amplitude	81.8 (76.8 to 87.0)	80.1 (74.7 to 86.4)
	Mean difference (95% CI)	1.69 (-3.34 to 6.73)	

Effect estimate per comparison	CMAP after long exercise test	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p = 0.50

Analysis description	**Secondary analysis** **Myotonia by EMG (RADM) (scale of 1 to 3)**		
Analysis population and time point description	Modified intent to treat (n=56) Analysis at Week 4 (end of treatment period)		
Descriptive statistics and estimate	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	56	56

variability	Mean (95% CI) myotonia grade (RADM)		2.05 (1.75 to 2.33)	2.62 (2.39 to 2.86)
	Mean difference (95% CI)		-0.568 (-0.812 to -0.325)	
Effect estimate per comparison	Graded myotonia by EMG (RADM)	Comparison groups	Mexiletine vs. Placebo	
		Wilcoxon test		
		Effect of treatment	p < 0.001	
Analysis description	**Secondary analysis** **Myotonia by EMG (RTA) (scale of 1 to 3)**			
Analysis population and time point description	Modified intent to treat (n=56) Analysis at Week 4 (end of treatment period)			
Descriptive statistics and estimate variability	**Treatment group**		**Mexiletine**	**Placebo**
	Number of subjects		56	56
	Mean (95% CI) myotonia grade (RTA)		2.07 (1.73 to 2.37)	2.54 (2.28 to 2.76)
	Mean difference (95% CI)		-0.464 (-0.675 to -0.254)	
Effect estimate per comparison	Graded myotonia by EMG (RTA)	Comparison groups	Mexiletine vs. Placebo	
		Wilcoxon test		
		Effect of treatment	p < 0.001	
Analysis description	**Secondary analysis** **Individualised Neuromuscular Quality of Life (summary score)**			
Analysis population and time point description	Modified intent to treat (n=51) Analysis at Week 4 (end of treatment period)			
Descriptive statistics and estimate variability	**Treatment group**		**Mexiletine**	**Placebo**
	Number of subjects		51	51
	Mean (95% CI) INQoL summary score		14.0 (11.6 to 16.5)	16.7 (14.0 to 19.4)
	Mean difference (95% CI)		-2.69 (-4.07 to -1.30)	
Effect estimate per comparison	INQoL summary score	Comparison groups	Mexiletine vs. Placebo	
		Wald test		

		Effect of treatment	p < 0.001
Analysis description	**Secondary analysis** **Short Form 36 - Physical Composite Score**		
Analysis population and time point description	Modified intent to treat (n=57) Analysis in participants who experienced weakness in either period		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Number of subjects	57	57
	Mean (95% CI) SF-36 physical composite score	44.8 (41.9 to 47.4)	39.2 (35.9 to 41.9)
	Mean difference (95% CI)	5.58 (3.44 to 7.72)	
Effect estimate per comparison	SF-36 physical composite score	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p < 0.001
Analysis description	**Secondary analysis** **Short Form 36 - Mental Composite Score**		
Analysis population and time point description	Modified intent to treat (n=57) Analysis at Week 4 (end of treatment period)		
Descriptive statistics and estimate variability	**Treatment group**	**Mexiletine**	**Placebo**
	Period 1		
	Number of subjects	28	29
	Mean (95% CI) SF-36 mental composite score	47.4 (44.0 to 50.2)	47.7 (44.2 to 51.3)
	Mean difference (95% CI)	-0.351 (-5.87 to 5.17)	
	Period 2		
	Number of subjects	29	25
	Mean (95% CI) SF-36 mental composite score	53.1 (50.3 to 55.8)	42.7 (36.8 to 48.3)
	Mean difference (95% CI)	10.4 (0.941 to 20.6)	
Effect estimate per	SF-36 mental	Comparison groups	Mexiletine vs. Placebo

comparison	composite score for Period 1	Wald test	
		Effect of treatment	p = 0.90
	SF-36 mental composite score for Period 2	Comparison groups	Mexiletine vs. Placebo
		Wald test	
		Effect of treatment	p = 0.03

Logigian et al. (2010)

Table 28: Logigian *et al.* (2010): Study Design

Study objective	To determine if mexiletine is safe and effective in reducing myotonia in myotonic dystrophy type 1 (DM1).
Design	These were 2 single-centre, randomised, double-blind, placebo-controlled cross-over trials, the first using a mexiletine dosage of 150 mg 3 times daily (tid) and the second using 200 mg tid. In each trial, the 2 treatment periods were 7 weeks in duration, separated by a 4- to 8-week washout period. Those who participated in both trials (n = 10) were required to wait at least 8 weeks after the end of the first trial to enrol in the second trial.
Study location	United States (1 centre).
Number of subjects/ Inclusion criteria	A total of 30 participants were enrolled in the 2 trials: 20 in the 150 mg tid trial (June 1, 2000–March 29, 2002) and 20 in the 200 mg tid trial (May 14, 2001–March 20, 2003); 10 participants enrolled in both trials. Patients were eligible if they were between the ages of 18 and 80, could walk 15 feet independently, had sufficient finger flexor strength to grasp a handle, met standard clinical criteria for the presence of myotonia (time for fingers to fully uncurl following maximal hand grip estimated by visual inspection to be 3 seconds or more, or percussion myotonia in wrist extensor and thenar muscles), satisfied clinical criteria for DM1, and had genetic confirmation of the diagnosis.
Test product **Dosage regimen**	Mexiletine was purchased from Roxane Laboratories, Inc., and placebo was prepared by the pharmacy at the University of Rochester. Active and placebo medication were re-encapsulated in gelatine capsules by the pharmacy to facilitate blinding. The dosage was titrated so that tid dosing was reached by day 7 of each treatment period. Medication was tapered over 6 days after the completion of each treatment period.
Route of administration	Oral administration
Duration of treatment	Treatment periods were 7 weeks in duration, separated by a 4- to 8-week washout period.

Criteria for evaluation	**Efficacy:** The primary outcome variable for efficacy was the average RT (time to decline in force from 90% to 5% of peak force [PF]). The right arm was used for measuring grip RTs after a maximal voluntary isometric contraction (MVIC) (Logigian *et al.*, 2005; Moxley *et al.*, 2007). In brief, each trial consisted of 6 MVICs, each lasting 3 seconds, with a 10-second rest period between each contraction. Three sets of measurements (trials) were performed with 10-minute intervals of rest between trials. An automated computer program first determined PF in kg units and then placed cursors on the declining, relaxation phase of the force recording at various levels of PF: 90%, 50%, and 5%. Secondary outcome variables included other average RTs (90%–10% of PF, 50%–5% of PF) and average PF. **Safety:** AEs. ECG outcomes, including PR interval, QRS interval, and QTc interval.
Sample size	The sample size of 20 participants was chosen to provide 80% power to detect a treatment effect of 0.66 SD units using a 2-tailed paired t test and a 5% significance level.
Randomisation and blinding	Participants were randomly assigned in each trial to 1 of 2 treatment sequences: mexiletine/placebo or placebo/mexiletine. The computer-generated randomisation plans included blocking to ensure approximate balance between the 2 treatment sequences. All drug was labelled with a participant ID number. Only the biostatistics programmer and the pharmacist had access to the treatment assignments. Drug was assigned sequentially.
Statistical analysis	The primary statistical analyses of the data from week 7 of each treatment period used an analysis of variance model that included effects for treatment, period, and participant. Mean mexiletine–placebo differences (treatment effects) and associated 95% CI were estimated using this model. Only participants who completed both treatment periods were included in the primary statistical analyses. The results of analyses that included data from all randomised participants (mixed-effects analysis of variance model) and those that excluded data from 3 participants with undetectable mexiletine levels yielded nearly identical results.
Additional available details	-

Results

Patient Population

Four participants dropped out of the studies: 2 participants in the 150 mg tid trial (1 on placebo and 1 on mexiletine, both due to family reasons and inability to fulfil the required time commitment) and 2 participants in the 200 mg tid trial (1 on placebo due to perceived lack of therapeutic benefit and 1 on mexiletine due to diarrhoea).

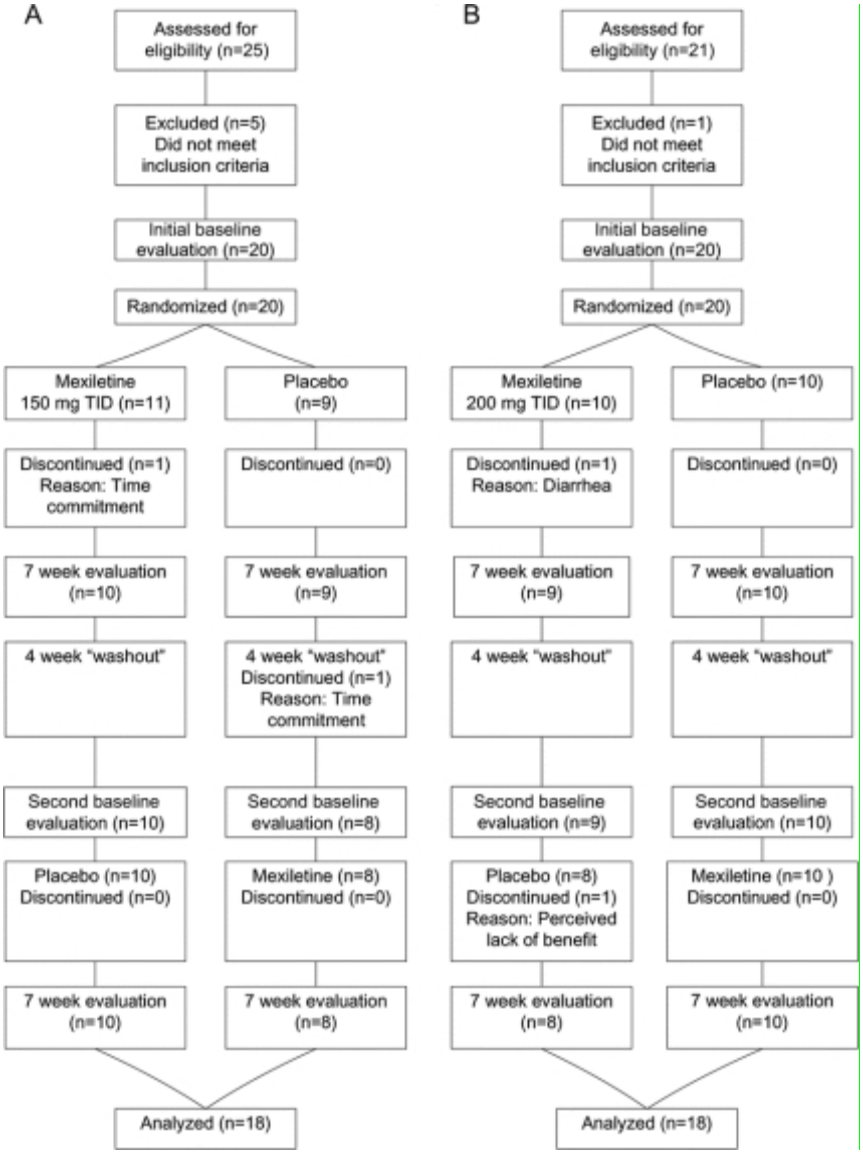


Figure 13: Consort flow diagram: Participant flow in the trial of mexiletine hydrochloride 150 mg tid (A) and in the trial of mexiletine hydrochloride 200 mg tid (B) (Logigian *et al.*, 2010)

The participants in both studies were middle-aged with a slight male predominance (Table below). Symptoms had been present for a mean of about 2 decades, and median CTG repeat sizes were approximately 500 in both groups with a minimum of 169.

Table 29: Demographic and Clinical Characteristics at Baseline (Logigian *et al.*, 2010)

	Trial	
	150 mg 3 times daily	200 mg 3 times daily
No.	20	20
Age, y	46.2 (9.0)	42.6 (8.6)
Male (%)	60%	65%
Caucasian (%)	95%	100%
Age at symptom onset, y	23.6 (8.5)	21.5 (9.1)
CTG repeat size		
Median	538.5	485.0
Quartiles	(278.5, 709.5)	(278.5, 726.0)
Peak force, grip (kg)	11.2 (7.5)	8.9 (4.6)
Relaxation time (s)		
90%-5% of peak force	2.15 (1.28)	2.80 (1.40)
90%-10% of peak force	1.61 (1.01)	1.95 (1.09)
50%-5% of peak force	1.76 (1.13)	2.39 (1.36)
EKG data, ms		
PR interval	198 (19)	193 (29)
QRS interval	106 (32)	100 (30)
QT_c interval	415 (27)	410 (27)

[a]Values are mean (standard deviation) unless otherwise indicated.

Efficacy Results

The MVIC grip traces showed prolonged 90%–5% RTs, particularly in the terminal portion of the relaxation phase. In both trials, the RTs were elevated at baseline and during placebo treatment with mean 90%–5% RTs of over 2 seconds. Mexiletine at the 150 mg tid and 200 mg tid dosages was associated with a significant reduction in RT, with mean reductions of 48% (90%–5% RT), 48% (90%–10% RT), and 55% (50%–5%) with 150 mg tid and mean reductions of 52% (90%–5% RT), 51% (90%–10% RT), and 58% (50%–5%) with 200 mg tid. In both the 150 mg tid and 200 mg tid trials, 17 of the 18 participants (94%) had a shorter 90%–5% RT on mexiletine than on placebo. There was a significant improvement in grip PF with 150 mg tid mexiletine compared to placebo, but this was not the case with 200 mg tid mexiletine.

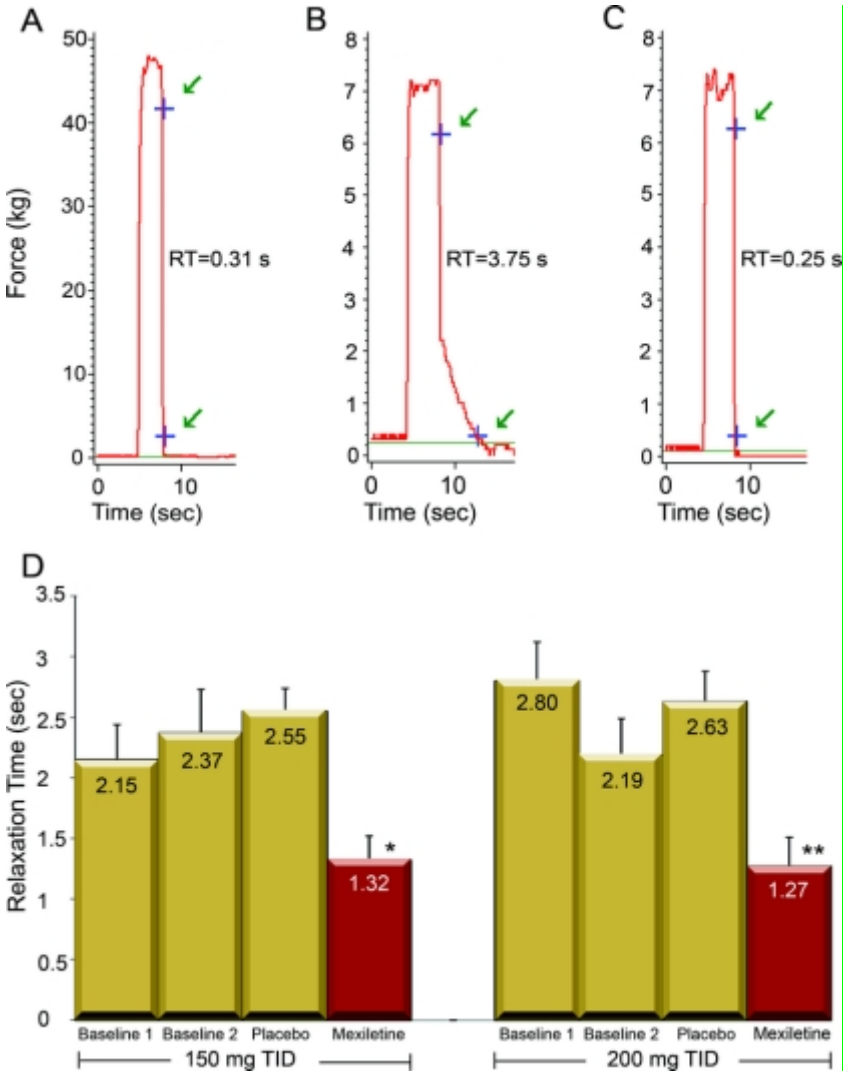


Figure 14: Grip Relaxation Time (Myotonia) (Logigian *et al.*, 2010)

Maximum voluntary handgrip force traces in (A) a normal subject, and in DM1 participant 1843, (B) before and (C) after treatment with 7 weeks of mexiletine 200 mg tid. Automated software placed cursors (arrows) on the declining force trace at 90% and 5% of PF. The 90%–5% hand grip RTs are denoted to the right of each trace.
(D) Mean 90%–5% hand grip RTs at the 2 baseline visits, and on placebo and mexiletine treatment for the 150 mg tid trial (left) and the 200 mg tid trial (right). The extensions of the bars represent 1 SEM. p Values for mexiletine treatment-related improvement in RT were *0.0004 (150 mg tid) and **0.001 (200 mg tid).

Trough blood levels of mexiletine were somewhat higher with 200 mg tid (0.86 ± 0.48 µg/mL, range 0–1.70 µg/mL) than with 150 mg tid (0.54 ± 0.28 µg/mL, range 0 1.15 µg/mL). Mexiletine blood levels reached the therapeutic range for treating arrhythmia (0.5–2.0 µg/mL) in 13 patients (68%) with 200 mg tid and in 10 patients (55%) with 150 mg tid. Three participants (1 in the 150 mg tid trial and 2 in the 200 mg tid trial) had a mexiletine blood level of 0. When these possible non-compliers were removed, the blood levels achieved the therapeutic range in 76% of those on 200 mg tid and 59% of those on 150 mg tid.

Table 30: Summary of Efficacy for Trial Logigian *et al.* (2010)

Title: A Randomised, Placebo Controlled, Clinical Efficacy Trial of Mexiletine for Myotonic Dystrophy Type-1 (DM1)			
Study identifier	Logigian *et al.* (2010)		
Design	Two randomised, double blind, placebo controlled cross-over trials		
	Duration of main phase:		150 mg tid trial: 22 months (01 June 2000-29 March 2002) 200 mg tid trial: 23 months (14 May 2001-20 March 2003)
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Comparative analysis		
Treatments groups	Mexiletine		150 mg tid trial and 200 mg tid trial: Double-blind, cross-over mexiletine. Duration: 7 weeks, 20 randomised in each trial
	Placebo		150 mg tid trial Double-blind, cross-over placebo. Duration: 7 weeks, 20 randomised 200 mg tid trial Double-blind, cross-over placebo. Duration: 7 weeks, 19 randomised
Endpoints and definitions	Primary endpoint	Handgrip myotonia (relaxation time 90%-5%)	After an MVC, measure of time to relax from 90% to 5% of PF at week 7 over 2 days
	Secondary endpoint	Handgrip myotonia (relaxation time 90%-10%)	After an MVC, measure of time to relax from 90% to 10 % of PF at week 7 over 2 days
	Secondary endpoint	Handgrip myotonia (relaxation time 50%-5%)	After an MVC, measure of time to relax from 50% to 5 % of PF at week 7 over 2 days
	Secondary endpoint	Handgrip myotonia (peak force)	PF at week 7 over 2 days
Database lock	Unknown		

Results and Analysis			
Analysis description	**Primary Analysis** **Handgrip myotonia (relaxation time 90%-5%)**		
Analysis population and time point description	Patients who completed both treatment period (n=18 in each trial) Both trials: analysis at week 7 (mean relaxation time determined by averaging values over 2 days of evaluation)		
Descriptive statistics and estimate variability	Treatment group	Mexiletine	Placebo
	150 mg tid trial		
	Number of subjects	18	18
	Relaxation time (s) 90%-5%	1.32	2.55
	Adjusted mean difference (95% CI)	-1.23 (-1.81 to -0.64)	
	200 mg tid trial		
	Number of subjects	18	18
	Relaxation time (s) 90%-5%	1.27	2.63
	Adjusted mean difference (95% CI)	-1.36 (-2.09 to -0.63)	

Effect estimate per comparison	Handgrip myotonia (relaxation time 90%-5%) in 150 mg tid trial	Comparison groups	Mexiletine vs. Placebo
		Analysis of variance model	
		Effect of treatment	p = 0.0004
	Handgrip myotonia (relaxation time 90%-5%) in 200 mg tid trial	Comparison groups	Mexiletine vs. Placebo
		Analysis of variance model	
		Effect of treatment	p = 0.001

Analysis description	**Secondary Analysis** **Handgrip myotonia (relaxation time 90%-10%)**		
Analysis population and time point description	Patients who completed both treatment period (n=18 in each trial) Both trials: analysis at week 7 (mean relaxation time determined by averaging values over 2 days of evaluation)		
Descriptive statistics	Treatment group	Mexiletine	Placebo

and estimate variability	150 mg tid trial		
	Number of subjects	18	18
	Relaxation time (s) 90%-10%	0.92	1.76
	Adjusted mean difference (95% CI)	-0.84 (-1.35 to -0.33)	
	200 mg tid trial		
	Number of subjects	18	18
	Relaxation time (s) 90%-10%	0.98	1.98
	Adjusted mean difference (95% CI)	-1.00 (-1.63 to -0.37)	

Effect estimate per comparison	Handgrip myotonia (relaxation time 90%-10%) in 150 mg tid trial	Comparison groups	Mexiletine vs. Placebo
		Analysis of variance model	
		Effect of treatment	p = 0.003
	Handgrip myotonia (relaxation time 90%-10%) in 200 mg tid trial	Comparison groups	Mexiletine vs. Placebo
		Analysis of variance model	
		Effect of treatment	p = 0.004

Analysis description	**Secondary analysis** **Handgrip myotonia (relaxation time 50%-5%)**		
Analysis population and time point description	Patients who completed both treatment period (n=18 in each trial) Both trials: analysis at week 7 (mean relaxation time determined by averaging values over 2 days of evaluation)		
Descriptive statistics and estimate variability	Treatment group	Mexiletine	Placebo
	150 mg tid trial		
	Number of subjects	18	18
	Relaxation time (s) 50%-5%	0.98	2.18
	Adjusted mean difference (95% CI)	-1.19 (-1.79 to -0.60)	
	2000 mg tid trial		
	Number of subjects	18	18

	Relaxation time (s) 50%-5%		0.92	2.19
	Adjusted mean difference (95% CI)		-1.27 (-1.96 to -0.57)	
Effect estimate per comparison	Handgrip myotonia (relaxation time 50%-5%) in 150 mg tid trial	Comparison groups	Mexiletine vs. Placebo	
		Analysis of variance model		
		Effect of treatment	p = 0.0006	
	Handgrip myotonia (relaxation time 50%-5%) in 200 mg tid trial	Comparison groups	Mexiletine vs. Placebo	
		Analysis of variance model		
		Effect of treatment	p = 0.001	
Analysis description	**Secondary analysis** **Handgrip myotonia (peak force)**			
Analysis population and time point description	Patients who completed both treatment period (n=18 in each trial) Both trials: analysis at week 7 (mean relaxation time determined by averaging values over 2 days of evaluation)			
Descriptive statistics and estimate variability	Treatment group		Mexiletine	Placebo
	150 mg tid trial			
	Number of subjects		18	18
	Peak force (kg)		11.0	10.2
	Adjusted mean difference (95% CI)		0.80 (0.05 to 1.55)	
	200 mg tid trial			
	Number of subjects		18	18
	Peak force (kg)		9.8	9.7
	Adjusted mean difference (95% CI)		0.13 (-0.40 to 0.65)	
Effect estimate per comparison	Handgrip myotonia (peak force) in 150 mg tid trial	Comparison groups	Mexiletine vs. Placebo	
		Analysis of variance model		
		Effect of treatment	p = 0.04	

	Handgrip myotonia (peak force) in 200 mg tid trial	Comparison groups	Mexiletine vs. Placebo
		Analysis of variance model	
		Effect of treatment	p = 0.61

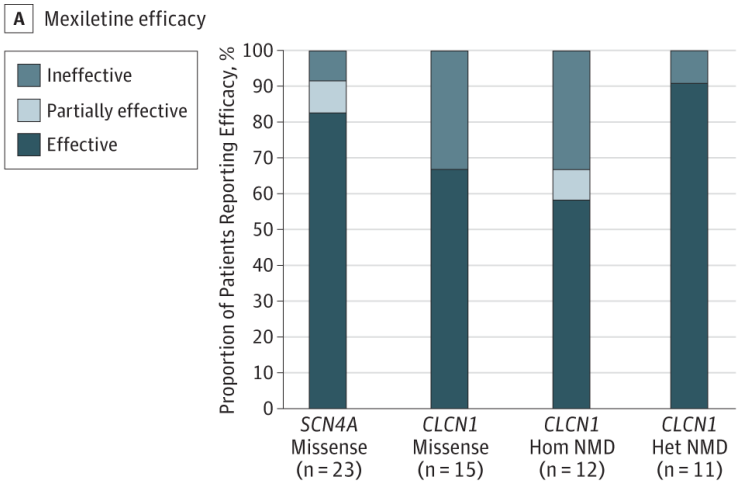
Other Studies of Interest with Mexiletine in Adults with Myotonic Disorders

a) Long-term efficacy and safety of mexiletine (Suetterlin *et al.*, 2015)

This retrospective review of a large skeletal muscle channelopathy patient cohort in the UK assessed all patients with genetically confirmed NDM or hyperkalemic periodic paralysis prescribed mexiletine with a minimum of 6 months follow-up. The standard dose titration was increments of 50 to 100 mg of mexiletine per week until symptoms resolved or a total daily dose of 600 mg was reached.

A total of 122 patients were identified; 63 met inclusion criteria. Forty patients had mutations in CLCN1, 21 in SCN4A, and 2 in both CLCN1 and SCN4A (subsequently analysed with the SCN4A group). The mean length of follow-up was 4.8 years (range, 6 months to 17.8 years).

Efficacy was classified based on subjective patient report as documented by the clinician. Patients with CLCN1 missense mutations required significantly more mexiletine than those with SCN4A mutations (Figure below). Eight of 11 patients (72.7%) who stopped mexiletine previously because of inefficacy or intolerable AEs found it effective and tolerable on retrial. Twelve patients were refractory to mexiletine treatment.



A Patient-reported mexiletine efficacy according to genotype.

B Effective dose

	SCN4A Missense	*CLCN1* Missense	*CLCN1* Hom NMD	*CLCN1* Het NMD
Effective dose of mexiletine mean (SD) [No.], mg	333 (177) [21][a]	550 (85) [10][a]	463 (160) [8]	420 (175) [10]

B Mean effective dose of mexiletine by genotype.

Patients who found mexiletine ineffective (n = 12) were excluded

[a] Post hoc unpaired t test P = 0.001.

Figure 15: Mexiletine Efficacy and Mean Effective Dose by Genotype (Suetterlin *et al.*, 2015)

b) Illustration of mexiletine efficacy (Ginanneschi *et al.*, 2017a)

This is a case report investigating the cause of transient weakness in MC and the mechanism of action of mexiletine in reducing weakness. This case report is of particular interest because it provides as

supplementary material two videos, one describing the symptoms of MC (Ginanneschi *et al.*, 2017c) and one showing the outstanding improvement in patient's condition thanks to mexiletine (200 mg tid) (Ginanneschi *et al.*, 2017b). Both videos are provided in Module 5.4.

c) Additional efficacy data in DM1 based on an uncontrolled study (Contardi *et al.*, 2012)

Reports on the use of mexiletine in patients with DM1 are rather scarce. On top of the publication by Logigian *et al.* (2010), mexiletine use was also reported to be beneficial in a few other studies and case reports (Reisecker *et al.*, 1983; Kwiecinski *et al.*, 1992; Contardi *et al.*, 2012).

The study by Contardi *et al.* (2012) was a prospective, open-label, uncontrolled study evaluating neuromuscular function and disability status of patients with DM1 before and after 3-6 months of treatment with mexiletine (400 mg/day).

Table 35 below shows mean total and areas score, and functional measurements before and after therapy, with a significant improvement of myotonia, VAS and functional measurements except chair test.

Table 31: Scale Scores Before and After Therapy (Contardi *et al.*, 2012)

	Basal condition		**After mexiletine therapy**		**Mann Whitney Test**
	Mean	**SD**	***Mean***	**SD**	
Total score	26.6	12.4	19.1	10.1	0.030
Neuropsychological area	3.1	2.8	3.1	3.1	0.822
Motor area	11	5.9	10.7	6.1	0.899
Myotonia area	8.3	1.9	6.3	2.3	0.007
Daily life activity area	4.1	3.8	3.0	3.0	0.472
Epworth sleepiness scale	7.7	4.3	6.9	3.7	0.455
Visual analogue scale	73	27.6	35.3	24.3	0.000
Relaxation time necessary to open hands completely 10 successive times	43.2	27.6	21.9	12.3	0.007
Relaxation time necessary to open eyes completely 10 successive times after maximum contraction	22.3	8.0	16.9	6.1	0.025
Time necessary to stretch out the tongue 10 successive times	16.7	5.7	12.5	3.3	0.013
Time necessary to get up from a chair 10 successive times	40.8	29.2	29.9	14.5	0.272

Of note, all 18 patients treated with mexiletine, 400 mg/day obtained clinical resolution of myotonia without side-effects (e.g. cardiac arrhythmia, worsening of muscle weakness tested by dynamometer and daytime sleepiness).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Myotonic syndromes are characterised by the difficulty of muscle relaxation after voluntary muscle contraction. The extent and intensity of muscular involvement varies from disorder to disorder, but is also influenced by disease duration, patients muscular activity and environmental conditions. All these aspects are difficult to tackle in a syndromic based clinical trial.

The term "myotonic disorders" is covering a broad group of diseases affecting sodium and chloride channels (see Figure , from Kortman et al., 2012):

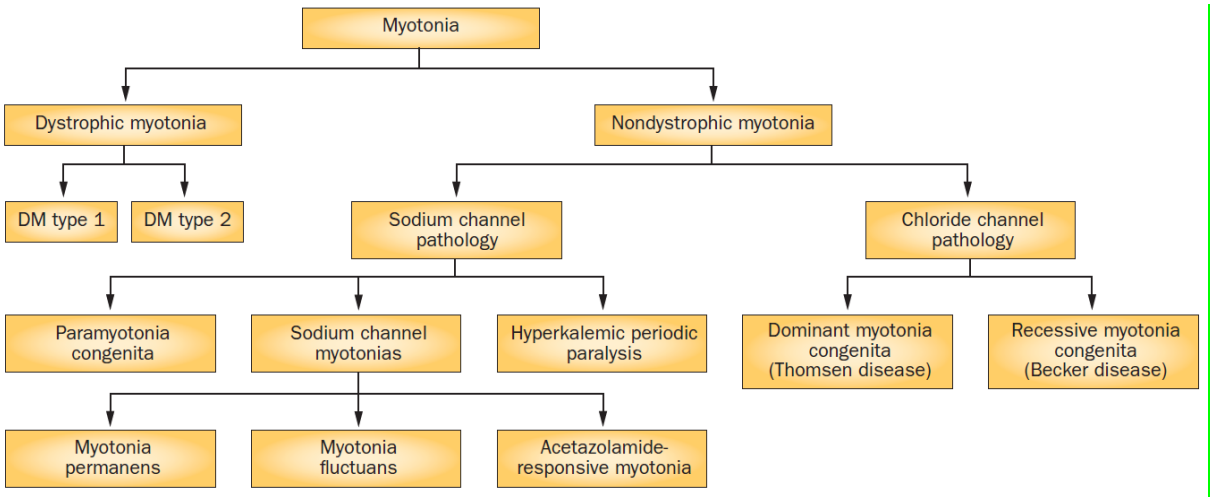


Figure 16: Myotonic disorders

The applicant has submitted one clinical trial, with a primary endpoint based on a PRO to report stiffness and secondary endpoints that indirectly relate to muscle function, besides QoL and CGI endpoints, in a single crossover, 2x18 day treatment design. The primary endpoint is prone to be affected by the sequence (MEX-PBO vs. PBO-MEX) especially due to the placebo effect. This placebo effect is a serious concern, as several patients improved under placebo and others worsened under active treatment.

Given the orphan nature of myotonic syndrome, one cannot expect that a big patient sample can be enrolled. Therefore, the choice of the primary endpoint and key secondary endpoints is very important, and the applicant could have included other endpoints (namely direct muscle strength assessment), besides the discussed endpoints. Another important aspect is the fact that the MAA did not include any dystrophic myotonias in the trial.

Having in mind that applicant presented data describing the effect of mexiletine on muscle stiffness in PC, MC and DM type 1, there is a gap of knowledge regarding the effect of mexiletine on muscle stiffness in other conditions covered by term "myotonic disorders". The possibility to extrapolate efficacy data from one myotonic disorder to another one based on data describing similarity between pathophysiological mechanisms and clinical and functional measurements/scales supported by the relevant biomarkers has been minimally discussed in terms of safety. Of the tabled studies, 6 out of 20 involved 123 DM type 1 patients. Logigian et al, 2010 study has studied the handgrip as primary endpoint, for 7 weeks. In the discussion it is clearly stated "One limitation of our trials is that they show relatively short-term benefits of mexiletine on handgrip relaxation. We do not know if this effect is durable over months to years, or if it is associated with improvement in quality of life.

Inclusion criteria in the MYOMEX study included a clinician-based decision about the need to treat (many patients do not require treatment until the disease is moderate to severe). Taking into account that only

patients with severe enough myotonia were included in the MYOMEX study, this is described in section 5.1 of the SmPC.

The titration of the study drug occurred during the titration phase by increasing the starting 200 mg/day dose by 200 mg/day every 3 days until the target dose was reached. All patients were titrated to the maximal dose – 600mg/day. It is important to note that the study was not designed to evaluate treatment effect on muscle stiffness at each dose level. On the other hand, it could be noted that, some patients had already significant reduction of stiffness score on day 4 (200 mg once a day) in the MYOMEX study. The mexiletine plasma levels are highly variable according to the applicant. It is agreed that even at least some patients at low plasma concentrations had relatively acceptable clinical beneficial effect of mexiletine. The posology in section 4.2 of the SmPC reflects that different dose levels could be effective and allows a treating physician to make a choice.

Efficacy data and additional analyses

Two populations of non DM patients have been studied in a controlled, 18 treatment days single crossover trial. For most of these patients the active treatment has shown a response on the PRO measurements:

- Stiffness as measured by a VAS: absolute change from baseline -100-mm scale, 100 mm worst score: 24.3 (MEX) vs. 66.2 (PBO);
- Percent of subjects with a stiffness VAS score difference ≥50 mm: 57.1 (MEX) vs. 13.6 (PBO) and clinical measurements;
- Chair test: absolute change from baseline (seconds to stand-circle-sit): -2.1 (MEX) vs. 0.2 (PBO);
- CGI (Percent of patients with Global impression of treatment efficiency at end-of-treatment): 91.7 (MEX) vs. 20.0 (PBO).

A total of 10 patients with MC and 4 patients with PC were treated with mexiletine before entering the MYOMEX study. 4 patients with MC and 1 patient with PC were randomized to Placebo-mexiletine group, while 5 patients with MC and 1 patient with PC were randomized to the mexiletine-placebo group. Randomization of 1 patient with MC and 2 patients with PC is not clearly described. Only 3 patients with MC were mexiletine naïve. Since 14 out of 25 patients included into the MYOMEX study were treated with mexiletine previously for a prolonged period (median treatment duration for MC = 73 months, for PC = 30 months), it is likely that these patients were also aware of treatment effect and possibly overestimated the absence of the effect when were randomized to placebo group in the first treatment period.

The statistically significant interaction between treatment periods for the stiffness score was observed in the study by Statland et al., 2012 as also pointed by the applicant. The applicant rejected carry-over hypothesis because there was no statistically significant difference between two baseline periods observed.

The applicant combined the data from two treatment periods and claimed that for all NDM patients treated with mexiletine the median stiffness VAS score improved by -42.0, while patients treated with placebo worsened by 2.0 on the median stiffness VAS score. The applicant explained that the evaluation by patient reflects myotonia assessment over the last 3 days and that it is not an assessment of myotonia at the precise moment of evaluation. The applicant also confirmed the fact that the choice of 50% as the relevant cut-off for efficacy assessment has been empirical. There has not been a consensus statement or a pilot trial where this value could have been chosen as the minimally relevant. The rationale presented by the applicant was based on a similarity to pain. Pain is distinct from stiffness, especially when stiffness is not caused by a central or neuropathic failure but due to a local muscle failure to relax. For instance, the absolute VAS score accepted as a MCID is 9mm for pain, which was the mean stiffness improvement under placebo in the mITT.

Despite the above criticism, the face validity of the VAS with the cutoff point of 50% improvement and either the most stringent absolute 50mm or the less stringent 25mm seem to be reasonable. There is a marked difference between the responders of mexiletine under the 50% + 25mm vs placebo, a greater difference than what is usually observed in pain trials, where placebo effect in the study short duration is of a higher magnitude. It would be further substantiated if the 50% + 25mm would also correlate to the QoL improvement on a patient to patient basis, but it was considered based on those data that a response on the PRO measurements had been shown for most of the patients under active treatment.

There was clear difference for baseline data for chair test between "placebo-mexiletine" and "mexiletine-placebo" groups of MC patients ("placebo-mexiletine" group median time – 9s and "mexiletine-placebo" group median time – 7s). The effect of mexiletine treatment was also mostly apparent in the MC group and less obvious in the PC group. One could speculate that a chair test for patients with PC with primarily affected muscles in the upper extremities and face was less appropriate compared to patients with MC, especially patients with Becker's MC where legs are primarily affected.

The treatment with mexiletine had effect on other symptoms like weakness, locking, pain and fatigue. It appears that patients with PC had better effect on these parameters compared to MC patients. Similar observations were observed for subdomains activities, independence, social relationship, emotions, body image as well as overall quality of life. Especially striking differences between these two groups of patients were observed for independence (change after mexiletine treatment MC -3.9 and PC -29.6) and social relationship (change after mexiletine treatment MC -4.1 and PC -22.7). These data seem to indicate that for some NDMs, like MC, mexiletine has less effect on patient's independence and social relationship. There was also some discussion with the applicant around the fact that yotonia can affect different muscle groups (eyelids, mouth tongue, hands and proximal legs). The relaxation time (RT) following maximal force handgrip reflects muscle stiffness in forearm finger flexors. Myotonia can be highly variable between patients, or even within the same patient between different muscles or within the same day. Furthermore, the progressive muscle weakness might dominate the clinical picture thus masking the presence of myotonia. It seems that majority of investigators as well as PC and MC patients reported mexiletine treatment as effective.

Logigian et al., 2010:

The authors evaluated mexiletine treatment in patients with DM type 1 in this study. The baseline 1 and 2 values for relaxation time (RT) especially for the 200 mg (mexiletine hydrochloride) TID trial seem to be quite different. Whether the observed numerical differences in the mexiletine effect on the RT for 150mg tid and 200mg tid could be considered a real dose response is difficult to conclude because of low number of patients. The relaxation time is considered to be a clinical biomarker indicating proof of principle of mexiletine treatment. However, it is not supported by the patients reported evaluation of muscle stiffness or quality of life changes. It is not clear what change on the relaxation time could be considered by the patient as clinically relevant improvement on muscle stiffness.

Unlike what the applicant states, TUG is a test where muscle weakness is better and more frequently assessed than myotonia. Still, it can be admitted that under the study conditions, patients should rarely have muscle weakness, and if so they would probably postpone study visit and assessment.

The applicant described different tools which are used to assess quality of life in DM type 1 patients – SF-36 and INQoL. However, as also pointed out by the Applicant mexiletine treatment effects on these outcomes are not presented in the Logigian et al 2010 study.

Additional expert consultation

The Neurology SAG members unanimously agreed that the available data on efficacy and safety of mexiletine in DM are limited. Recognizing the use in clinical practice, and based on the mechanism of

action, the SAG experts did not doubt that mexiletine can indeed show efficacy in myotonia in DM, but the effect size and its influence on the functioning and QOL of DM patients remains unclear, it is also not clear that a potential effect on myotonia would translate into functional benefit. The experts agreed that additional, controlled data are required before a definite B/R ratio can be established for DM patients.

2.5.4. Conclusions on the clinical efficacy

Myotonic disorders are chronic life-long debilitating conditions characterised by pain, fatigue, and muscle stiffness, resulting in frequent falls and disability. Mexiletine has long been used for the treatment of dystrophic and non-dystrophic myotonic disorders (Deutsche Gesellschaft für Neurologie, 2012; Hoffman et al., 2012; Heatwole et al., 2013), but robust evidence has been lacking.

The CHMP acknowledged the difficulties to conduct studies in those rare condition and in particular methodological drawbacks from the MYOMEX study.

However, data from the MYOMEX study discussed above were considered sufficient to support clinical efficacy in NDM patients.

The discussion on the extrapolation of efficacy results from NDM to DM patients concluded that there was a lack: a)data on relationship between handgrip myotonia results and quality of life or any global, functional or patient related endpoint that could serve as anchor; b) data which might allow on the adequate dose regimen for DM patients (Logigian et al 2010 data do not sufficiently support MYOMEX regimen). In conclusion, the CHMP considered that there were satisfactory data to support clinical efficacy in NDM patients but not in DM patients.

2.6. Clinical safety

Mexiletine was approved as an antiarrhythmic and its afety profile in the antiarrhythmic indications is well-established.

Safety data initially submitted in this application, to support the proposed indication for symptomatic treatment of myotonic disorders in adults, included:

- Safety data from the MYOMEX clinical study in 25 patients with non-dystrophic myotonias
- Six published studies included patients with myotonic disorders (3 controlled studies and 3 uncontrolled studies)
- Post-marketing safety data
    - four PSURs related to indication of myotonic disorders covering a 2-year period (2010 to 2012)
    - data from the Quintiles IMS database from 2011 to 2016 (number of mexiletine units sold)
    - two PSURs related to antiarrhythmic indications and one of them contained cumulative safety information until the cut-off date of 2 October 2008

Patient exposure

Clinical trial

MYOMEX study included 25 patients with NDMs (13 Myotonia congenita (MC) and 12 Paramyotonia congenita (PC)); with mexiletine dosing 200 mg/day for 3 days, 400 mg/day for 3 days and 600 mg/day

for an additional 12-16 days; and total treatment duration of 19 days (mean 19 days, median 19 days, range 10-21 days). This is a limited number and short follow-up.

Published studies

Supportive safety information from six published studies included 224 patients with myotonic disorders (122 patients in 3 controlled studies and 102 patients in 3 uncontrolled studies).—

With regard to collecting/registering AEs in the three controlled studies, it was either not reported (two of the three studies) or not systemically performed. Furthermore there was no available information on the assessment of causality. Safety information from the three uncontrolled studies was limited and there was also risk of underreporting.

Overall, the safety information from these six published studies could not constitute to a solid ground for categorizing frequencies of adverse events due to their limitations such as unclearness in methodology with regard to collecting/registering AEs, and information not available with regard to the assessment of causality. Thus the safety data from these six published studies were not taken into account in the calculation of the exposure; but presented for information purposes in subsequent sections.

Post-marketing safety data

Supportive post-marketing safety data for the proposed indication of myotonic disorders included four PSURs covered a 2-year period from 2010 to 2012, with an estimation of 186 to 558 patients over 2 year. Furthermore, data from the Quintiles IMS database are available from 2011 to 2016 (number of mexiletine units sold); which are in line with those reported in the PSURs.

In general, cardiac involvement is common in DM type 1 (DM1) and includes conduction abnormalities with arrhythmia and conduction blocks; and for DM type 2 (DM2) cardiac problems appear to be less severe and frequent as compared with the DM1. Mexiletine has been approved as an antiarrhythmic for the treatment of ventricular arrhythmias since 1975 (IBD); and the most important safety issue is that mexiletine can trigger arrhythmia or aggravate an existing arrhythmia, whether or not it has been diagnosed. The use of mexiletine in DM patients especially DM1 is, therefore, a potentially serious risk because of the disease pathologies associated with an increased risk of cardiac rhythm and conduction complications.

From a safety perspective, as dystrophic myotonias (DMs) especially the most severe cases of DM1 have cardiac involvement, it is important to discuss safety issues separately for the DM patients and the NDM patients. The MYOMEX study, however, only included NDM patients (13 MC and 12 PC).

Additionally, one PSUR related to the antiarrhythmic indications (2005-2008-bi) contains cumulative safety information with estimated exposure to mexiletine covering several millions of patient-years, since mexiletine's IBD until the cut-off date of 2 October 2008.

The available information (ADRs experienced with mexiletine in the myotonia indication) is too limited to be able to "discuss eventual difference in reporting DM/NDM (also their sub-types if known)".

Adverse events

Overview of AEs

The Table 36 below summarises the proportion of patients with AEs during the MYOMEX Study, together with the number of TEAEs.

Table 32: Overview of Adverse Events – Safety Population (Study MYOMEX)

Diagnosis	Type of Adverse Event	Placebo		Mexiletine	
		Number of AEs	Patient* n (%)	Number of AEs	Patient* n (%)
MC	Any AE	9	4 (30.8%)	16	6 (46.2%)
N=13	Related AE**	8	3 (23.1%)	13	4 (30.8%)
	Severe AE	0	0	1	1 (7.7%)
	Serious AE	0	0	0	0
	Death	0	0	0	0
	AE leading to treatment withdrawal	0	0	1	1 (7.7%)
	AE requiring concomitant medication	1	1 (7.7%)	3	2 (15.4%)
PC	Any AE	5	5 (41.7%)	24	9 (75.0%)
N=12	Related AE**	0	0 (0%)	12	7 (58.3%)
	Severe AE	0	0	0	0
	Serious AE	0	0	0	0
	Death	0	0	0	0
	AE leading to treatment withdrawal				
	AE requiring concomitant medication	3	3 (25.0%)	5	4 (33.3%)
Total	**Any AE**	**14**	**9 (36.0%)**	**40**	**15 (60.0%)**
N=25	**Related AE****	**8**	**3 (12.0%)**	**25**	**11 (44.0%)**
	Severe AE	**0**	**0**	**1**	**1 (4.0%)**
	Serious AE	**0**	**0**	**0**	**0**
	Death	**0**	**0**	**0**	**0**
	AE leading to treatment withdrawal	**0**	**0**	**1**	**1 (4.0%)**
	AE requiring concomitant medication	**4**	**4 (16.0%)**	**8**	**6 (24.0%)**

* Patient with at least one AE
**Probable, possible or unknown relationship to study drug
AE: adverse event; MC: myotonia congenita; PC: paramyotonia congenita
Source: CSR MYOMEX, Table 12-2

The MYOMEX study included a total 25 NDM patients, 13 MC and 12 PC.

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Incidence of AEs was 60% in patients receiving mexiletine, which is more commonly reported than that in patients receiving placebo (36%). Incidence of drug-related AEs was 44% in patients receiving mexiletine, also higher than that reported in patients under placebo (12%). One severe AE was reported by one (4%) patient under treatment with mexiletine. After this event, the subject withdrew from the study prematurely.

There were no SAEs or death reported during the study.

Common Treatment-Emergent Adverse Events

Table 33: Summary of Adverse Events by System Organ Class and by Treatment – Safety Population (Study MYOMEX)

Diagnosis	SOC	Placebo		Mexiletine	
		Number of AEs	Patient[1] n (%)	Number of AEs	Patient[1] n (%)
MC	**Overall**	**9**	**4 (30.8%)**	**16**	**6 (46.2%)**
N=13	Cardiac Disorders	0	0 (0%)	1	1 (7.7%)
	Ear and Labyrinth Disorders	0	0 (0%)	1	1 (7.7%)
	Gastrointestinal Disorders	2	2 (15.4%)	1	1 (7.7%)
	General Disorders and Administration Site Conditions	3	2 (15.4%)	4	2 (15.4%)
	Injury, Poisoning and Procedural Complications	0	0 (0%)	2	2 (15.4%)
	Musculoskeletal and Connective Tissue Disorders	0	0 (0%)	2	2 (15.4%)
	Nervous System Disorders	2	2 (15.4%)	3	2 (15.4%)
	Respiratory, Thoracic and Mediastinal Disorders	1	1 (7.7%)	0	0 (0%)
	Skin and Subcutaneous Tissue Disorders	1	1 (7.7%)	0	0 (0%)
	Vascular Disorders	0	0 (0%)	2	2 (15.4%)
PC	**Overall**	**5**	**5 (41.7%)**	**24**	**9 (75.0%)**
N=12	Blood and Lymphatic System Disorders	1	1 (8.3%)	0	0 (0%)
	Ear and Labyrinth Disorders	0	0 (0%)	1	1 (8.3%)
	Eye Disorders	0	0 (0%)	1	1 (8.3%)
	Gastrointestinal Disorders	0	0 (0%)	6	5 (41.7%)
	Infections and Infestations	3	3 (25.0%)	6	5 (41.7%)
	Musculoskeletal and Connective Tissue Disorders	0	0 (0%)	1	1 (8.3%)
	Nervous System Disorders	1	1 (8.3%)	2	1 (8.3%)
	Psychiatric Disorders	0	0 (0%)	4	4 (33.3%)
	Reproductive System and Breast Disorders	0	0 (0%)	1	1 (8.3%)
	Respiratory, Thoracic and Mediastinal Disorders	0	0 (0%)	1	1 (8.3%)
	Skin and Subcutaneous Tissue Disorders	0	0 (0%)	1	1 (8.3%)
All	**Overall**	**14**	**9 (36.0%)**	**40**	**15 (60.0%)**
patients[2]	Blood and Lymphatic System Disorders	1	1 (4.0%)	0	0 (0%)
N=25	Cardiac Disorders	0	0 (0%)	1	1 (4.0%)
	Ear and Labyrinth Disorders	0	0 (0%)	2	2 (8.0%)
	Eye Disorders	0	0 (0%)	1	1 (4.0%)
	Gastrointestinal Disorders	2	2 (8.0%)	7	6 (24.0%)
	General Disorders and Administration Site Conditions	3	2 (8.0%)	4	2 (8.0%)
	Infections and Infestations	3	3 (12.0%)	6	5 (20.0%)
	Injury, Poisoning and Procedural Complications	0	0 (0%)	2	2 (8.0%)
	Musculoskeletal and Connective Tissue Disorders	0	0 (0%)	3	3 (12.0%)
	Nervous System Disorders	3	3 (12.0%)	5	3 (12.0%)
	Psychiatric Disorders	0	0 (0%)	4	4 (16.0%)
	Reproductive System and Breast Disorders	0	0 (0%)	1	1 (4.0%)
	Respiratory, Thoracic and Mediastinal Disorders	1	1 (4.0%)	1	1 (4.0%)
	Skin and Subcutaneous Tissue Disorders	1	1 (4.0%)	1	1 (4.0%)
	Vascular Disorders	0	0 (0%)	2	2 (8.0%)

[1] Patient with at least one AE; [2] Total = MC + PC
AE: Adverse event; MC: Myotonia congenita; PC: Paramyotonia congenita; SAF: Safety population.
Source: MYOMEX CSR, Table 12-3

Evaluation of AEs including their frequencies should be based on the common treatment-emergent AEs in all patients, by System Organ Class and Preferred Term. A table for common treatment-emergent AEs, with regard to Summary of Adverse Events (all AEs, i.e. all patients) by System Organ Class and Preferred Term (safety population - MYOMEX Study), could not be found but has been now provided.

Based on all AEs by System Organ Class and Preferred Term for all patients in the MYOMEX study which included 25 NDM patients, the most common AEs are under SOC Gastrointestinal Disorders (2 patients

with 3 nausea and 2 patients with abdominal pain upper in the mexiletine group; 1 patient with nausea and none with abdominal pain upper in the placebo group); and SOC Psychiatric Disorders (3 patients with insomnia in the mexiletine group but none in the placebo group). The preferred terms reported by 2 patients in the mexiletine group but by none in the placebo group included vertigo, fall, and muscle contracture.

Published scientific literature

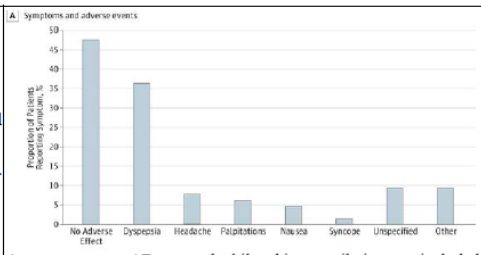
The Table 38 below summarised the AEs reported in the six identified published studies

Table 34: Summary of Adverse Events Reported in Published Scientific Literature

<table>
<tr><th>Reference</th><th>Number of Subjects</th><th>Treatment Regimen</th><th>Most Common Adverse Events</th><th>Severity of Adverse Events</th><th>Serious Adverse Events</th><th>Other Significant Adverse Events</th></tr>
<tr><td colspan="7">Controlled studies</td></tr>
<tr><td>Statland et al. (2012)</td><td>Mexiletine: 58
Placebo: 55</td><td>600 mg per day (200 mg tid) for 4 wk</td><td>
<table>
<tr><th>Adverse Event Category</th><th>Mexiletine Treatment</th><th>Placebo Treatment</th></tr>
<tr><td>Cardiac</td><td>1</td><td>1</td></tr>
<tr><td>Constitutional</td><td>3</td><td>0</td></tr>
<tr><td>Dermatologic/skin</td><td>1</td><td>2</td></tr>
<tr><td>Gastrointestinal</td><td>9</td><td>1</td></tr>
<tr><td>Infection</td><td>1</td><td>3</td></tr>
<tr><td>Lymphatics</td><td>0</td><td>1</td></tr>
<tr><td>Musculoskeletal/soft tissue</td><td>0</td><td>2</td></tr>
<tr><td>Neurologic</td><td>5</td><td>1</td></tr>
<tr><td>Pain</td><td>4</td><td>0</td></tr>
<tr><td>Total</td><td>24</td><td>11</td></tr>
</table>
AEs were more frequently reported in the gastrointestinal category (9 patients [16%] in the mexiletine group and 1 patient [2%] in the placebo group), neurologic category (5 patients [9%] in the mexiletine group and 1 patient [2%] in the placebo group) and pain category (4 patients [7%] in the mexiletine group and none in the placebo group).
There were 2 reported cardiac AEs both found incidentally on ECG at the end of week 4 (1 patient had bradycardia in the mexiletine group that resolved on follow-up ECG and 1 patient had premature ventricular complexes in the placebo group). Neither necessitated stopping the study.</td><td>Not reported</td><td>One SAE determined to be not study related (narcotic withdrawal)</td><td>2 subjects (3%) in the mexiletine group dropped out due to AEs:
1 migraine
1 gastrointestinal discomfort</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Number of Subjects</th><th>Treatment Regimen</th><th>Most Common Adverse Events</th><th>Severity of Adverse Events</th><th>Serious Adverse Events</th><th>Other Significant Adverse Events</th></tr>
<tr><td>Logigian et al. (2010)</td><td>150 mg:
Mexiletine: 19
Placebo: 19

200 mg:
Mexiletine: 20
Placebo: 18</td><td>450 or 600 mg per day (150/200 mg tid) for 7 wk</td><td>
<table>
<tr><th></th><th colspan="2">150 mg 3 times daily trial</th><th colspan="2">200 mg 3 times daily trial</th></tr>
<tr><th>Event</th><th>Mexiletine</th><th>Placebo</th><th>Mexiletine</th><th>Placebo</th></tr>
<tr><td>Gastrointestinal distress[b]</td><td>6</td><td>4</td><td>6</td><td>0</td></tr>
<tr><td>Respiratory</td><td>4</td><td>2</td><td>4</td><td>5</td></tr>
<tr><td>Headache</td><td>2</td><td>1</td><td>5</td><td>6</td></tr>
<tr><td>Arthralgia</td><td>4</td><td>3</td><td>1</td><td>1</td></tr>
<tr><td>Lightheadedness</td><td>1</td><td>0</td><td>3</td><td>0</td></tr>
<tr><td>Sore throat</td><td>0</td><td>0</td><td>4</td><td>1</td></tr>
<tr><td>Tremor</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
</table>
[a]Values reported are the number of subjects who ever had the event (multiple occurrences are counted only once for the same subject).
[b]Includes heartburn, nausea, vomiting, diarrhea, and abdominal pain.
AEs that seemed to be more common with mexiletine were mild upper gastrointestinal distress (12 patients [31%] in the combined mexiletine group and 11% in the combined placebo group) and lightheadedness (4 patients [10%] in the combined mexiletine group and none in the placebo groups).</td><td>Mild</td><td>None</td><td>One patient discontinued the 200 mg trial (due to diarrhoea)</td></tr>
<tr><td>Kwiecinski et al. (1992)</td><td>Mexiletine: 24</td><td>400 mg/day for 2 wk then 600 mg/day 2 wk</td><td>Two patients (8%) on mexiletine had some epigastric distress, which was prevented by taking the drug with food.</td><td>Not reported</td><td>Not reported</td><td>None</td></tr>
</table>

Reference	Number of Subjects	Treatment Regimen	Most Common Adverse Events	Severity of Adverse Events	Serious Adverse Events	Other Significant Adverse Events
Uncontrolled studies						
Suetterlin et al. (2015)	63	Increments of 50 - 100 mg of mexiletine per wk until symptoms resolved or a total daily dose of 600 mg was reached, for a minimum of 6 mo. Length of follow-up: 6 mo - 18 yrs.	 Any symptom or AE reported while taking mexiletine was included unless there was a clear alternative precipitant. Because some patients reported more than 1 AE, the total exceeds 100%. B Distribution of adverse events Adverse Event SCN4A Missense CLCN1 Hom NMD CLCN1 Het NMD Dyspepsia 11 6 4 2 B Distribution of adverse events Adverse Event SCN4A CLCN1 Missense CLCN1 Hom NMD CLCN1 Het NMD Dyspepsia 11 6 4 2 Headache 1 2 2 0 Palpitations 3 0 1 0 Nausea 1 0 2 0 Syncope 0 1 0 0 Unspecified 2 1 3 0 Other[a] 2 2 2 0 None 9 7 5 9 CLCN1 missense: all patients with CLCN1 missense mutations only (dominant or recessive myotonia congenita); heterozygous (Het) NMD, patients with recessive myotonia congenita with 1 CLCN1 missense mutation and 1 CLCN1 mutation associated with nonsense mediated decay; homozygous (Hom) NMD, patients with recessive myotonia congenita with 2 mutations associated with nonsense mediated decay; and SCN4A missense, all patients with SCN4A mutations. [a]Other AEs were breathlessness (3.1%), vivid dreams (1.5%), tremor and dizziness (1.5%), loose stool, change in ejaculate and fatigue (1.5%), blepharospasm, and the inability to focus (1.5%).	Not reported	None	Sixteen of the 23 patients (69.6%) who reported dyspepsia required dyspeptic therapy, despite which 4 stopped taking mexiletine.
Lo Monaco et al. (2015)	21	Individual dosage	Upper gastrointestinal distress in two patients (10%)	Mild	None	None
Contardi et al. (2012)	18	400 mg/day over 3 to 6 mo	No side effects were reported	-	None	None

In one controlled study by Logigian et al. (2010), AEs were reported partly with Preferred Term. AEs that seemed to be more common with mexiletine were mild upper gastrointestinal distress (12 patients [31%] in the combined mexiletine group and 11% in the combined placebo group) and the reported gastrointestinal distress included heartburn, nausea, vomiting, diarrhoea, and abdominal pain (no more details were reported).

Overall:

- The most frequently occurring AEs in subjects receiving mexiletine, based on these six published studies, was Gastrointestinal Disorders SOC, and in which included dyspepsia, nausea, upper gastrointestinal distress, vomiting, diarrhoea, and abdominal pain. It is noted that the proposed SmPC includes nausea and abdominal pain but not vomiting and diarrhoea. These AEs were included in section 4.8 of the proposed SmPC.

- Neurologic AEs were also frequently reported by Statland et al. 2012 (five in mexiletine treatment and one in placebo). One SAE has been reported Statland et al. 2012 (narcotic withdrawal; determined not to be study related). The reported AEs in the published studies included light-headedness, dizziness, syncope, and tremor. The Applicant was asked to discuss portion of serious arrhythmia which is an explain factor to the AEs dizziness, hypotension and syncope. A warning about the symptoms of arrhythmia is in the SmPc.

- A few cardiac AEs were reported by Statland et al. 2012 (incidentally on ECG at the end of week 4: one patient had bradycardia in the mexiletine group that resolved on follow-up ECG and one patient had pre-mature ventricular complexes in the placebo group; but the two patients did not withdraw from the study). Bradycardia is included in the SmPC.

- Seven subjects (3%) discontinued study or treatment due to an AE (six were in the Gastrointestinal Disorders SOC (1 due to gastrointestinal discomfort, 1 due to diarrhoea, 4 due to dyspepsia); and one due to a migraine).

In summary,although it was acknowledged that there were limitations in the published studies, the reported AEs from those six published studies did not reveal additional safety concerns as compared to those already established.

Adverse events of special interest

Cardiac safety

Safety profile of mexiletine in the antiarrhythmic indications is well-established. The most important safety issue is that mexiletine can trigger arrhythmia or aggravate an existing arrhythmia, whether or not it has been diagnosed. Mexiletine can cause adverse effects that are directly linked to blockade of sodium channels and among these adverse effects, cardiovascular problems, especially proarrhythmia defined as either the onset of a new arrhythmia or the aggravation of a pre-existing arrhythmia.

In general, DM type 1 (DM1), considered as the most common form of muscular dystrophy in adults, is a more severe disease than DM type 2 (DM2). The core features in classic adult-onset DM1 are distal muscle weakness. Cardiac involvement is common in DM1 and includes conduction abnormalities with arrhythmia and conduction blocks. But cardiac problems appear to be less severe and frequent for DM2 as compared with the DM1.

The use of mexiletine in DM patients especially DM1 is, therefore, a potentially serious risk because of the disease pathologies associated with an increased risk of cardiac rhythm and conduction complications. The clinical study (MYOMEX) only included NDM patients; and the safety data of mexiletine from the published studies, however, included DM patients without cardiovascular problem. Thus the use of mexiletine in patients with DM has not been supported.

Dosing related adverse events

Based on the product information of mexiletine hydrochloride indicated for the treatment of ventricular arrhythmias, mexiletine plasma levels of at least 0.5 µg/ml are generally required for therapeutic response and an increase in the frequency of central nervous system adverse events has been observed when plasma levels exceed 2 µg/ml. Thus the dosage of mexiletine recommended in the approved arrhythmia indications is individualised on the basis of response and tolerance and targeted a therapeutic range of plasma concentration approximately 0.5 to 2 µg/ml. Supportive data/published data were provided with regard to the severity of CNS effects increasing with the total daily dose of mexiletine in the arrhythmia indications, since it isrelevant to this application as a therapeutic range of plasma concentration in myotonic disorders is not thought to exceed the upper limit of the 2 µg/ml. Few studies have reported correlations between central nervous system side effects and mexiletine dose and/or serum concentration. A study bybookmark9 Campbell et al. (1978) included 156 patients (153 had ischaemic heart disease) who received mexiletine (i.v. or p.o) in the treatment of arrhythmia; a statistically significant relationship existed between plasma concentration and daily dose although inter-patient variability was large, 5.5% of the concentrations were associated with severe side effects within the range of 0.75 - 2 µg/mL, and when the concentrations rose to 2 µg/mL or more, severe adverse effects (including CNS) were seen in 19% of these concentrations. The MYOMEX study reported that steady-state serum mexiletine concentrations (ranged 0.5 to 1.9 µg/ml) are in the same range as those reported in patients with ventricular arrhythmias. Three (12.0%) patients treated with mexiletine experienced 5 mild AEs related to Nervous System Disorders. In general major CNS side effects are not expected to occur, in the dose range as recommended in the SmPc.

Off label use in children

Off label use in children concerns not only age but also indication. SmPC clearly states that Namuscla should only be used in the adult population (section 4.1) and that its safety and efficacy for proposed indication is not yet established in children aged 0 to 18 years (section 4.2).

The literature search submitted by the Applicant providing the available safety data in children is adequate. From its analysis, for doses of mexiletine reaching similar plasma concentrations, evidence so far does not suggest that the frequency of AEs reported in children is very different than that usually reported in adults. Scarcity of data, however, precludes definite conclusions. A Paediatric Investigation Plan (PIP; Procedure No. EMEA-002012-PIP01-16) submitted under Article 7 of Regulation (EC) 1901/2006 for Mexiletine hydrochloride capsules was approved on 2 June 2017 (Decision No. P/0155/2017). At this point, proposed routine risk minimisation measures are considered sufficient for the considered important potential risk 'Off-label use in children'.

It is acknowledged that mexiletine is a class Ib antiarrhythmic which has been used alone and in combination with other antiarrhythmic agents for treatment of ventricular arrhythmia for several decades and it is still available in some countries for arrhythmia indications. While most of the post-marketing safety data is related to this use, the Applicant will carefully monitor all reports of use of Namuscla in arrhythmia indications. No further actions are deemed necessary.

There is a potential risk that the maximal recommended total daily dose could result in plasma concentration exceed the upper limit of the therapeutic range, in particular for patient who is a CYP2D6 poor metabolizer, and/or with risk factors that would result in significant increase of plasma concentration such as marked right-sided congestive heart failure thus reducing hepatic metabolism and severe hepatic impairment.

The dose should not exceed 500 mg/day (as mexiletine) and this is reflected in the SmPC.

DRESS

In total 38 cases were received and reviewed for an evaluation in 2007 and reveal a rather uniform pattern of the diagnostic criteria for DRESS: The occurrence in close temporal relationship of 1-2 months (~75%), systemic involvement (~70%), fever (~50%) as well as the positive patch or DLST test in nearly the half of patients provide some evidence for a contributory role of mexiletine. Thus DRESS has been included in the SmPC sections 4.4 and 4.8.

In addition, the Stevens-Johnson syndrome is included in the proposed SmPC; and it is noted in the serious suspected ADRs presented in the PSUR (2005-2008); the cumulative number of ADRs reported under the SOC Skin and Subcutaneous Tissue Disorders included 34 ADRs of Stevens-Johnson syndrome.

Serious adverse event/deaths/other significant events

No SAEs were reported during the MYOMEX study.

One event led to premature treatment discontinuation in the MYOMEX study (tachycardia [SOC: Cardiac Disorders] in a context of anxiety). The event was graded as severe and considered as related to mexiletine.

One MC patient discontinued due to an AE in the MYOMEX study (tachycardia in a context of anxiety) which was judged as severe and considered as related to mexiletine. The AE tachycardia is covered in the proposed SmPC (4.8).

No deaths were reported during the MYOMEX Study.

Laboratory findings

The clinical laboratory parameters tested during the MYOMEX study revealed no additional safety concerns compared to those already established.

No trend of change in any clinical laboratory parameter was reported in the published studies.

No significant change in ECG parameters in NDM patients based on MYOMEX clinical trial and the published study (with dose up to 600 mg/day (as mexiletine hydrochloride)). No significant change in ECG parameters in DM patients based on the published study (with dose up to 600 mg/day (as mexiletine hydrochloride)). The use of mexiletine in patients with DM especially long-term use in DM1 remains to be a potentially serious risk because of the disease pathologies associated with an increased risk of cardiac rhythm and conduction complications.

Safety in special populations

Age

The claimed indication does not include the paediatric population. It is known that age of onset for myotonic disorders (both DM and NDM) included infancy, childhood and teen years. Thus off-label use of mexiletine in paediatric population is likely, however there is limited information with regard to the safety of mexiletine in this population. The Applicant discussed potential risks related to off-label use of mexiletine in paediatric population including those AEs related to CNS especially under longer time use and/or use in those having significant risk factors that could potentially result in significant increase of plasma concentrations and thus causing severe CNS AEs. Taken together, it is agreed that in general major CNS side effects are not expected to occur, if mexiletine doses follow recommendation in the SmPC.

About 14% of administered mexiletine is excreted as unchanged compound. Experience in patient with myotonic disorders aged > 65 years is limited (only one patient (with MC) was > 65 years in the MYOMEX clinical study). In the SmPC section 4.2, it is proposed that no dosage adjustment is required in patients aged 65 years and over; which is considered acceptable.

Race

The dosage of mexiletine recommended in the approved arrhythmia indications is individualised on the basis of response and tolerance; and the dosage are targeted a therapeutic range of plasma concentration approximately 0.5 to 2 µg/ml.

A therapeutic range of plasma concentration in this indication proposed for myotonic disorders is not known but it should not exceed the upper limit of the 2 µg/ml which was based on the CNS AEs. The steady state C_{2h} determined based on the MYOMEX study (25 NDM patients) were 1.1±0.4 µg/ml (range 0.5 to 1.9 µg/ml). There is a potential risk that the maximal recommended total daily dose could result in plasma concentration exceed the upper limit of the therapeutic range, in particular for patient who is a CYP2D6 poor metabolizer and thus causing severe AEs / CNS AEs.

Since the worldwide distribution of the CYP2D6 poor metaboliser phenotype varies considerably, racial differences in AEs related to the mexiletine use can be anticipated.

Gender

Gender was not a significant co-variate for clearance of mexiletine, based on the Clinical Pharmacokinetic Assessment Report. A difference in safety/AE profiles of mexiletine based on gender is not expected.

Body Weight

Oral mexiletine is usually administered as a fixed dose regimen. The recommended mexiletine dosage is not based on body weight. However, a negative correlation between plasma mexiletine concentrations and body weight is generally observed. A similar observation has been made during the MYOMEX Study, where mexiletine concentrations were slightly higher in PC patients, who had a lower body weight at baseline than MC patients. This information is reflected in the SmPC.

CYP450 Polymorphism

The systemic exposure of mexiletine is expected to be about 2-fold higher in CYP2D6 PMs (poor metabolizers) compared to EMs (extensive metabolizers) following an oral dose of 200 mg, based on the Clinical Pharmacokinetic Assessment Report. From clinical safety point of view, there is a potential risk that the maximal recommended total daily dose could result in plasma concentration exceed the upper limit of the therapeutic range for patient who is a CYP2D6 poor metabolizer and thus causing severe AEs / CNS AEs (see ***Race***).

Hepatic and Renal Impairment

Based on the Clinical Pharmacokinetic Assessment Report, about a 3.5-fold higher exposure of mexiletine was seen in subjects with liver cirrhosis compared to healthy subjects. The t1/2 increased to ca 29 h in cirrhotic patients compared to ca 10 h in healthy ones. Currently in the SmPC section 4.2, it is proposed that mexiletine should not be used in patients with severe hepatic impairment, which is considered acceptable.

About 14% of administered mexiletine is excreted as unchanged compound. In the SmPC section 4.2, it is proposed that no dosage adjustment is considered necessary in patients with mild or moderate renal impairment; and the use of mexiletine is not recommended in patient with severe renal impairment due to limited experience with mexiletine in this patient population.

Use in Pregnancy, Reproduction and Lactation

Mexiletine is known to cross the placenta and is readily transferred into human breast milk, where it can be present at higher concentrations than in maternal plasma at corresponding time-points. However, assuming an infant's daily milk intake of 500 mL and a maternal plasma concentration of 2 µg/mL, it is unlikely that an infant would have an ingestion of more than 1.25 mg of mexiletine in any 24 hour period. This information was included in the SPC and, as a precautionary measure, it was considered that is preferable to avoid the use of Namuscla during pregnancy

Smoking

About 25% lower exposure of mexiletine is expected in smokers as compared to non-smokers.

The Applicant provided data to populate the table which discriminates adverse event by age range in section 4.6 "Safety in special populations" No relevant new safety information arises from requested data to populate the table which discriminates adverse event by age range, which was obtained from Myomex study. Experience with mexiletine in patients with myotonic disorders aged > 65 years is very limited, with only one patient (with MC) above 65 years in Myomex study, who had no reported adverse events.

Immunological events

Several cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were consistently reported in association with the use mexiletine and, therefore, a warning related to these potentially fatal

cutaneous AEs has been included in section 4.4. Also, the term 'Potentially lethal drug hypersensitivity syndrome' has been substituted with the well-recognised term "Drug reaction with eosinophilia and systemic symptoms" (DRESS) in the tabulated list of AEs in the Section 4.8.

Considering the high number and severity of the reported Serious Cutaneous Adverse Reaction (SCAR) Stevens-Johnson syndrome (i.e. 34 reported cases as stated within the PSUR covering the period 2005-2008), RMP was updated to include the term 'Severe Cutaneous Adverse Reactions' (SCARs), which include DRESS and Stevens-Johnson syndrome, as an Important Identified Risk. Routine risk minimization measures are proposed, and additional pharmacovigilance activities are planned, comprising a registry study to be initiated in December 2019 to determine the long-term safety and tolerability of mexiletine in the treatment of myotonic disorders (final study report due date in January 2025). This is considered adequate.

Safety related to drug-drug interactions and other interactions

The total exposure of mexiletine was about 2-fold higher in CYP2D6 poor metabolizers compared to extensive metabolizers after an oral dose of 200 mg, and co-treatment with ciprofloxacin (strong CYP1A2 inhibitor) resulted in ca 1.15-fold increase in exposure of mexiletine (if assuming full complete inhibition). CYP1A2 may be the major metabolic pathway in CYP2D6 PMs and mexiletine is also known as a moderate CYP1A2 inhibitor. Therefore there may be clinical consequences for the dose titration procedure due to autoinhibition of CYP1A2 thus potentially leading to time dependency in CYP2D6 PMs with increasing exposure over time as well as clinical consequences of concomitant treatment with CYP1A2 inhibitors in CYP2D6 PMs This has been discussed and satisfactorily addressed by the applicant.

Discontinuation due to adverse events

One MC patient discontinued due to an AE in the MYOMEX study (tachycardia in a context of anxiety) which was judged as severe and considered as related to mexiletine.

Overall in the six published studies, seven subjects discontinued study or treatment due to an AE (six were in the Gastrointestinal Disorders SOC (1 due to gastrointestinal discomfort, 1 due to diarrhoea, 4 due to dyspepsia); and one due to a migraine).

Post marketing experience

Post-Marketing Data in Patients with Myotonic Disorders

For myotonic disorders, supportive post marketing experience included 4 PSURs covered a 2-year period from 1 November 2010 to 31 October 2012. Very few adverse events have been reported.

Overall, these PSURs do not reveal additional safety concerns in patients with myotonic disorders compared to adverse events described for antiarrhythmic treatment; however, their ability to evaluate frequency of AEs related to mexiletine use in patients with myotonic disorders are limited.

Furthermore, data from the Quintiles IMS database are available from 2011 to 2016 (number of mexiletine units sold); which are in line with those reported exposure in the PSURs, . But no safety data are presented for this period.

Post-Marketing Data in Patients with Cardiac Disorders

One PSUR covered a 3-year period from 2005 to 2008 and contains cumulative safety information until the cut-off date of 2 October 2008; which reported a total exposure of approximately 494,000 patient-years and based on approximate sales numbers it can be extrapolated that the exposure to

mexiletine in patients with arrhythmia covers several millions of patient-years, since mexiletine's IBD until the cut-off date of 2 October 2008.

Safety profile of mexiletine in the antiarrhythmic indications is well-established. The PSURs do not reveal additional safety concerns as compared to those already established. But there are issues raised when comparing the proposed AEs in section 4.8 of the SmPC with the serious suspected ADRs presented in the PSUR (2005-2008); such as in the proposed SmPC (4.8), AE under SOC Hepatobiliary Disorders is "asymptomatic increase of hepatic enzymes", however, the cumulative number of ADRs reported under the SOC Hepatobiliary Disorders in the PSUR included AEs as per the Table 39. The Applicant has updated section 4.8 of the SmPC under the SOC Hepatobiliary Disorders as discussed above.

Table 35

Serious suspected ADRs MedDRA preferred term	**Cumulative No of ADRs**	**Reference**
HEPATOBILIARY DISORDERS		
Hepatic lesion	**1**	
Liver disorder	**16**	6.3.2.15
Hepatic function abnormal	78	
Acute hepatic failure	**1**	
Hepatitis	26	
Hepatitis acute	**2**	

Additionally, three health professional confirmed cases have been reported in patients with myotonia in France during this reporting period (2008-2010) and two of them were serious and concern the same patient. The Applicant has provided the requested narratives of the two cases (2010-FF-00628FF and 2010-FF-00629FF) concerning the same patient, which were health professional confirmed and reported in France during a PSUR reporting period oct-2008 to oct-2010. In both cases, malaise or dyspnoea on exercise could be explained by arrhythmia during exercise and the events were considered serious due to the hospitalization or prolongation of hospitalization. However, the both subjects were later re-exposed of mexiletine with a negative rechallenge and no new safety issues were observed.

2.6.1. Discussion on clinical safety

Exposure

Safety data from MYOMEX study included only NDM patients (in total 25 patients: 13 MC and 12 PC) who received maximal total daily dose of mexiletine (as hydrochloride) 600 mg (200 mg t.i.d.), with total treatment duration up to 19 days (mean 19 days, median 19 days, range 10-21 days), this is a limited number of subjects and short follow-up, and thereby limited value in order to establish clinical safety although there is a placebo group.

Supportive safety information from six published studies included 224 patients with myotonic disorders (122 patients in 3 controlled studies and 102 patients in 3 uncontrolled studies). However, the safety information from these six published studies could not constitute to a solid ground for categorizing frequencies of adverse events due to their limitations such as unclearness in methodology with regard to collecting/registering AEs, and information not available with regard to the assessment of causality. But the safety/AE data from these six published studies are presented for information purposes.

Supportive post-marketing safety data for the proposed indication of myotonic disorders included: Four PSURs covered a 2-year period from 2010 to 2012, with an estimation of 186 to 558 patients over 2 year. Furthermore, data from the Quintiles IMS database are available from 2011 to 2016 (number of

mexiletine units sold); which are in line with those reported in the PSURs, according to the applicant. But no safety data are presented for this period. The applicant provided information on AEs including narrative on relevant cases and discuss eventual difference in reporting DM/NDM. It is acknowledged that the exact diagnosis of patients with myotonia who received mexiletine in France since 2010 is not available.

Based on market sales, 1,346,500 units of MEXILETINE AP-HP 200 mg capsule have been distributed during the period of 01.11.2012 to 29.01.2018. One spontaneous serious case has been reported during the period covered by this analysis . This patient experienced disorder speech, stutter and diplopia. The analysis of the available information, including the positive rechallenge, suggests a probable association of the administration of mexiletine with the occurrence of disorder speech, stutter and diplopia. 'Diplopia' is already listed in the SPC with a frequency 'not known'. Although the AE 'stutter' is unexpected according to the SPC, considering that 'speech disorders' is listed as 'uncommon', at this point, no further actions are deemed

In summary, the exposure is limited for the applied indication, but there is a substantial exposure for antiarrhythmic indication.

Adverse events

Safety profile of mexiletine in the antiarrhythmic indications is well-established. The most important safety issue is that mexiletine can trigger arrhythmia or aggravate an existing arrhythmia, whether or not it has been diagnosed. Mexiletine produces reversible gastrointestinal and nervous system adverse reactions; and an increase in the frequency of central nervous system adverse events was observed when plasma levels exceed 2 µg/ml. Other important AEs related to mexiletine use are related to SOC subcutaneous tissue disorders including DRESS and Stevens-Johnson syndrome.

Based on all AEs by System Organ Class and Preferred Term for all patients in the MYOMEX study which included 25 NDM patients, the most common AEs are under SOC Gastrointestinal Disorders (2 patients with 3 nausea and 2 patients with abdominal pain upper in the mexiletine group; 1 patient with nausea and none with abdominal pain upper in the placebo group); and SOC Psychiatric Disorders (3 patients with insomnia in the mexiletine group but none in the placebo group). The preferred terms reported by 2 patients in the mexiletine group but by none in the placebo group included vertigo, fall, and muscle contracture.

The supportive safety data consisting of six published studies, however, only one controlled study by Logigian et al. (2010) reported AEs partly with Preferred Term. AEs that seemed to be more common with mexiletine were mild upper gastrointestinal distress (12 patients [31%] in the combined mexiletine group and 11% in the combined placebo group) and the reported gastrointestinal distress included heartburn, nausea, vomiting, diarrhoea, and abdominal pain (no more details were reported).

Cardiovascular disorders

Myotonic disorders are rare diseases which are serious and considered to be long-term debilitating conditions which are divided into two groups, non-dystrophic myotonia (NDM) and dystrophic myotonia (DM).

NDM

The NDMs are a heterogeneous, but clinically similar group of rare hereditary neuromuscular disorders caused by mutations in the skeletal muscle sodium (SCN4A) and chloride channels (CLCN1). Typically, NDM presents with muscle stiffness as the primary symptom, in the absence of severe weakness and muscle wasting, and rarely suffer cardiac damage.

DM

DMs are autosomal dominant, complex, multisystemic diseases with a core pattern of clinical presentation including myotonia, muscular dystrophy, cardiac conduction defects, posterior iridescent cataracts, and endocrine disorders. Clinically, DM is heterogeneous (type 1 (DM1) and type 2 (DM2)). In general, DM1, considered as the most common form of muscular dystrophy in adults, is a more severe disease than DM2. The core features in classic adult-onset DM1 are distal muscle weakness. Cardiac involvement is common in DM1 and includes conduction abnormalities with arrhythmia and conduction blocks. DM2 has variable manifestations, but cardiac problems appear to be less severe and frequent compared with DM1.

Mexiletine produces use-dependent block of sodium channels, with a higher affinity for depolarized Na+ channels (in open state). Mexiletine exerts the singular use-dependent block of sodium currents which occurs during repetitive depolarization. This is effected owing to its higher binding affinity to activated or inactivated channels, providing the basis for the selective action on pathologic membrane (i.e. those characterized by excessive firing of action potentials). The result of this activity is anticonvulsant, antiarrhythmic, and antimyotonic properties in nerve, heart, and skeletal muscle. But mexiletine can cause adverse effects that are also directly linked to blockade of sodium channels and among these adverse effects, cardiovascular problems; especially proarrhythmia, defined as either the onset of a new arrhythmia or the aggravation of a pre-existing arrhythmia, are the most of concern.

SmPC

The applicant has provided safety data/published data from the antiarrhythmic indications supporting the text concerning the safety profile of mexiletine and the proposed AEs and/or their frequency categories in patients with myotonic disorders, and from which source they have been derived. Accordingly, list of ADRs have been revised and section 4.8 has been updated. Particularly: 'vomiting' and 'diarrhoea' have been added with a frequency 'not known'; 'Hepatic function abnormal' has been added with a frequency of 'rare'; 'Liver disorder', 'Hepatitis' and 'Drug-induced liver injury' have been added with a frequency of 'very rare'; 'DRESS' has been indicated with a frequency of 'very rare'.

The major concern that mexiletine can trigger arrhythmia or aggravate an existing arrhythmia, whether or not it has been diagnosed, has been partially mitigated by the applicant with both routine and additional risk minimisation measures and pharmacovigilance activities, which include: cardiac monitoring (section 4.4 has been updated e.g. to recommend ECG evaluation in patients with a history of fainting, palpitation, shortness of breath, lipothymia, and syncope) and contraindicated use in certain conditions, Education Guides for Patients and Healthcare Professionals, targeted follow-up questionnaires, Patient Alert Card.

Risk minimisation measures for other Important identified risks related to mexiletine use, particularly those related to SOC 'subcutaneous tissue disorders' have been updated and also properly addressed in the SPC and RMP.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

The safety data is based on several sources ranging from a small placebo controlled clinical study (MYOMEX) in 25 NDM patients with short treatment duration, to supportive safety data in patients with myotonic disorders in six published studies and post marketing experience. Literature data has limitations considering the reporting of safety information, and there are potential differences in post marketing experience from myotonic indication (PSURs covering a period of 2010 to 2012) compared to exposure from arrhythmia indications.

The vast majority of knowledge regarding the safety profile of mexiletine will be based on data from the antiarrhythmic indications. The Applicant provided safety data derived from the antiarrhythmic indications supporting the text concerning the safety profile of mexiletine and the proposed AEs and/or their frequency categories in patients with myotonic disorders, and from which source they have been derived. Section 4.8 has been updated accordingly.

In conclusion the CHMP considered the safety data satisfactory for the NDM population but not for the DM as there are notably cardiac safety concerns which would need to be addressed by additional data in this population particularly prone to cardiac abnormalities.

2.7. Risk Management Plan

Safety concerns

Table 36: 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 7. Off-label use in DM1 and DM2 patients
Missing information	8. Long term use in adult patients with myotonic disorders 9. Effect on fertility and use in pregnancy 10. Safety in elderly 11. Use in patients with severe renal impairment

Pharmacovigilance plan

Summary of additional Pharmacovigilance activities

Table 37: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Registry study (Planned)	To determine the long-term safety and tolerability of Namuscla for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorder	1. Severe cutaneous adverse reactions 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 5. Increased frequency of seizure episodes in patients with epilepsy 6. Off-label use in DM1 and DM2 patients 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	Study protocol Patients will be enrolled for a period of 2 years. Periodic update on data collection	Provided for PRAC review and endorsement within 1 month from European Commission decision Initiation: December 2019 First patient in: July 2020 Last patient, last in: July 2022 Final Study Report: December 2025 Included in PSUR

Risk minimisation measures

Table 38: Summary of pharmacovigilance and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Severe cutaneous adverse reactions	Routine risk minimisation measures: SmPC section 4.3.and 4.8. PL section 2 and 4 Additional risk minimisation measures: None	Additional pharmacovigilance activities: Registry(ies)
Cardiac arrhythmia	Routine risk minimisation measures: SmPC section 4.3, section 4.4, section 4.5 and section 4.8. PL section 2 and 4 Additional risk minimisation measures: 1. Educational guide for HCPs 2. Patient alert card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire, to monitor and further characterise the risk of cardiac arrhythmia. Additional pharmacovigilance activities: Registry(ies)
Risk of toxicity of CYP1A2 substrate with narrow therapeutic window such as theophylline, caffeine or tizanidine	Routine risk minimisation measures: SmPC section 4.5. PL section 2 Additional risk minimisation measures: None	Additional pharmacovigilance activities: Reigstry(ies)
Risk of decreased mexiletine clearance and thus associated risk of adverse reactions of mexiletine in patients with hepatic impairment	Routine risk minimisation measures: SmPC section 4.2, 4.4 PL section 2 Additional risk minimisation measures: 1. Educational guide for HCPs	Additional pharmacovigilance activities: Registry(ies)
Increased frequency of seizure episodes in patients with epilepsy	Routine risk minimisation measures: SmPC section 4.4., 4.8 PL section 2 Additional risk minimisation measures: None	Additional pharmacovigilance activities: Reigstry(ies)
Off-label use in children	Routine risk minimisation measure: SmPC section 4.2. PL section 2 Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Off-label use in DM1 and DM2 patients	Routine risk minimisation measure: SmPC section 4.1 PL section 1 Additional risk minimisation measures: None	Additional pharmacovigilance activities: Registry(ies)
Long term use in adult patients with myotonic disorders	Routine risk minimisation measure: None Additional risk minimisation measures: None	Additional pharmacovigilance activities: Registry(ies)
Effect on fertility and use in pregnancy	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Additional risk minimisation measures:	Additional pharmacovigilance activities: Registry(ies)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	
Safety in elderly	Routine risk minimisation measures: SmPC section 4.2. Additional risk minimisation measures: None	Additional pharmacovigilance activities: Registry(ies)
Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC Section 4.2. and 4.4 Additional risk minimisation measures: None	Additional pharmacovigilance activities: Registry(ies)

Conclusion

The CHMP and PRAC considered that the RMP version 1.1 (dated 16 October 2018) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

Based on the safety profile in the target population, the CHMP is of the opinion that a separate entry in the EURD list for Namuscla is needed, as it cannot follow the already existing entry for mexiletine. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The term "myotonic disorders" covers a broad group of diseases characterized by common symptom of muscle stiffness (see Table 43 below):

Table 39: Myotonic disorders

	Dystrophic myotonia	**Non-dystrophic myotonia**				
	Dystrophic myotonia type 1 (DM1)	**Thomsen myotonia congenita (dominant)**	**Becker myotonia congenita (recessive)**	**Paramyotonia congenita**	**Periodic paralysis**	**Potassium-aggravating myotonia**
Gene	DMPK	Chloride channel (CLCN1)		Sodium channel (SCN4A)		
Locus	19q	7q	7q	17q	17q	17q
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant
Age of onset	Infancy to early adult	Infancy	Early childhood	Infancy	Infancy to early childhood	Childhood to early teens
Myotonia	Severe	Moderate to severe	Severe	Moderate to severe	Asymptomatic to severe	Asymptomatic to severe
Distribution of myotonia	Distal more than proximal	Generalised; face, arms > legs	Generalised; legs > face, arms	Face (eyelids), hands, thighs	Generalised if present	Proximal more than distal

There are no disease-modifying treatments available for myotonic disorders. The pharmacological and non-pharmacological measures e.g., avoiding cold, low-potassium diet - are used to treat muscle symptom of muscle stiffness. Myotonia which can be present in both conditions DM and NDM is treated with sodium channel blockers (phenytoin, procainamide, carbamazepine and tocainidine). In addition, some anti-myotonic effects of quinine, amitryptiline, calcium channel blockers, benzodiazepines, prednisone are used to treat myotonia.

In addition, it is important to point out that while muscle stiffness is a recognized important problem for patients suffering from NDM, it is considered to be less important symptom for patients with DM type 1.

3.1.2. Available therapies and unmet medical need

Current Treatment Options for Myotonic Disorders

Mexiletine is a class Ib antiarrhythmic medication, structurally similar to lidocaine, that was initially developed as a treatment for ventricular arrhythmias with subsequent use in long QT syndrome (Heatwole et al., 2013). Mexiletine is the only medicinal product approved in the EU for the symptomatic treatment of myotonic disorders. This authorisation has been granted in France in 2010 through a national procedure.

Besides mexiletine, other antiarrhythmics such as tocainide (Kwiecinski et al., 1992), flecainide (Desaphy et al., 2013), propafenone (Alfonsi et al., 2007) and procainamide (Finlay, 1982) have shown similar effects on sodium channel function and some efficacy on myotonic disorders. However, most of them cannot be recommended as treatment for myotonia, because of associated severe side effects.

Antiepileptics with sodium blocking properties have also been evaluated in myotonic disorders and were shown to have some efficacy, such as phenytoin (Kwiecinski et al., 1992) and carbamazepine (Sechi et al., 1983).

Besides pharmacological treatment, lifelong physiotherapeutic treatment of the muscular weakness is recommended in order to counteract contractures and progression of the muscular weakness. In subjects with myotonic disorders associated with warm-up phenomenon, continual slight exercise to maintain the "warmed-up" state is recommended. In those with cold sensitivity (such as PC), a warm environment is a good prophylaxis.

The applicant has provided selected recommendations / international guidance: German, Dutch and Scottish. No EU or US global guidance has been discussed. However, all the presented guidances have a lowest common denominator which is mexiletine in the proposed dosages.

3.1.3. Main clinical studies

The applicant performed one phase 3 study (MYOMEX), and presented 3 randomized, double blinded, cross-over, placebo-controlled studies, one randomized, single blinded, placebo-controlled study, 2 prospective open label studies and one retrospective review of a patient cohort described in literature in order to support the efficacy claim. Key information on the MYOMEX and the Statland study is provided in the Table 44 below.

Table 40: Overview of Main clinical studies with Mexiletine

Study ID/ Country	Study Design and Objectives	Treatment Regimen	Study Population	Number of Subjects
Efficacy/Safety Pivotal Study				
MYOMEX EU (France)	Multi-centre, double-blind, placebo-controlled; cross-over (2 treatment periods of 18 days) study with a 4-day wash-out period, to compare the effects of mexiletine versus placebo in patients with myotonia congenita (MC) and paramyotonia congenita (PC).	600 mg (as mexiletine hydrochloride) per day (200 mg tid) for 18 days	Subjects with myotonic disorders (MC, PC)	Randomised: 25 Dosed (cross-over): 25 mexiletine 25 placebo
Literature*				
Controlled studies				
Statland et al. (2012) US, Canada, EU (UK, Italy)	A randomised, double-blind, placebo-controlled 2-period crossover Phase 2 study to determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDM.	600 mg (as mexiletine hydrochloride) per day (200 mg tid) for 4 wk	Subjects with myotonic disorders (NDM)	Randomised: 59 Dosed (cross-over): 59 mexiletine 59 placebo

3.2. Favourable effects

The efficacy of mexiletine treatment in NDM patients (PC and MC) was evaluated in the MYOMEX study performed by the applicant and study described by Statland et al. 2012. The primary efficacy variable of muscle stiffness score change measured on self-reported VAS score at baseline and day 18 was higher for mexiletine treatment compared to placebo in MYOMEX study (mexiletine = -41,7, placebo = -9.0; $p<0.001$). Similarly, the lower muscle stiffness score following mexiletine treatment compared to placebo treatment during the first treatment period was reported in Statland et al., 2012 study (mexiletine = 2.53, placebo = 4.21; $p<0.001$).

The secondary efficacy variables like chair test (mexiletine=-2.1, placebo=0.2; $p<0.0007$), individualized neuromuscular quality of life questionnaire (overall quality of life, mexiletine=-20.7, placebo=2.6, $p<0.001$), CGI efficacy index (investigator, mexiletine=91.7%, placebo=20.0%; $p<0.0001$), clinical myotonia rating scale (severity, mexiletine=-29.8, placebo=-6.2; $p<0.001$; disability, mexiletine=-5.1, placebo=-0.8, $p<0.001$) supported the primary efficacy variable in MYOMEX study.

The secondary endpoints of clinical relevance analysed in the Statland et al., 2012 study - pain score, weakness score, tiredness score, clinical handgrip myotonia, clinical eye closure myotonia, individualized neuromuscular quality of life score were supporting the observed effect on the primary efficacy variable (the corresponding statistical significance $p<0.001$ for all comparisons).

3.3. Uncertainties and limitations about favourable effects

The uncertainty regarding of the observed effect of mexiletine treatment on muscle stiffness reported in the MYOMEX study is related to the cross-over design of the study. Since a potential overestimation of the treatment effect was observed in the study with the similar design described by Statland et al., 2012, it is reasonable to assume that there is a substantial risk for similar overestimation of the treatment effect to be present in the MYOMEX study too.

A substantial number of patients in the MYOMEX clinical study (14 out of 25) have been treated with mexiletine before the clinical trial. It is also noted that 24.1% of patients randomized to "mexiletine then placebo" group and 20% of patients randomized to "placebo then mexiletine" group have been previously treated with mexiletine in the Statland et al., 2012 study. However, the potential effect of this earlier exposure to mexiletine was apparently little on the reported treatment effect during the first treatment period in the MYOMEX study in spite of the observed overestimation of treatment effect in the second treatment period described in the Statland et al. 2012 study.

The applicant presented analysis of both primary and secondary variables after subgrouping of NDM patients to PC (sodium channelopathy) and MC (chloride channelopathy). For the primary variable there was no obvious difference between PC and MC in response to mexiletine treatment. However, for some of secondary variables the mexiletine treatment seems to have more pronounced effect in PC patients compared to MC patients, e.g. change from baseline for INQoL items "independence" PC =-29.6, MC=-3.9, "social relationship" – PC=-24.4, MC=-4.1; "locking" – PC=-50, MC=-27.9; "pain" - PC=-34.2, MC=-17.8. Albeit the small sample, these differences seem not to relate to the different pathophysiological mechanisms or clinical features of PC and MC patients or just is a chance finding because of small number of patients. It is interesting that in the paper by Suetterlin et al., 2015 patients with sodium channel mutations were treated with lower so called effective mexiletine dose compared to patients with chloride channel mutations.

Analysis of most secondary variables in the Statland study is performed in the overall population without taking into account different treatment periods. SF-36 showed no statistical significance when analysed only for the first period, while having statistical significance for the overall population.

Mexiletine treatment effect on muscle stiffness in patients with DM type 1 was evaluated in study by Logigian et al., 2010, Kwiecinski et al., 1992 and Contardi et al., 2015. Study by Kwiecinski et al. 1992 included 9 patients with the DM type 1, but the results were not presented separately for this patient group. Study by Contardi et al., 2015 was an open label uncontrolled study evaluating specific scale for DM type 1 patients (n=18). Only Study by Logigian et al., 2010 had randomized double blind placebo-controlled controlled design. However, DM type 1 patients in this study represents very small group (n=30) and only effect on one specific instrumental clinical assessment (relaxation time) was evaluated in this study. The uncertainty of the efficacy results in DM type 1 patients is further exaggerated by the unknown consequences of including 10 patients from the first mexiletine trial to the second one. The small number of patients with DM type 1 treated with mexiletine and evaluated is difficult to justify, since DM type 1 is the most common form of myotonic disorders and only in Sweden approximately 1000 patients with this disorder could be identified according to the National Board of Health and Welfare (2015). The relationship between observed changes in the RT and clinically meaningful change of muscle stiffness in DM type 1 patients is not clear at the present moment.

The efficacy of mexiletine in randomized, double-blind, placebo-controlled clinical trials was evaluated only in patients with PC, MC and DM type 1. The disorders covered by the term "myotonic disorders" represent a rather broad spectrum of diseases with different underlying pathophysiological mechanisms, clinical picture and relative importance of muscle stiffness.

3.4. Unfavourable effects

The safety data is based on several sources ranging from a small placebo controlled clinical study (MYOMEX) in 25 NDM patients with short treatment duration, to supportive safety data in patients with myotonic disorders in six published studies and post marketing experience. Literature data has limitations considering the reporting of safety information, and there are potential differences in post marketing experience from myotonic indication (PSURs covering a period of 2010 to 2012) compared to exposure from arrhythmia indications.

The safety profile of mexiletine in the antiarrhythmic indications is well-established. The most important safety issue is that mexiletine can trigger arrhythmia or aggravate an existing arrhythmia. Mexiletine produces reversible gastrointestinal and nervous system adverse reactions; and an increase in the frequency of central nervous system adverse events was observed when plasma levels exceed 2 µg/ml. Other important AEs related to mexiletine use are related to SOC subcutaneous tissue disorders including DRESS and Stevens-Johnson syndrome.

Based on all AEs by System Organ Class and Preferred Term for all patients in the MYOMEX study which included 25 NDM patients, the most common AEs are under SOC Gastrointestinal Disorders (2 patients with 3 nausea and 2 patients with abdominal pain upper in the mexiletine group; 1 patient with nausea and none with abdominal pain upper in the placebo group); and SOC Psychiatric Disorders (3 patients with insomnia in the mexiletine group but none in the placebo group).

One controlled study by Logigian et al. (2010) reported AEs partly with Preferred Term. AEs that seemed to be more common with mexiletine were mild upper gastrointestinal distress (12 patients [31%] in the combined mexiletine group and 11% in the combined placebo group) and the reported gastrointestinal distress included heartburn, nausea, vomiting, diarrhoea, and abdominal pain (no more details were reported).

Overall, the reported AEs from one clinical study; six published studies and PSURs did not reveal additional safety concerns in patients with myotonic disorders as compared to already well-established experience.

3.5. Uncertainties and limitations about unfavourable effects

The exposure is limited for the applied indication, so information from the substantial exposure for antiarrhythmic indications has to be extrapolated to that of the proposed target population. Moreover, treatment of myotonic conditions with mexiletine is for symptom relief and not cure, and exposure may be expected to occur over long time.

The applicant has modified routine RMMs in the proposed SmPC section 4.3 and 4.4 based on experience from antiarrhythmic indications, using an established risk-classification and recommendations in timing of investigations from European Society of Cardiology guidelines.

The applicant has modified satisfactorily the proposed contraindications for mexiletine, together with additional references for cardiac contraindications including ventricular tachyarrhythmia, heart block, myocardial infarction, symptomatic coronary artery disease, heart failure, atrial tachyarrhythmia, sinus node dysfunction, co-administration with medicinal products inducing torsades de pointes. In particular the applicant has grouped the terms "congestive heart failure", "systolic left ventricular dysfunction with an ejection fraction <45%" and "symptomatic cardiomyopathy", into the single term "heart failure with mid-range (40-49%) and reduced (<40%) ejection fraction", in line with the definition of the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski et al., 2016), and together with additional supporting publications the conclusion is that

mexiletine is contraindicated in case of heart failure with mid-range (40-49%) and reduced (<40%) ejection fraction because of the proarrhythmic effects of mexiletine.

The applicant has also addressed the remaining issue regarding how the potentially serious safety risks of mexiletine including proarrhythmic effects could be detected and managed in a timely manner, especially given challenges such as unpredictable clinical course of individual patients. Section 4.4 of the SmPC includes a cardiac evaluation added shortly after treatment start (e.g. within 48 hours). Regarding patients with cardiac abnormalities or prone to such abnormalities additional cardiac monitoring is recommended through detailed cardiac evaluation including ECG before any dose increase; and ECG, 24-48 hour Holter-monitoring and echocardiography during maintenance treatment as part of routine cardiac assessment (at least annually, or more frequently if considered necessary). In general, aggravation of arrhythmia is an early event, occurring within several days of initiating an antiarrhythmic drug therapy or increasing the dose of the drug. Mexiletine has a mean elimination half-life of 10 hours ranged 5 to 15 hours. Thus the proposed addition of a cardiac evaluation (e.g. within 48 hours after treatment start) is considered reasonable; although it is known that this can also occur as a late event during treatment of mexiletine, and a worsening of arrhythmia may not be precipitated by the proposed non-invasive methods. An increased mexiletine plasma concentration is a risk factor for patients with cardiac abnormalities or prone to such abnormalities, thus the corresponding additional cardiac monitoring is also recommended after any dose increase.

It is important to manage the potentially serious safety risks of mexiletine with sufficient risk minimisation measures (RMMs). Additional risk-minimization measures have been proposed, and a reminder not to continue long-term treatment in a patient not responding or experience benefit of the treatment is also part of the SmPC.

3.6. Effects Table

Table 41: Effects Table for MYOMEX

Effect	Short Description	Unit	Mexiletine	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects of Mexiletine for the Symptomatic Management of Non-Dystrophic Myotonia						
Stiffness as measured by a VAS: absolute change from baseline	Most common and severe reported symptom	100-mm scale	All patients (N=25): 24.3 MC patients (N=13): 29.2 PC patients (N=12): 19.0	All patients (N=25): 66.2 MC patients (N=13): 66.1 PC patients (N=12): 65.8	Small study (n=13 MC and n=12 PC) No MCID available Short-term data (day 18) Subjective outcome; PRO may be susceptible to exaggeration if patients guessed their treatment assignment / Significant effect of the treatment ($p < 0.001$) Advantages of a PRO: records the patient experience as it occurs; no bias of interpretation by an interviewer	MYOMEX Study

Effect	Short Description	Unit	Mexiletine	Placebo	Uncertainties/ Strength of evidence	References
Percent of subjects with a VAS difference ≥50 mm	Most common and severe reported symptom Measure of symptomatic relief	%	All patients (N=25): 57.1 MC patients (N=13): 50 PC patients (N=12): 63.6	All patients (N=25): 13.6 MC patients (N=13): 10 PC patients (N=12): 16.7	Only in subjects with baseline value ≥50 mm. / Stringent "responder analysis" based on subjects with a ≥50 mm improvement in VAS score (i.e. very marked) Relative difference: 4.2 (all patients) / 5.0 (MC) / 3.8 (PC)	MYOMEX Study
Stiffness as reported on the IVR dairy: mean estimate of treatment	Most common and severe reported symptom Measure of symptomatic relief	9-point scale	Period 1 (N=57): 2.53 Period 2 (N=57): 1.60	Period 1 (N=57): 4.21 Period 2 (N=57): 5.27	Carry-over effect was observed Short-term data (week 4) Subjective outcome; PRO may be susceptible to exaggeration if patients guessed their treatment assignment / Significant effect of the treatment ($p < 0.001$ for period 1 and $p = 0.04$ for period 2) MCID can be set at 0.75 (Stunnenberg et al., 2015) Advantages of a PRO: records the patient experience as it occurs; no bias of interpretation by an interviewer	Statland et al. (2012)
Chair test: absolute change from baseline	Functional test measuring the time needed to stand up from a chair, walk around the chair and sit down again Measure of functional improvement	seconds	All patients (N=25): -2.1 MC patients (N=13): -3.4 PC patients (N=12): -0.8	All patients (N=25): 0.2 MC patients (N=13): 0.5 PC patients (N=12): 0	No MCID available Short-term data (day 18) Chair test times for patients with PC were already short at baseline and could not be further improved / Significant effect of the treatment ($p = 0.001$) Objective endpoint allowing quantification of the myotonia	MYOMEX Study
Handgrip myotonia: mean estimate of handgrip time (s) and of time to relax from 90% to 5% of maximal force	Functional test quantifying the handgrip myotonia using a grip dynamometer Measure of functional improvement	seconds	Handgrip (N=57): 0.164 Handgrip (90% to 5% RT) (N=57): 0.321	Handgrip (N=57): 0.494 Handgrip (90% to 5% RT) (N=57): 0.429	No MCID available Short-term data (week 4) / Significant effect of the treatment ($p < 0.001$) Objective endpoint allowing quantification of the myotonia	Statland et al. (2012)

Effect	Short Description	Unit	Mexiletine	Placebo	Uncertainties/ Strength of evidence	References
Eyelid myotonia: time to open eyes after closing	Functional test quantifying the eyelid myotonia Measure of functional improvement	seconds	All patients (N=57): 0.161	All patients (N=57): 0.474	No MCID available Short-term data (week 4) / Significant effect of the treatment (p < 0.001) Objective endpoint allowing quantification of the myotonia	Statland et al. (2012)
INQoL: Weakness, absolute change from baseline or *value at week 4	Questionnaire on experienced muscle weakness (symptom) Measure of quality of life improvement	100-point scale	All patients (N=25): -32.8 MC patients (N=13): -26.3 PC patients (N=12): 39.	All patients (N=25): -1.7 MC patients (N=13): 0.8 PC patients (N=12): 4.4	No MCID available Short-term data (day 18) Subjective outcome / Significant effect of the treatment (p < 0.001) Assessment of the health status of patients with muscle disorders using a specific validated tool	MYOMEX Study
INQoL: Weakness, absolute change from baseline or *value at week 4	Questionnaire on experienced muscle weakness (symptom) Measure of quality of life improvement	100-point scale	All patients (N=35): 45.7	All patients (N=35): 49.3	No significant effect of the treatment (p = 0.24)	Statland et al. (2012)
INQoL: Overall Quality of Life, absolute change from baseline	Aggregation of the results of the questionnaires on the 5 life domains (activities, independence, social relationships, emotions, and body image) Measure of quality of life improvement	100-point scale	All patients (N=25): -20.7 MC patients (N=13): -11.9 PC patients (N=12): -29.4	All patients (N=25): 2.6 MC patients (N=13): 3.1 PC patients (N=12): 2.1	No MCID available Short-term data (day 18) Subjective outcome / Significant effect of the treatment (p < 0.001) Assessment of the health status of patients with muscle disorders using a specific validated tool	MYOMEX Study
INQoL: Overall Quality of Life, absolute change from baseline	Aggregation of the results of the questionnaires on the 5 life domains (activities, independence, social relationships, emotions, and body image) Measure of quality of life improvement	100-point scale	All patients (N=51): 14.0	All patients (N=51): 16.7	No MCID available / Significant effect of the treatment (p < 0.001)	Statland et al. (2012)
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Gastrointestinal disorders	Incidence of abdominal pain and nausea	%	20	8	Most common SOC drug-related disorder	(1)
			16	2		(2)
	Incidence of heartburn, nausea, vomiting, diarrhoea and abdominal pain		31	11		(3)
Psychiatric disorders	Incidence of insomnia	%	12	0	Drug-related disorder	(1)
Nervous system disorders	Incidence of nervous system disorders	%	12	8	Drug-related disorder	(1)
			9	2		(2)
Cardiac disorders	Incidence of tachycardia		4	0	Drug-related disorder; no marked variations in 12-lead ECG parameters between baseline and the end of treatment period	(1)
Ear and labyrinth disorders	Incidence of vertigo		8	0	Drug-related disorder	(1)

Notes: (1) Myomex study; no serious AE reported (2) Statland et al., 2012 (3) Logigian et al., 2010

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

Myotonic disorders are hereditary, rare diseases caused by a malfunction of skeletal ion channels (channelopathy) which share the main clinical symptom of muscle myotonia. The major goal of this treatment is to alleviate the muscle stiffness. While muscle stiffness is considered to be important disabling medical problem for patients with NDM, it is considered less disabling for patients with DM type 1. The reduction of muscle stiffness is expected to lead to improved quality of life, which could be related to improved capability for patients to remain professionally active or might allow continue hobby activities retaining their social relationships. For patients with NDM the observed self-reported improvement in muscle stiffness following mexiletine treatment was accompanied by reported positive change in quality of life. The main effect outcomes rely on patients' reporting and a large proportion of patients in the MYOMEX study were not mexiletine treatment naïve. This may lead to the estimation of effect being overly optimistic. However, taking all available data into consideration the efficacy and safety of mexiletine in NDM has been demonstrated in the randomised, placebo-controlled MYOMEX study. The applicant also applied for treatment of patients with dystrophic myotonia. However, the CHMP considered that the submitted literature references did not firmly support the clinical relevance of the observed changes in muscle stiffness in DM type 1 patients.

Importance of unfavourable effects

The exposure is limited for the applied indication, but there is a substantial exposure for antiarrhythmic indication. And extrapolating from those experiences, the risk of inducing arrhythmia is the most serious adverse event to mitigate. The applicant has modified routine RMMs in the proposed SmPC section 4.3 and 4.4 using an established risk-classification and recommendations in timing of investigations from

European Society of Cardiology guidelines. The applicant has further modified the proposed contraindications for mexiletine, together med justification and additional references for cardiac contraindications and in particular the applicant has proposed to regroup the terms "*congestive heart failure*", "s*ystolic left ventricular dysfunction with an ejection fraction <45%" and "symptomatic cardiomyopathy*", into the single term "*heart failure with mid-range (40-49%) and reduced (<40%) ejection fraction*", in line with the definition of the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski et al., 2016), and together with additional supporting publications. However, an increased mexiletine plasma concentration is a risk factor for patients with cardiac abnormalities or prone to such abnormalities, thus the corresponding additional cardiac monitoring is also be recommended after any dose increase. Thereby the CHMP considered the importance of the unfavourable effects, especially the cardiac risk, to be well reflected by the RMMs and in the labelling of the product.

3.7.2. Balance of benefits and risks

The benefits of mexiletine treatment in patients with myotonia in non-dystrophic myotonic disorders have been confirmed further to the above-mentioned methodological issues (notably carry over effect, placebo effect, treatment duration, inclusion criteria) have been discussed and resolved. Satisfactory measures have been agreed in relation to the safety risks, notably increased risk for cardiac arrhythmias.

The benefit-risk of mexiletine for the symptomatic treatment of myotonia in NDM patient population is established as positive.

3.7.3. Additional considerations on the benefit-risk balance

n/a

3.8. Conclusions

The overall B/R of Namuscla is positive in the treatment of myotonia in adult patients with non-dystrophic myotonia (NDM).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Namuscla is favourable in the following indication:

Symptomatic treatment of myotonia in adult patients with non-dystrophic myotonia

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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.

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 Namuscla maintenance treatment, a detailed cardiac evaluation should be carried out every 24-48 hour. Holter-monitoring and echocardiography are 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;

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

Not applicable.

Paediatric Data

A Paediatric Investigation Plan (PIP; Procedure No. EMEA-002012-PIP01-16) submitted under Article 7 of Regulation (EC) 1901/2006 for Mexiletine hydrochloride capsules was approved on 2 June 2017 (Decision No. P/0155/2017).

The European Medicines Agency has deferred the obligation to submit the results of studies with Namuscla in all subsets of the paediatric population in the symptomatic treatment of myotonic disorders

No significant studies in the agreed paediatric investigation plan Decision No P/0155/2017 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.

The safety and efficacy of mexiletine in children and adolescents aged 0 to 18 years have not been established yet. No data are available.

This has been reflected in the SmPC.

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