NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Lupin

2. **Clarification questions and company responses**

3. **Patient and professional groups and NHS organisation submissions** from:
   a. Muscular Dystrophy UK
   b. Association of British Neurologists

4. **Expert personal perspectives** from:
   a. Fiona Norwood, Consultant Neurologist & Honorary Senior Lecturer at King's College Hospital – clinical expert, nominated by Lupin
   b. David Lockyer, Head of Broadgate at British Land – patient expert, nominated by Muscular Dystrophy UK
   c. Rob Burley, Director of Campaigns, Care and Support at Muscular Dystrophy UK – patient expert, nominated by Muscular Dystrophy UK
   d. Fiona Marley, Head of Highly Specialised Commissioning at NHS England – commissioning expert, nominated by NHS England

5. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews (KSR)

6. **Evidence Review Group report – factual accuracy check**

7. **Technical report**

8. **Technical engagement response from the company** Lupin

9. **Technical engagement responses from consultees and commentators:**
   a. Muscular Dystrophy UK
   b. Association of British Neurologists

10. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

11. **Extra model calculations after technical engagement**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Document B

Company evidence submission

December 2019

File name	Version	Contains confidential information	Date
ID1488 Mexiletine Company Evidence Submission	**V1.0 Final**	**Yes**	**09 December 2019**

Contents

Tables and figures

Abbreviations

Abbreviation	Description
ADM	Abductor digiti minimi
AE	Adverse event
ANT	Alive on Treatment (health state)
AOT	Alive no Treatment (health state)
CGI	Clinical global impression
CI	Confidence interval
CLCN1	Skeletal muscle voltage gated chloride channel gene
CMAP	Compound muscle action potential
CMS	Clinical myotonia rating scale
ECG	Electrocardiogram
EMA	European Medicines Agency
EMG	Electromyography
EPAR	European public assessment report
HR	Heart rate
HRQoL	Health-related Quality of Life
INQoL	Individualized neuromuscular quality of life
IQR	Interquartile range
IVR	Interactive voice response
MA	Marketing Authorisation
MC	Myotonia congenita
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention to treat
NDM	Non-dystrophic myotonia
PMC	Paramyotonia congenita
PP	Per protocol
PSURs	Periodic Safety Update Reports
PT	Preferred term
SAF	Safety
SCN4A	Skeletal muscle voltage gated sodium channel gene
SD	Standard deviation
SF-36	36-Item Short Form Survey
SOC	System organ class
VAS	Visual analogue scale

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with non-dystrophic myotonic (NDM) disorders requiring treatment of symptomatic myotonia.	As per scope. It is estimated that 50-70% of patients are symptomatic and require treatment (1), see Appendix M.	Not applicable
Intervention	Mexiletine	Mexiletine	Not applicable
Comparator(s)	Established clinical management without mexiletine, including but not limited to: • Lamotrigine • Best supportive care	Established clinical management without mexiletine, is placebo (i.e. no treatment) in the base case. Best supportive care is assumed to be received by all patients by the time they require treatment with mexiletine and, according to the NICE Final Scope, include physiotherapy, lifestyle adaptations, mobility aids and occupational assistance. Resource use data in NDM is not available, however, patients in the MYOMEX study were asked to continue with their usual care whilst in the trial. Therefore, it can be	We agree with the NICE Final Scope that lamotrigine is one of a number of antiarrhythmic and antiepileptic medicines that have been used off-label for the pharmacological treatment of NDM. However, it is not assessed in the base case for the following reasons: • Lamotrigine is not an established treatment in clinical practice in England and Wales. Lupin conducted market research following the Decision Problem meeting with NICE involving eight neurology centres in the England and Wales, including the National

		assumed that usual care for the study population was best supportive care. It should be noted that best supportive care includes coping strategies developed by patients, regardless of treatment choice, as illustrated in discussions with patients and clinicians (Appendix L and M) and (2).	Hospital for Neurology and Neurosurgery (NHNN), Queens Square Centre for Neuromuscular Diseases, London) in November 2019. This showed that lamotrigine is not established in practice with less than 3% of patients currently on or having ever received lamotrigine (3). In addition, a UK patient survey of 27 NDM patients conducted in November 2019 demonstrated only 4.2% of patients (1 responder) had ever been prescribed lamotrigine (2), supporting the market research findings that lamotrigine is not established practice in the NHS – see Section B.1.3.7. • Mexiletine is the first-choice treatment – and the most widely used – treatment for myotonic symptoms in NDM patients. • Lamotrigine is not licensed for the indication in this submission in the UK or any other country and no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients. • Lamotrigine is not recommended as first-choice in any guidance (4-7) and when mentioned, listed solely as second-choice therapy – for use when mexiletine is either

			contraindicated, ineffective or not tolerated. • There are no randomised/ non-randomised clinical trials, that assess the impact of lamotrigine in comparison with established first-choice treatment for symptoms of myotonia in NDM patients. • The only available evidence for lamotrigine is a recent RCT by Andersen et al which was conducted between 2013 and 2015, and published in 2017. Despite this the market research does not indicate an increase in use in the UK since that could at all suggest established use in the NHS (8). This trial also lacks common outcome measures and results to enable any indirect treatment comparison with mexiletine NDM RCTs. Some endpoints such as SF-36 were also incomplete and possibly inaccurately reported – this is described in more detail in Section 2.9.1. Efforts were made to contact the lamotrigine trial and other two mexiletine trial authors (Statland et al and Stunnenberg et al) to obtain patient level data but without success.

Outcomes	The outcome measures to be considered include: • muscular symptoms (including stiffness and weakness) • fatigue • motor function • pain • adverse effects of treatment • health-related quality of life.	The outcomes presented listed in the scope are presented where results are available for these outcomes.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The economic modelling should include the costs associated with genetic testing for mutations in CLCN-1 and SCN4A gene coding in people with myotonic disorders who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the	Cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year in this study. The time horizon is lifetime. Costs are considered from an NHS and Personal Social Services perspective. Cost of genetic testing for mutations in CLCN-1 and SCN4A gene coding will be considered, according to the assumption that not all patients currently receiving unlicensed mexiletine are genetically confirmed with NDM. This cost will be added to the first year only to address this.	Genetic testing is already provided as a highly specialised service by the National Hospital for Neurology and Neurosurgery (NHNN), Queens Square Centre for Neuromuscular Diseases – a part of University College London and the national diagnostic centre for NDM. Thus, the infrastructure is already in place for the diagnosis of NDM and funded by NHS England. The economic model includes the costs associated with genetic testing for mutations in CLCN-1 and SCN4A gene coding in people with myotonic disorders in the base case. This cost is removed in scenario analysis. The eligible population are diagnosed NDM patients and the availability of NaMuscla

	Guide to the Methods of Technology Appraisals		will not drive diagnosis. Only diagnosed patients, as per NHS England Standard Contract (6), are currently offered the option for treatment if symptoms impact quality of life. By this stage patient's symptoms are likely to be severe enough that any strategies they have developed to cope with their condition such as avoiding triggers or performing muscle warming routines (effectively best supportive care) will not be sufficient and the patient may benefit from treatment. Hence, there is no evidence that the rate of diagnosis will change and market research carried out by Lupin that confirms 87% of patients with NDM have been tested (3). For these reasons, cost of genetic testing need not be accounted for, but it has been done to satisfy the NICE scope.

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Mexiletine (NaMuscla®)
Mechanism of action	Mexiletine blocks channels in muscle cells which allow sodium ions (electrically charged particles) to pass in and out of the cell. Mexiletine blocks sodium channels with a stronger potency in situations of excessive burst of action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block), as occurring in diseased tissues, rather than on physiological excitability (resting or tonic block)(9). These sodium channels play a role in the contraction and relaxation of muscles and are hyperactive in patients with myotonic disorders, causing excessive contractions and stiffness. By blocking these channels, mexiletine reduces the stiffness that occurs when these excessive contractions are prolonged (10). Mexiletine is, therefore, mostly active on muscle fibres subject to repeated discharges (such as skeletal muscles). It improves myotonic symptoms by decreasing muscle stiffness through reduction of the delay of muscle relaxation (9) i.e. it reduces the rate of contractions and hence the associated stiffness.
Marketing authorisation/CE mark status	NaMuscla was granted Marketing Authorisation by the European Medicines Agency (EMA) on 18th December 2018 (10). Mexiletine was granted orphan medicinal product designation on 19th November 2014 in the treatment of myotonic disorders. The Committee on Orphan Medicinal Products (COMP), in its review of orphan medicinal designation procedural history, recommended that NaMuscla, for treatment of myotonic disorders is not removed from the Community Register of Orphan Medicinal Products on the 8th November 2018. The COMP noted that the indication for NaMuscla falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product. The marketing authorisation is for the 'symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. <u>Historical context</u> The active substance, mexiletine, has been used for a long time as the first-choice treatment of NDM, used outside of its recommended license as an antiarrhythmic treatment. The first marketing authorisation (MA) for mexiletine (Mexitil) was granted in 1975 to Boehringer Ingelheim, as an antiarrhythmic medicinal product. Mexitil was discontinued in 2008 for commercial reasons. However, to meet requirements from patients and physicians in France, a marketing authorisation for mexiletine was granted in France in 2010 for the treatment of myotonic symptoms. Mexiletine, has been used for a long time as the first-choice treatment of NDM, with access in the UK more recently relying on special import from other countries such as Canada. However NaMuscla is now the only medicinal product approved across the EU for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders (10).

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	NaMuscla is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders (NDM) (9). Before starting mexiletine treatment, detailed and careful cardiac evaluation (ECG, 24-48-hour Holter-monitoring and echocardiography) should be carried out in all patients in order to determine the cardiac tolerability of mexiletine. A cardiac evaluation is recommended shortly after treatment starts (e.g. within 48 hours). Throughout treatment with mexiletine, and in relation with dose changes, cardiac monitoring of patients must be adapted as a function of the heart condition of each patient: - In patients without cardiac abnormalities, periodic ECG monitoring is recommended (every 2 years or more frequently if considered necessary). Caution is required when a patient has mild or moderate hepatic impairment – a slower titration (biweekly) is recommended. Patients who are CYP2D6 poor metabolisers may exhibit higher mexiletine blood level and so require at least 7 days prior to dose increases to ensure a steady state has been reached. NaMuscla is not recommended in patients with severe renal impairment as experience with this is limited. Safety and efficacy have not been established in children 18 years and under (9).
Method of administration and dosage	NaMuscla is an oral preparation which should be administered with water and in an upright position, preferably at mealtimes to reduce the risk of digestive intolerance. The recommended starting dose, as stated in the summary of product characteristics (SmPC), is one capsule of 167 mg mexiletine base per day (*equal to 200 mg mexiletine hydrochloride*). Patients are dose titrated up, according to clinical response, after at least 1 week of treatment, to a daily dose of 333 mg mexiletine daily (i.e. two capsules per day or equivalent to 400 mg mexiletine hydrochloride). After at least 1 further week of treatment, the dose can be further increased to 500 mg daily (three capsules per day or equivalent to 600 mg mexiletine hydrochloride) based on clinical response. Hence, maintenance dosage is according to the intensity of a patient's symptoms and clinical response can be achieved between a daily dose of 167 mg and 500 mg (i.e. 1 to 3 capsules per day). Mexiletine is taken regularly, on a daily basis, to address patient symptoms (9).
Additional tests or investigations	Prior to initiating mexiletine treatment, detailed and careful cardiac evaluation should be carried out. Maintenance also requires continued cardiac monitoring which should be adapted as per the condition of the patient's heart(9).
List price and average cost of a course of treatment	List price: £5,000 for a pack of 100 capsules (11). Average cost of treatment at a dose of 333 mg mexiletine daily (i.e. two capsules per day or equivalent to 400 mg mexiletine hydrochloride): • Per month (30 days) – £3,000 • Per year – £36,500

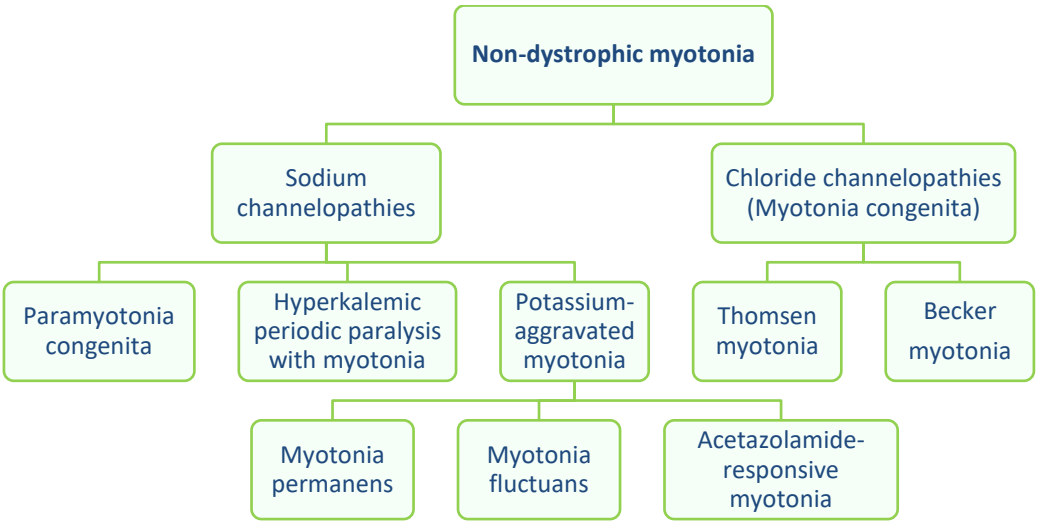
Patient access scheme (if applicable)	A simple discount Patient Access Scheme (PAS) has been submitted to PASLU and NHS England.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1. Overview of non-dystrophic myotonia (NDMs)

The NDMs are a heterogeneous group of rare, genetic diseases caused by mutations in muscle chloride or sodium ion channels which do not have the systemic features and dystrophic weakness of dystrophic myotonia (DMs)(12). They can be categorised according to the affected pathway (see Figure 1), each with differences in presentation and symptoms (13, 14), as well as phenotypic overlap (15).

Figure 1: Sub-classification of non-dystrophic myotonias



Although sub-category differences between the various genotypes of NDM exist, the common features of NDM relate to myotonia which is seen on examination as delayed muscle relaxation following muscle contraction or following mechanical stimulation such as percussion. The underlying muscle membrane hyper-excitability manifests electro-physiologically as repetitive muscle fibre after-discharges (13, 15). Voluntary muscle contraction leads to prolonged muscle contraction (12) due to sustained bursts of action potentials that originates from muscle fibres. These bursts persist for several seconds following the ceasing of physical activity causing a delay to the relaxation of the muscle contraction. This delay is known as myotonia and is often described by patients as 'stiffness'(16).

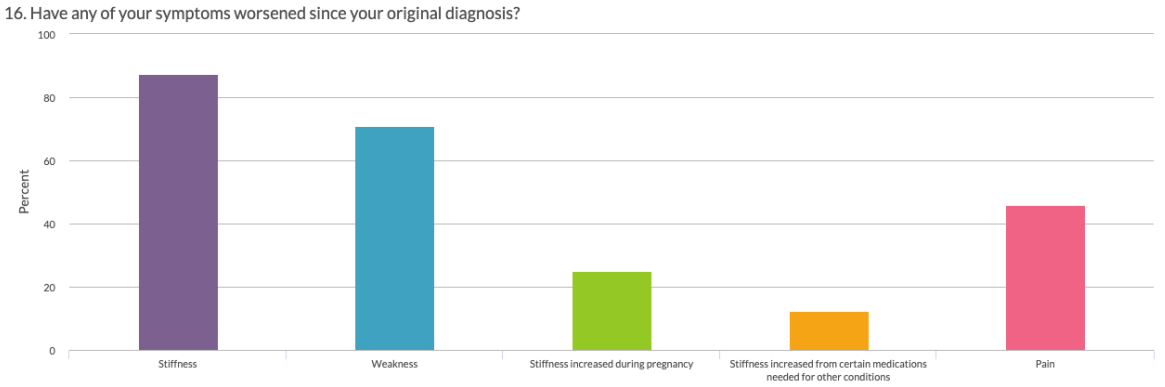
Myotonic disorders are hereditary, rare diseases caused by a malfunction of skeletal ion channels (channelopathy) which share the main clinical symptom of muscle myotonia. Myotonic disorders comprise dystrophic myotonias (DM) and non-dystrophic myotonias (NDM). The DMs are characterized by fixed muscle weakness, systemic features, and dystrophic changes on muscle biopsy. Fixed weakness and dystrophic changes are less common, but can be seen in the NDM, and myopathic changes may be noted on muscle biopsy (12).

Myotonia congenita (MC) is the most common of the NDMs which is caused by a mutation in the CLCN-1 gene encoding for the main skeletal muscle chloride channel CIC-1, as illustrated in Figure 1. Patients often have a hypertrophic, muscular build with percussion myotonia on examination. Patients with MC are most symptomatic during rapid voluntary movements following a period of rest (action myotonia) (16).

Paramyotonia congenita (PMC) is caused by missense mutations of the muscle sodium channel SCN4A gene on chromosome 17. Symptoms suffered by patients can be precipitated by rest after exercise, fasting and cold which is often referred to as “paradoxical myotonia” (16).

The detailed natural history and determinants of morbidity have yet to be prospectively studied (13) and so the underlying disease progression is unknown but data suggests that disease severity worsens over time, where 58% of patients in one study reporting that the severity of their myotonia had increased since the onset of symptoms (17). A UK patient survey (Figure 2) found that 87.3% of patients reported their stiffness and 70.8% reported their weakness had worsened since diagnosis (2).

Figure 2: UK NDM patient survey (November, 2019) – Worsening of symptoms since diagnosis(2)



Value	Percent	Responses
Stiffness	87.5%	21
Weakness	70.8%	17
Stiffness increased during pregnancy	25.0%	6
Stiffness increased from certain medications needed for other conditions	12.5%	3
Pain	45.8%	11

B.1.3.2 Incidence and prevalence

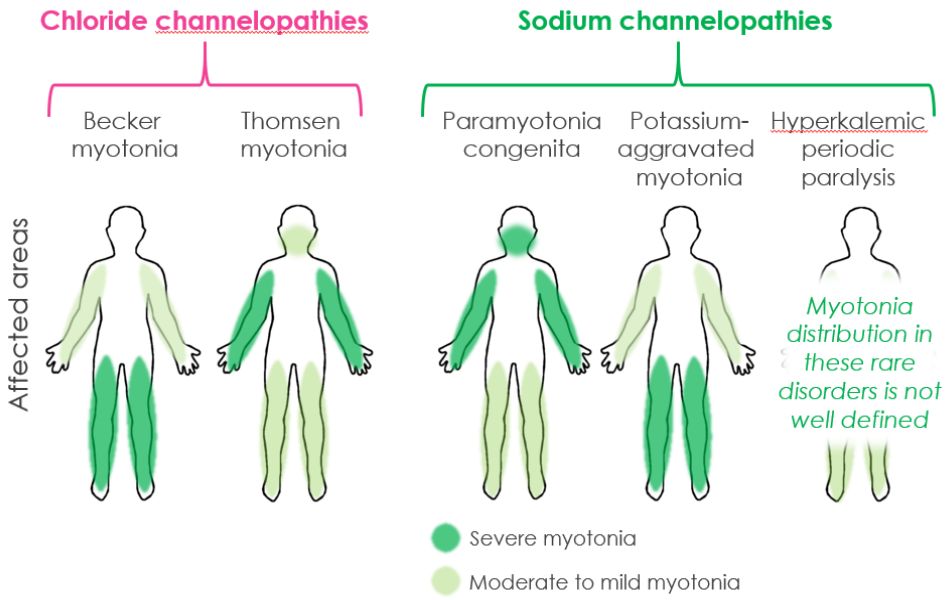
Non-dystrophic myotonias are less common than dystrophic myotonias, with the prevalence in England estimated at 0.75 per 100,000 people (18) equating to 330 adults in England with NDM. There are no incidence figures available for NDM.

B.1.3.3. Clinical presentation of myotonia

The primary symptom of NDM disorders is skeletal muscle stiffness caused by genes coding for skeletal ion channels i.e. myotonia. 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. Additional common symptoms include pain, weakness and fatigue (13).

The location and severity of the myotonia differs between the different clinical phenotypes of the NDM disorders, as shown in Figure 3 which highlights that in some forms of NDM, the most severe sites affected are the legs, (e.g. Becker myotonia) while in others, the legs are less severely affected while other areas (arms, face) are more severely affected by myotonia. However, whilst the figure below illustrates the typical sites of the body that are affected for the different phenotypes this can vary. Experts consulted by Lupin agreed the figure below is a reasonable representation of the disease but stated there can be heterogeneity in the severity in the parts of the body affected across the different channelopathies.

Figure 3: Patterns of myotonia in NDM (13, 15, 19)



The muscle stiffness that patients typically present with is with an absence of severe fixed weakness or muscle wasting which is in contrast to the DMs. Patients with DM present with progressive muscle weakness as well as multisystem involvement (16).

Age of onset of NDM symptoms is typically in infancy or childhood, although onset in adults is also seen (17). Generally, NDMs do not affect survival in adults, however, they can cause significant lifetime morbidity which affects an individual's health-related quality of life (HRQoL). Patients with muscular expressed, pathogenetic channelopathies experience associated symptoms of muscle stiffness, pain, or weakness, fatigue, inability to relax a tight grip or to stand and/or sit with ease, are unable to walk fast when needed and likeliness of falls in varying degrees in each of the different forms of the disease (12, 17, 19, 20). The length of time that a myotonic attack will last can range from seconds to minutes, and it can be anything from slightly uncomfortable to completely disabling (13, 21). In patients where the muscles for swallowing are affected by myotonia, it is possible that difficulties in swallowing increase the risk of aspiration, which increases the risk of pneumonia. The unpredictability of the NDM episodes is likely to cause significant anguish for patients and their families. Furthermore, patients with NDM can experience significant lifetime morbidity due to stiffness and pain related to myotonia.

B.1.3.4. Diagnosis

Diagnosis of non-dystrophic myotonias involves the assessment of symptoms as well as medical history, assessment of muscle hypertrophy, examination of the patient and family members, electrodiagnostic testing, as well as judicious confirmatory laboratory and genetic tests (10) to exclude other causes of myotonia, including DM and Pompe disease.

In England confirmatory genetic testing of non-dystrophic myotonia requires highly specialised services for its diagnosis and management.

Section 48 of the Manual for Prescribed Specialised Services 2017/18 (22) and the NHS Standard Contract for Diagnostic Service for Rare Neuromuscular disorders describe the diagnostic services for muscle channelopathies (6), and the accompanying patient advice and initiation of treatment which are provided by the one Highly Specialist Rare Neuromuscular Disorders Centre in the UK, namely the National Hospital for Neurology and Neurosurgery (NHNN), Queens Square Centre for Neuromuscular Diseases, London (23).

Many patients report experiencing substantial delay in seeking clinical help for symptoms and obtaining a diagnosis (6). In one study, the mean duration to diagnosis was in the order of approximately 8 to 12 years (17) and in a recent UK patient survey only 29.6% of patients received a diagnosis of NDM within 5 years (2), which can add significant additional costs to the NHS. Research by Imperial College Health Partners found that the average cost per patient for a person with a rare disease during the 10 years prior to diagnosis was £13,000 (24).

B.1.3.5. Impact on quality of life

Whilst there is little evidence (due to a lack of natural history studies) that NDM patients have a reduced life-expectancy compared to the general population, myotonic symptoms result in a significant impact to daily living and also mental health. Episodes of myotonia (attacks) in NDM may be experienced as frequently as daily by NDM patients (17). Treatment for myotonia

is focused on reducing the involuntary muscle action's potential bursts without blocking the voluntary muscle stimulation. It is important that patients with potassium-aggravated myotonia and paramyotonia congenita modify their lifestyles to avoid the triggers of their diseases such as potassium ingestion or cold temperatures (25).

Similarly, the mainstay for symptomatic management in NDM focuses on avoiding activities that trigger myotonic responses. Patients tend to avoid triggers such as the cold, stressful situations (e.g. presenting at meetings), anxiety about going to new places where may need to walk up or down stairs or avoiding such places where there may be many stairs (e.g. theatre) leading to a more sedentary lifestyle (Appendix L and (2)). Sudden forceful contractions are to be avoided, and instead, a gradual increase of muscular exertion is used to promote warm-up before developing symptomatic muscle stiffness in chloride channelopathies (15). Even getting up from a seat is also a problem, especially if the patient has not been able to warm their muscles up first (see Appendix L). While these myotonia episode prevention strategies may seem logical, they are not always pragmatic options and they too impact on the patient's daily activities. Such strategies effectively form best supportive care (BSC) for patients with NDM and many will have learnt these by themselves over many years and tried to implement them prior to diagnosis by a specialist.

Disease burden is constant and lifelong, and severity of symptoms are perceived by patients to increase over the years (17). In a cross-sectional study, 62 NDM patients, all off treatment, completed a standardised interview. All patients complained of myotonia with over 90% experiencing myotonia on a daily basis. Fifty-eight percent of patients claimed the severity of their myotonia had increased in severity since symptom onset (17).

Disability rates in NDM are high and associated with substantial restrictions and impact on daily living, resulting in patients being dependent on others at unpredictable times. The effects of NDM may result in patients experiencing crippling disability from their lack of strength (19). In the pivotal phase III study of mexiletine in NDM (MYOMEX), only [redacted]% of patients could feed, [redacted]% could dress, [redacted]% could climb stairs and [redacted]% of patients could undertake their own daily hygiene needs normally, respectively at baseline. [redacted] percent and [redacted]% of patients could speak and write normally and only [redacted]% described the ability to walk as normal (1). The baseline scores for each of the disability categories highlight the significantly disabling impact of disease (Figure 4).

Figure 4: Proportion of MYOMEX patients reporting a score of 0 (no disability) on the disability rating scale

In a Dutch cross-sectional study of 62 untreated patients with genetically confirmed NDM, 63% reported muscle weakness and 47% experienced painful myotonia (17, 26). Myotonia and painful myotonia was described as severe (score ≥5 on a numerical rating scale of 1 to 10) in 70% and 77% of patients respectively (26). Mobility impairments, such as difficulty climbing stairs (80%) , standing up quickly (73%) and running (82%), were reported by patients in this study (26). A recent UK patient survey (2) also found that NDM caused anxiety (65%), injuries from falls (69%), inability to participate in sports (65%) and challenges in using public transport (57%). Difficulties in tasks such as preparing meals, typing, bathing and dressing were also reported, affecting 19-35% of patients (Figure 5).

Figure 5: UK NDM patient survey (November, 2019) - How does myotonia affect your daily life? (2)

Value	Percent	Responses
Public transportation is a challenge	57.7%	15
School settings cause stress (stairs, hand fatigue when writing, awkward gait, falls, etc)	53.8%	14
Hard to find employment that accommodates issues caused by stiffness	26.9%	7
Difficulty driving a car to work or store	11.5%	3
Difficulty typing	23.1%	6
Cannot participate in most sports	65.4%	17
Cold exposure makes symptoms worse	84.6%	22
Bullied or teased by classmates or coworkers	23.1%	6
Social activities are restricted because of stiffness	61.5%	16
Anxiety related to negative experiences (falling, shaming, bullying)	65.4%	17
Injuries from falls	69.2%	18
Certain foods worsen myotonia	23.1%	6
Difficulty lifting (babies and toddlers, groceries, boxes at work, etc)	50.0%	13
Difficulty preparing meals	19.2%	5
Difficulty bathing	34.6%	9
Difficulty dressing	23.1%	6
Other - please describe (click to view)	19.2%	5

The MyoPath survey, completed by 37 patients with NDM, indicated that therapy was required by 67% of patients to allow muscle warming before physical exertion and 50% to improve emotional well-being (27).

The MyoPath survey (27) also found that patients who reported treatment with mexiletine stated that it improved their ability to work or attend school, their overall mobility including taking public transplant or driving a car, completing activities of personal care for themselves and performing household tasks relating to their childcare responsibilities. In fact, respondents reported a significant or drastic improvement in the following as a result of mexiletine:

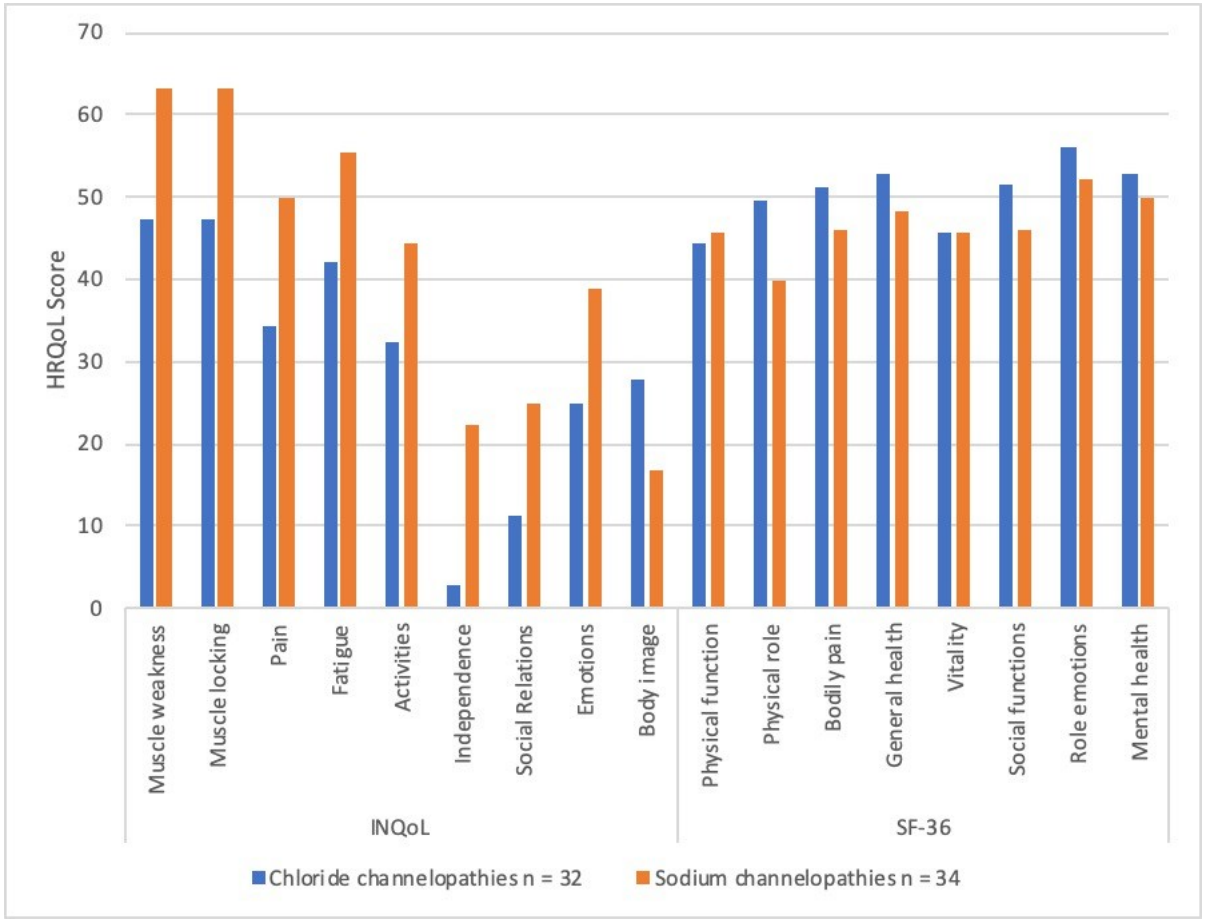
- 72% of patients in the ability to work
- 75% in ability to exercise or play sports
- 85% in overall mobility (e.g. leaving house or taking public transport)
- 82% ability to drive car
- 80% ability to take care of my child
- 77% ability to socialise and communicate with others (e.g. speaking in public, shaking hands)
- 66% ability to do tasks independently (e.g. dress, brush hair, brush teeth, tie shoes, feed myself)
- 91% emotional well-being

- 82% confidence in my abilities

Health related quality of life instruments in NDM

Trivedi et al (15) conducted a quality of life QoL study in 95 patients of which 32 and 34 were confirmed to have chloride channelopathies and sodium channelopathies, respectively - the remaining patients had myotonias unrelated to NDM. It should be noted that a significant number of these patients were already on treatment and so cannot be referred to as 'untreated' at baseline. The researchers used two measures of HRQoL to evaluate the impact of NDM on daily living – the Individualized Neuromuscular Quality of Life Questionnaire (INQoL) and the Short Form Survey, SF-36. The results are shown in Figure 6 which demonstrates that the channelopathies in NDM significantly impacts negatively on QoL, restricting daily life, particularly with respect to muscle weakness, muscle locking (myotonia, stiffness), pain and fatigue (15).

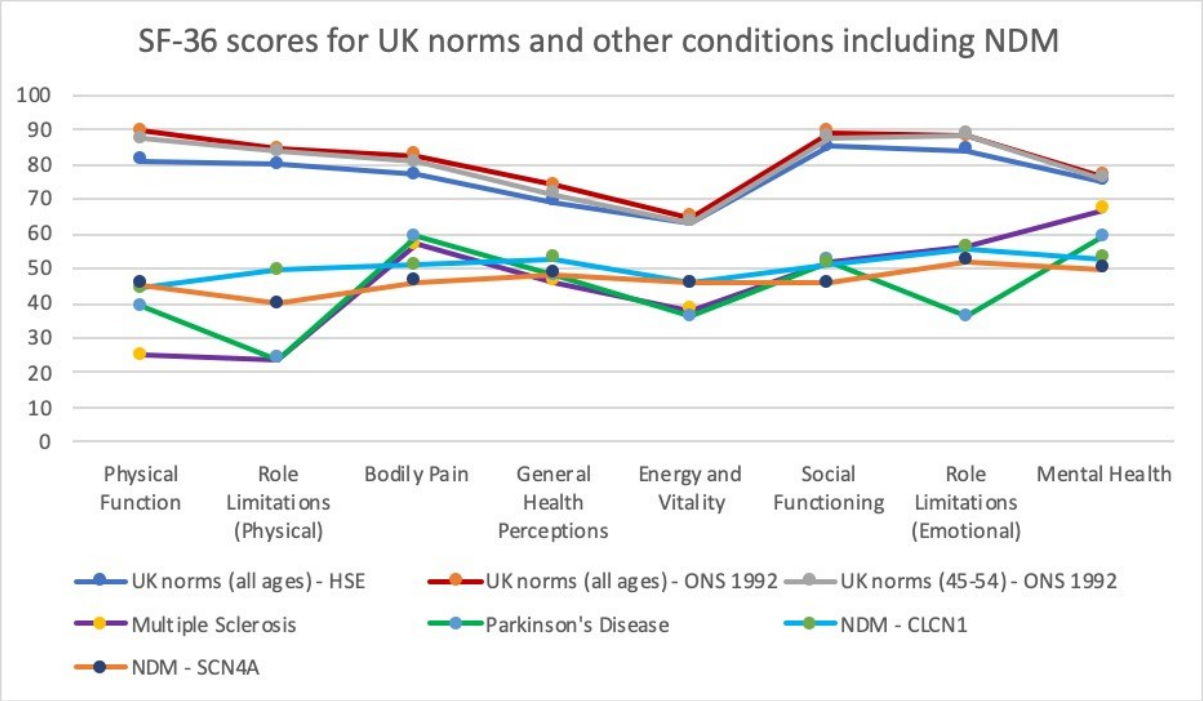
Figure 6: Quality of life data in NDM using INQoL and SF-36(15)



INQoL: The higher the score, the worst is the perception of the patient's QoL [The range of responses were from 2.78 (low impact) for 'Independence' in chloride channelopathies to 63.2 for 'Muscle weakness' and 'Muscle locking sodium channelopathies]
SF-36: The lower the score, the more disability. HRQoL = health related quality of life

Whilst generic measures of HRQoL that are applicable across multiple diseases such as the Short Form Survey, SF-36, are helpful for broad comparisons they may fail to address clinically important aspects of the disease impact of specific disorders (28). Figure 6 suggests a lack of variability in QoL between channelopathies and across domains when SF-36 is used to assess QoL. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability, the higher the score the less disability i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability (29). By comparing the SF-36 scores for patients with NDM to average UK SF-36 norms for people aged 50-59 years Figure 7 (30), it is evident that the impact of NDM is throughout all dimensions of QoL assessed by SF-36. Patients included in the NDM QoL study had a median age of 42 years and 46 years for chloride channelopathies and sodium channelopathies, respectively, yet had markedly lower median scores (worse QoL) in all the domains, including mental as well as physical health. The average SF-36 scores for NDM patients are similar to that recorded for patients with multiple sclerosis and Parkinson's disease as shown in Figure 7.

Figure 7: Mean scores for SF-36 dimensions for UK norms Multiple Sclerosis, Parkinson's disease and median SF-36 scores for non-dystrophic myotonia



HSE – Health Survey for England (HSE) 1996; ages 16+ (n=16,443) (31)
ONS – British ONS Survey 1992 (n=2,056 of which 9% were from Scotland) (32)
Multiple Sclerosis (n=636) (28)
Parkinson's Disease (n=227) (28)
NDM – non-dystrophic myotonia (n=34 chloride channel mutations – CLCN1; n=32 sodium channel mutations – SCN4A)(15). A significant number of these patients were already on treatment on entering the study.

However, for NDM, such generic measures are unable to effectively capture the disease impact of muscle weakness and muscle locking presented above so will not represent the true impact on quality of life for patients with NDM.

The Individualized Neuromuscular Quality of Life Questionnaire (INQoL) is a patient-reported outcome questionnaire that describes the disease-related impact of neuromuscular diseases on patients (33, 34).

It is constructed of 4 main domains that are further divided into 12 subdomains. Each subdomain is composed of questions that vary in number from 3 to 14 items. Responses are sought on a 6 to 7-point Likert scale. Raw data are converted to a score of 0–100 for every subdomain, with higher scores indicating a greater impact on QoL. 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)
- Overall QoL (overall INQoL-QoL is an aggregation of parts of 5 subdomains (activities, independence, social relationships, emotions, and body image) (35).

In summary, INQoL includes 45 items, 10 sections, yielding 11 scores and one total score.

The INQoL has the advantage of recording specific disease symptom impacts omitted by the SF-36 questionnaire such as locking, independence and body image (34, 36). INQoL also has the advantage that the effects of symptoms are separated from questions about life domains. This separation allows “shifts” in patients’ internal standards to be identified if satisfaction with life domains has altered independently from a change in perceived symptoms. Sansone and colleagues concluded that INQoL was an appropriate measure because *“…it can quantify the impact of muscle symptoms that are specific to this group of patients (e.g. myotonia, muscle pain)”* (33). Trivedi and colleagues described INQoL as *“a more relevant instrument for determining symptom impact on quality of life in non-dystrophic myotonia compared with the generic SF-36”* (15). This is further confirmation of Figure 6 which shows SF-36 to be less capable of capturing disease nuances when compared with INQoL.

The inability of SF-36 to assess myotonia is particularly important as Sansone and colleagues state that *“…myotonia should be the treatment target for patients…and improvement of myotonia should be the primary outcome measure …”* (33).

With regards to sensitivity of a QoL measure, some SF-36 items are considered not relevant to muscle disease and could easily be influenced by other factors (34). Sansone and colleagues concluded that INQoL was more capable of capturing the *“physical limitations owing to the muscle condition”* than SF-36. INQoL also assesses *“the extent by which [myotonia] has a detrimental effect on QoL perception. This [enabled the authors] to pick out differences amongst the channelopathies that are not captured by SF-36 alone.”(33).*

experts consulted by Lupin unanimously agreed that INQoL more relevant and appropriate to capture the impact on the quality of life of NDM patients compared to SF-36 (Appendix M).

Qualitative insights on the impact of NDM on quality of life

There is a misconception that NDM is not impactful on the quality of life of patients. However, this is not the case. Myotonia has an important and meaningful impact on the quality of life of patients with adults often modifying their behaviour to compensate for their myotonia. The following insights from patients with NDM have been obtained from the MyoPath survey (27) (2018) and a Facebook group (37) which illustrate the impact NDM has on a patient's day to day living.

Patient Impact Verbatims from the 2018 MyoPath Survey (27)

- 'Lack of dexterity, movement'
- 'Myotonia symptoms increase under pressure & stress – i.e. when giving a presentation at work'
- 'Total desperation – like being paralyzed'
- 'Difficult to breathe'
- 'Trouble swallowing – trouble eating because cannot open jaw'
- 'Driving a car is out of the question'
- 'Difficulties at school - Bullying – social isolation – inability to participate in sports'
- 'Challenges with independence' – working, walking, climbing stairs, speaking, difficulty tying shoes, handling hot foods, eating/drinking cold foods – doing simple tasks
- 'Difficulty functioning on cold days'
- 'Always feeling on guard – being careful not to fall or have an accident'

Facebook group (37)

> *I hear many about public transportation. It often starts with children riding a school bus. Because our legs freeze up on stairs, this can be quite dangerous both boarding and unboarding. Kids especially are impatient and may shove someone that isn't going as quickly as they like. Even drivers can be quite rude. Riding the underground can have similar issues because of the press of people as you move forward. My great-grandfather with myotonia was actually hit by a train and killed. He was walking along a platform and apparently lost his balance when he was startled (sudden loud noises can do that or a sudden shove) and fell in the path of the train.*
>
> *Escalators in shopping centres are quite dangerous for us, both getting on and hopping off. And any time adrenaline levels go up because of anxiety like anticipating a problem, it will make the myotonia even worse. Something like stubbing a toe on an irregular sidewalk can call someone to fall headlong. With the dominant form of MC*

we can usually throw out our arms to catch ourselves, but in the recessive form it is a total body freeze and that has caused many head injuries for people with myotonia.

I was speaking to a young man last week who went in for a job interview. We have to keep moving our legs and flexing our hands to keep them warm if we know we're going to be required to stand up and walk smoothly or if we are going to be shaking hands with someone. He was so humiliated because of having to sit in a room full of job applicants and look like he had a nervous disorder. Often when we shake hands or grasp a doorknob, it takes several seconds for us to release the grip. This obviously doesn't make a good first impression on a prospective employer.

Being in a receiving line can truly be a nightmare. I was so afraid of having to walk down an aisle for my wedding and having to shake hands with everyone that I decided against having a large ceremony even when I was a teenager. Social activities can be very stressful because you are always having to anticipate what might make you stiff suddenly. I even avoided birthday parties as a child because a balloon popping might make me fall. These things are all minimised with effective medications.

Probably the biggest concern expressed to me is from parents with myotonia who are unable to respond quickly in an emergency or dangerous situation, for instance a toddler starting to run into the street. Mothers are often afraid to carry their babies up and down stairs. They are also quite concerned about allowing their children to participate in sports because of the greater risk of injury. The constant isometric force of pushing against stiff muscles create hypertrophied muscles to the point that one couple I know was turned in to social services and investigated for "making their toddler lift weights."

I've heard about many close calls related to swimming. Because even slightly cool water can reduce the enzyme activity of the chloride channel, this often affects us. If myotonia becomes severe, it can affect the diaphragm and breathing becomes difficult which causes even more adrenaline to be released from the panic. A lot of our members won't go near water. Playing in the snow or getting chilled can also cause quite severe stiffness. So many childhood activities are stressful and avoided.

Myotonia affecting the face seems to be more common with the dominant form. I have often been mistaken as drunk when trying to talk if my stiffness was bad because the tongue is a skeletal muscle affected by myotonia. Choking is very common in all types. The upper third of the oesophagus is skeletal muscle. We usually learn to take a few sips of water to try to get the muscles warmed up before swallowing larger bites of food. The eyes are often slow to change direction when you move them suddenly. And as I mentioned, eyelids are often quite stiff after sneezing or if a child is crying. In fact, that's often one of the first indications of myotonia in an infant or toddler...their eyes seem to get stuck closed when they cry.

A visit to the dentist is quite traumatic for many because any anaesthetic with a vasoconstrictor will immediately worsen myotonia in the jaw and it's very hard to open

it all the way. Of course, the most dangerous condition for us is the malignant hyperthermia (MH) type reaction from muscle paralysing agents like succinylcholine. We are also quite susceptible to cardiac arrest from hyperkalaemia during surgery if the wrong anaesthetics are used. I have never seen a study to determine if regular use of a sodium channel blocker like mexiletine might reduce the risk of MH in an emergency situation where immediate intubation is needed. But I suspect it would make a difference.

The saddest thing for me is to hear from all the young people who are actually suicidal because of the social stigma, bullying and despair related to this. When a condition is much more obvious like severe muscle wasting with myotonic dystrophy or having to be confined to a wheelchair, people tend to be more accepting and understanding. But when you look like you're an athlete because of the muscle hypertrophy and have no coordination or strength to match, it's quite humiliating. Because of the difficulties for some in trying to get and keep a job, many give up and go on disability even though they would love to work. Depression is much more common in men since they often feel they have no hope for supporting a family or even finding a mate who will accept their limitations. I have seen people's lives completely change when they are able to get and maintain medication to relieve the myotonia. But any interruption in that schedule due to shortages, doctors not renewing the prescription, etc. can be devastating. This happened several years ago when Boehringer quit manufacturing mexiletine in Europe and it was suddenly unavailable.

The final point regarding the ability to obtain mexiletine is supported by the MyoPath survey findings, where the ability to access mexiletine ‘drastically’ or ‘substantially’ reduced frequency of falling in 77% of patients and disruption in mexiletine treatment harmed 85% of patients (27, 38).

Patients with NDM feel a strong sense of emotional anguish. Other people do not understand NDM patients; they don’t understand why someone who looks normal, or even muscular, is unable to do what would be considered very simple things such as getting a card from their wallet. Others believe people with NDM are faking it. Significantly triggers such as cold, stress/ adrenaline, anxiety, sudden movement or shocks (noise), food, pesticide smells, movement or rest affect severity and frequency of symptoms and as such patients develop coping strategies to avoid the symptom triggers (avoid swimming, exercise, climbing stairs, theatre, award ceremonies, crowded or noisy areas) i.e. they live with the constant anxiety of needing to prepare themselves for a myotonic episode – see Appendix L for further details.

In summary, whilst NDM is not life limiting it has profound effects on patient’s quality of life which appear to be underappreciated from not only from a physical but also significantly from a psychological aspect.

B.1.3.6. Clinical pathway of care

As described above diagnosis is based on clinical evaluation with the genetic diagnosis and management recommendations confirmed via the NHS England commissioned highly

specialised service at NHNN, Queens Square Centre for Neuromuscular Diseases, London. Patients may have been seen by other specialists such as orthopaedic or mental health specialists and had unnecessary investigations e.g. MRIs over a period of many years before they are seen by a neurologist and the diagnosis of NDM is made, see Appendix M.

Once the diagnosis is made, mexiletine treatment is invariably initiated by a neurologist after discussion with the patient at either the NHNN, Queens Square Centre for Neuromuscular Diseases, London or one of the neurology centres commissioned by NHS England as a specialised service. By this stage patient's symptoms will be severe enough that any strategies they have developed to cope with their condition such as avoiding triggers or performing muscle warming routines (effectively best supportive care) will not be sufficient and the patient may benefit from treatment. Often physiotherapy, occupational or speech therapy might be required as part of supportive care but access to services is variable and often specialist physiotherapy input is required to support patients (Appendix M).

B.1.3.7. Position of mexiletine within pathway of care

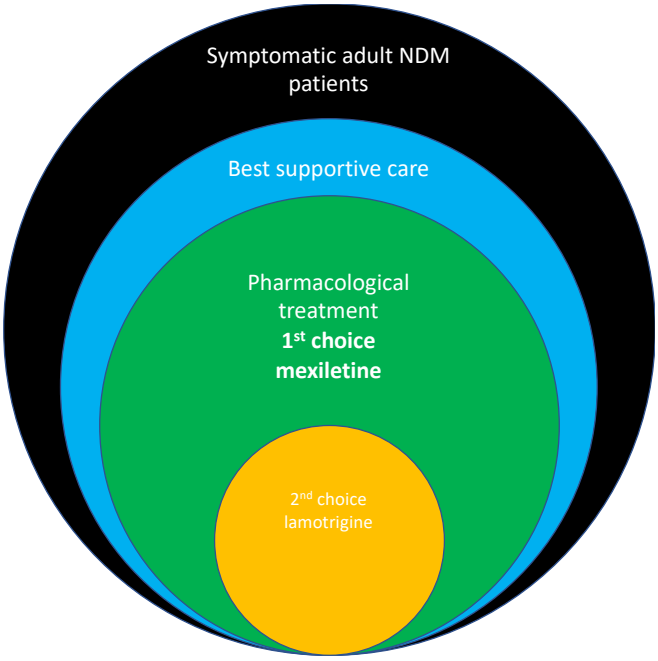
There are no NICE guidelines for the management of NDM and neither are there currently any over-arching, international treatment guidelines for NDM.

Mexiletine is listed as first-choice in the S1 guidelines of the German Society of Neurology, recommend the use of mexiletine as a first-choice treatment in patients with NDM (4), on the website of the NHNN, Queens Square Centre for Neuromuscular Diseases, London (23), and clinical experts have advised that current first-choice treatment in England is mexiletine (Appendix M)(3, 39). This is re-iterated in the NHNN and Muscular dystrophy UK responses to the NICE draft scope stating that mexiletine is currently first line treatment and standard of care for NDM, and has been used clinically in the UK for at least 10 years (40) and confirmed in Lupin's clinical expert elicitation (see Appendix M) and market research (3, 39).

Historically, medications of various pharmacological classes have been tried in the treatment of myotonic symptoms (41). These include sodium channel blockers which have been found to reduce sarcolemmal excitability, yet despite all attempts, none aside from mexiletine have demonstrated substantial benefits in clinical studies. Antiarrhythmics such as flecainide, procainamide and tocainide have shown some effects on sodium channel function and some efficacy on myotonic disorders but with an unfavourable safety and tolerability profile (42-44). Antiepileptics such as phenytoin and carbamazepine with sodium blocking properties have also been evaluated in myotonic disorders but only either as case reports or case series and no thorough clinical trials in NDM have been reported (8, 45).

The NICE Final Scope stated that lamotrigine is the most used alternative treatment and that other antiarrhythmic and antiepileptic medicines that have been used off-label do not form part of standard care. Figure 8 illustrates the feedback that was received from the NICE draft scope responses and listed in the final scope.

Figure 8: Illustration of pharmacological treatment as informed by NICE Final Scope



Lamotrigine as a comparator in NICE Final Scope

It was highlighted to Lupin during the Decision Problem meeting that lamotrigine as a comparator should be addressed as it is listed in the Final Scope based on feedback during the scoping process (40). In the NICE Final Scope it is stated that *"lamotrigine is the most used alternative. Other antiarrhythmic and antiepileptic medicines have been used off-label to manage the symptoms of myotonic disorders. However, this does not form part of standard care."*

It was emphasised to Lupin during the Decision Problem meeting that the NICE Committee would want to consider lamotrigine treatment as established NHS practice in England, irrespective of whether a treatment is licensed or whether it was a first-choice treatment or not, as stated in the NICE guide to the methods of technology appraisal (46). Following this feedback Lupin has met with clinical experts in the UK (see Appendix M), conducted market research (3) and a UK patient survey (2) to identify if lamotrigine is a treatment that is established in NHS practice. Results confirm this is not the case.

Market research involving eight neurology centres in the England and Wales (including the largest centre, the NHNN, Queens Square Centre for Neuromuscular Diseases, London) shows that lamotrigine is not established in practice with less than 3% of patients currently on lamotrigine (Table 3) (3).

Table 3: Current adult NDM patients currently receiving treatment for symptoms of myotonia (November 2019)

Total 371 adult NDM patients **currently under care** of 7 centres providing details of current management of NDM		
Numbers of patients below relate to current adult NDM patients **currently receiving treatment** for symptoms of myotonia, and does not include prior treatments:		
NDM patients **currently** treated:	1st line NDM patients	2nd line NDM patients
Total NDM patients currently treated	**132** (36% of total patients under care across 7 centres)	**78** (21% of total patients under care across 7 centres)
mexiletine	88 (67%)	27 (35%)
phenytoin	30 (23%)	25 (32%)
flecainide	10 (8%)	12 (15%)
acetazolamide	3 (2%)	14 (18%)
lamotrigine	1* (1%)	2 (3%)
Currently untreated patients	**161** (43% of total patients under care)	

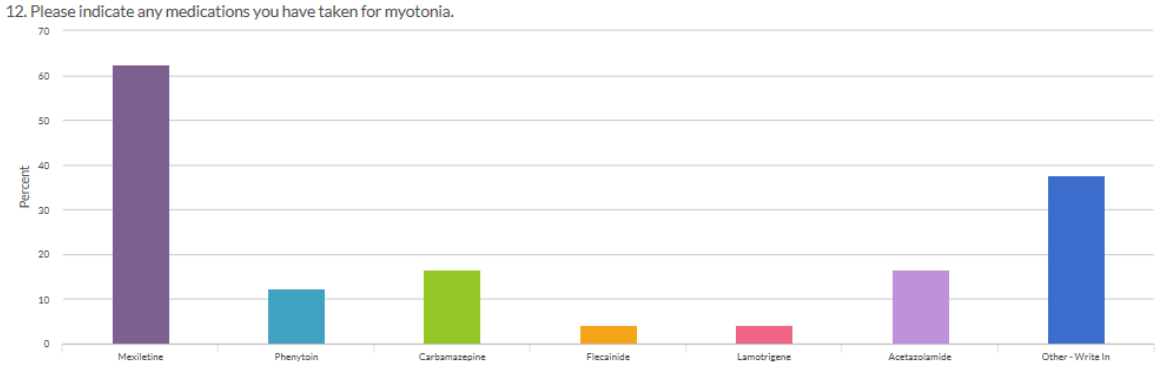
*Patient was already being treated with lamotrigine for depression and when referred for treatment of their symptoms of myotonia, as a result lamotrigine was continued to treat NDM .

NB: 12 patients' current treatment unknown (as question added after interview); excluded from totals above. 222 patients currently treated across 8 centres; 210 patients currently treated across 7 centres. For the one centre who only provided information for patients who had ever been treated, rather than currently treated (n=12 patients), none had ever taken lamotrigine.

NB: above data exclude patients who have been previously treated who have discontinued therapy.

A UK on-line patient survey, conducted in November 2019, found that 62.5% of patients had been treated with mexiletine treatment but only 4.2% of patients (1 respondent) had ever been treated with lamotrigine thus providing additional insight that lamotrigine is not established practice in the UK (2) – see Figure 9.

Figure 9: UK NDM patient survey of reported medication prescribed for myotonia (November, 2019)UK NDM patient survey of reported medication prescribed for myotonia (November, 2019)(2)



Value	Percent	Responses
Mexiletine	62.5%	15
Phenytoin	12.5%	3
Carbamazepine	16.7%	4
Flecainide	4.2%	1
Lamotrigene	4.2%	1
Acetazolamide	16.7%	4
Other - Write In (click to view)	37.5%	9

These data demonstrate that lamotrigine is not a relevant comparator in the appraisal as it is not established practice.

Furthermore,

- Lamotrigine is not recommended as first-line in any guidance and when mentioned, listed solely as second line therapy (4-6) – for use when mexiletine is either contraindicated, ineffective or not tolerated
- There are no randomised/non-randomised clinical trials, that assess the impact of lamotrigine in comparison with established first-line treatment for symptoms of myotonia in NDM patients
- The only available evidence for lamotrigine is a recent RCT by Andersen et al which was conducted between 2013 and 2015 and published in 2017 (8). Despite this the market research does not indicate an increase in use in the UK since that could at all suggest established use in the NHS
- Furthermore the Andersen et al trial lacks common outcome measures and results to enable any indirect treatment comparison with mexiletine NDM RCTs (8) – see Document B, Section B.2.9.1 for further details.

B.1.4 Equality considerations

No issues have been identified regarding equality.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Three randomised clinical trials which evaluated mexiletine were identified by the systematic literature review (SLR) described above. Of these trials, patient level data was available solely for the MYOMEX study. In addition, one retrospective review of a UK centre patient database was identified during the SLR sifting process and is included here as it provides additional insights on real-world use of mexiletine. The three trials and one retrospective review are described below.

The efficacy and safety of mexiletine in NDM has been studied in two independent multi-centre clinical studies (1, 47), and one series of aggregated, double-blind, randomised, placebo-controlled N-of-1-trial (48). The RCTs are further supported by a retrospective chart review from the UK describing the long-term use of mexiletine in NDM (49).

- MYOMEX study - aimed to evaluate the efficacy and safety of mexiletine in NDM (1)
- Statland et al (2012) - aimed to determine the effects of mexiletine for symptoms and signs of myotonia in NDM (47)
- Stunnenberg et al (2018)- an N-of-1 trial, aimed to investigate the effectiveness of mexiletine in NDM (48)

Supportive longer-term data are provided by a retrospective chart review by Suetterlin et al. (2015) (49):

- The study by Suetterlin et al. (49) was a retrospective review of a cohort of patients with large skeletal muscle channelopathy which was genetically confirmed NDM and provides data on long-term mexiletine use with observational data of up to 17.8 years of follow-up.

Table 4: Clinical effectiveness evidence – MYOMEX (NCT02336477) (1)

<table>
<tr><td>Study</td><td colspan="5">Efficacy and Safety of Mexiletine in Non-dystrophic Myotonias (NCT02336477)</td></tr>
<tr><td>Study design</td><td colspan="5">Randomized, double-blind, placebo-controlled, crossover trial (Phase III)</td></tr>
<tr><td>Population</td><td colspan="5">Adults aged between 18 and 65 years with genetically confirmed myotonia congenita and paramyotonia congenita with symptoms affecting at least 2 body segments that impact on at least 3 daily activities. (Intention-to-treat population 26 patients; 13 patients with myotonia congenita and 13 patients with paramyotonia congenita)</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Mexiletine hydrochloride 200 mg once per day up titrated by increments of 200 mg every three days to mexiletine hydrochloride 200 mg three times per day</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>X</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>X</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">Patient-level data was available for this study and the patient group is as per the marketing authorisation which is being evaluated in this submission. Long term effectiveness data also available including average dose used. Suetterlin et al data used for discontinuation rates in base case.</td></tr>
<tr><td>Reported outcomes specified in the decision problem

(outcomes in bold are incorporated into the economic model)</td><td colspan="5">• Score of stiffness severity on a self-assessment scale (100 mm VAS) [Time Frame: 18 days]
• Standardized EMG measures after repetitive short exercise test at cold and long exercise test [Time Frame: 18 days]
• Chair test: time needed to stand up from a chair, walk around it and sit down again [Time Frame: 18 days]
• Clinical myotonia scale - severity and disability scale of myotonia [Time Frame: 18 days]
• Quality of life scale (INQOL) [Time Frame: 18 days]
• CGI efficacy (Clinical Global Impression- Efficacy index) [Time Frame: 18 days]
• Adverse event rates (scenario analysis)</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Average dose (long-term follow-up data) (50)
Compliance rates</td></tr>
</table>

(outcomes in bold are incorporated into the economic model)	

Table 5: Clinical effectiveness evidence – Statland (NCT00832000) (47)

Study	Statland et al. (2012) (NCT00832000)				
Study design	A randomised, double-blind, placebo-controlled crossover phase II study				
Population	Adults aged older than 16 years with clinical symptoms or signs of non-dystrophic myotonia, and myotonic potentials on electromyography (Intention-to-treat population 59 patients; 34 patients with chloride channel mutations, 21 patients with sodium channel mutations, four with no mutation identified)				
Intervention(s)	Mexiletine hydrochloride 200 mg three times per day				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	X
	No	X		No	
Rationale for use/non-use in the model	This study investigated mexiletine in the population to be treated as per the licensed indication and includes some outcomes that are used in the economic model as a scenario analysis to the base case: • Compliance rates • Adverse reaction rates Efforts were made to contact the authors to obtain patient level data but without success.				
Reported outcomes specified in the decision problem	• Patient-reported Stiffness on the IVR [Time Frame: Weeks 3-4 of each period] • Patient Reported Pain on the IVR [Time Frame: Weeks 3-4 of each period]				

	• Patient Reported Weakness on the IVR [Time Frame: Weeks 3-4 of each period] • Compound Motor Action Potentials After Short Exercise Test [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Compound Motor Action Potentials After Long Exercise Test [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Quantitative Measure of Hand Grip Myotonia (Seconds) [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Graded Myotonia by Needle Electromyography - Right Abductor Digiti Minimi [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Clinical Hand Grip Myotonia Evaluation (Seconds) [Time Frame: The end of period 1 (week 4) and the end of period 2 (week 9)] • Clinical Eye Closure Myotonia Evaluation (Seconds) [Time Frame: The end of period 1 (week 4) and the end of period 2 (week 9)] • Graded Myotonia by Needle Electromyography - Right Tibialis Anterior [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Individualized Neuromuscular Quality of Life Scale - Summary Score [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Short Form 36 - Physical Composite Score [Time Frame: Participants who experienced weakness on mexiletine in either period 1 or period 2.] • Short Form 36 - Mental Composite Score [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • **Adverse event rates** (scenario analysis)
All other reported outcomes	• **Compliance rates** (scenario analysis)

Table 6: Clinical effectiveness evidence – Stunnenberg (NCT02045667) (48)

Study	Combining N-of-1 Trials to Estimate Population Clinical and Cost-effectiveness of Drugs Using Bayesian Hierarchical Modelling. The Case of Mexiletine for Patients with Non-Dystrophic Myotonia (NCT02045667)				
Study design	A series of aggregated, double-blind, randomized, placebo-controlled N-of-1-trials, performed in a single academic referral centre.				
Population	Adults with genetically confirmed NDM selected from the Dutch neuromuscular database. (Intention-to-treat population 30 patients; 19 patients with chloride channel mutations, 11 patients with sodium channel mutations)				
Intervention(s)	Mexiletine hydrochloride 200 mg three times per day				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	X
	No	X		No	
Rationale for use/non-use in the model	This study investigated mexiletine in the population to be treated as per the licensed indication and includes some outcomes that are used in the economic model as a scenario analysis to the base case: • Compliance rates (scenario analysis) • Adverse reaction rates (scenario analysis) Efforts were made to contact the authors to obtain patient level data but without success.				
Reported outcomes specified in the decision problem	• Change in patient-reported Stiffness on the IVR [Time Frame: Weeks 3-4 of each period - up to 44 weeks.] • Change in Patient-reported Pain on the IVR [Time Frame: Weeks 3-4 of each period - up to 44 weeks.] • Change in Patient-reported Weakness on the IVR [Time Frame: Weeks 3-4 of each period - up to 44 weeks.] • Change in Patient-reported Tiredness on the IVR [Time Frame: Weeks 3-4 of each period - up to 44 weeks.] • Change in Clinical myotonia bedside-tests (Seconds) [Time Frame: Week 4 of each period - up to 44 weeks.]				

	• Change in Muscle relaxation times measured with quantitative grip myometry (Seconds) [Time Frame: Week 4 of each period - up to 44 weeks.] • Change in Graded Myotonia by Needle Electromyography [Time Frame: Week 4 of each period - up to 44 weeks. • Change in mexiletine serum plasma concentration levels [Time Frame: Weeks 1 and 4 of each period - up to 44 weeks.] • Change in Individualized Neuromuscular Quality of Life Scale - Summary Score [Time Frame: Week 4 of each period - up to 44 weeks.] • Change in Short Form 36 - Physical Composite Score [Time Frame: Week 4 of each period - up to 44 weeks.] • Change in Short Form 36 - Mental Composite Score [Time Frame: Week 4 of each period - up to 44 weeks.] • **Adverse event rates** (scenario analysis)
All other reported outcomes	• **Compliance rates** (scenario analysis)

Table 7: Clinical effectiveness evidence – Suetterlin (49)

Study	Suetterlin et al (2015)				
Study design	Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies				
Population	Genetically confirmed non-dystrophic myotonia or hyperkalaemia periodic paralysis prescribed mexiletine with a minimum of 6 months follow-up.				
Intervention(s)	Mexiletine				
Comparator(s)	Best supportive care				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	X
	No	X		No	
Rationale for use/non-use in the model	Like all NDM RCTs of mexiletine, the available patient-level data which informs the economic model treated patients for short periods. This study presents long term effectiveness and also enables the calculation of an average effective treatment dose in				

	clinical practice (which aligns with that seen in the MYOMEX study and expert feedback), long-term discontinuation rate, as well as adverse event rates which were incorporated into the economic model. Therefore, the results of this study enabled the extrapolation of the outcomes over the model's time horizon.
Reported outcomes specified in the decision problem	• **Adverse event rates** (base case)
All other reported outcomes	• Efficacy was determined by patient report • **Average effective dose** (scenario analysis) • **Discontinuation rates** (base case) • Electrocardiograms (ECGs)

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study methodology

MYOMEX study (NCT02336477) (1)

MYOMEX was a multi-centre, randomised, double-blind, placebo-controlled, crossover (two treatment periods of 18 days), phase III study to evaluate the efficacy and safety of mexiletine for the symptomatic treatment of NDM.

The study inclusion criteria were genetically defined myotonia congenita and paramyotonia congenita; male and female participants aged between 18 and 65 who are able to comply with the study conditions; participants who experience myotonic symptoms severe enough to justify treatment with mexiletine. For the purposes of the MYOMEX study, criteria for patients who experience myotonic symptoms severe enough to justify treatment were considered as those with myotonia that involved at least two body segments (upper limb, lower limb or face) and that had an impact on at least 3 daily activities). This was to ensure that a relatively homogenous patient population was enrolled with respect to myotonia symptoms for the comparison of mexiletine to placebo. Additional inclusion criteria were participants who were drug-naïve or those receiving mexiletine at an effective dosage agreeing to stop treatment at least four days before inclusion; women: non-childbearing potential (i.e., postmenopausal or surgically sterile) or using a medically accepted contraceptive regimen; a pregnancy test

ensuring that they were not pregnant; and normal cardiac exam performed by a cardiologist including electrocardiogram, and cardiac ultrasound (if not done within 3 months before the trial) (1). Participants who experience myotonic symptoms severe enough to justify treatment with mexiletine evaluated:

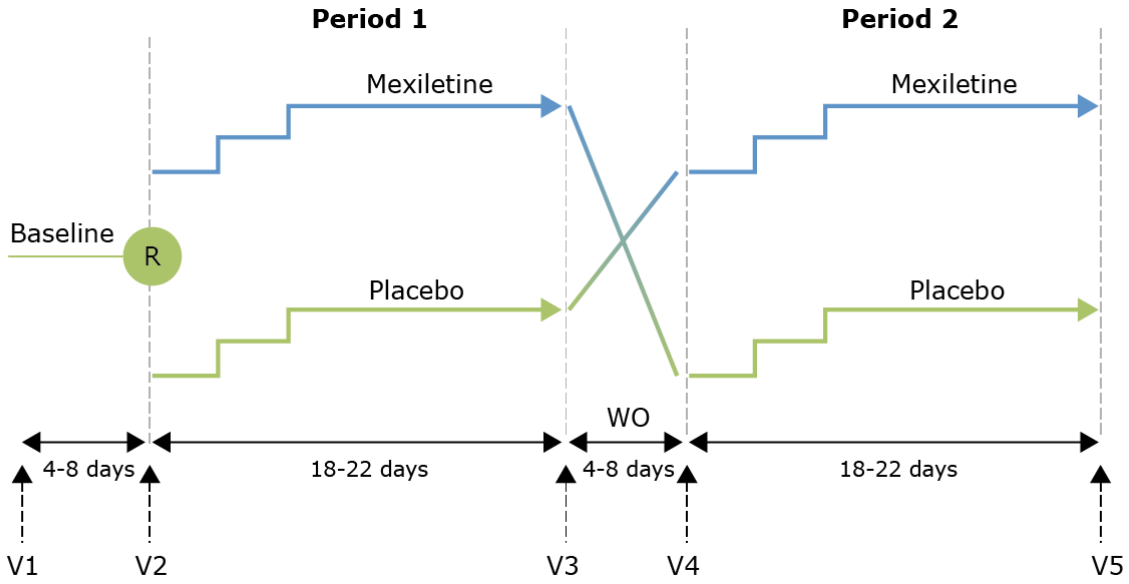
- Clinical criteria: myotonia is considered as severe if it involves at least two segments (upper limb, lower limb or face)
- Disabling criteria: myotonia is considered severe if patients notice impacts on at least 3 of the 7 daily activities listed in the disabling section of the clinical myotonia scale (CMS)

Patients were excluded if they experienced an intercurrent event which could interfere with the muscle function (infection, trauma, fracture); had coincidental renal, hepatic, respiratory, thyroid, other neuromuscular disease or heart disease that would contraindicate mexiletine or interfere with clinical evaluation; used any medications that can interfere with muscle function: diuretics, antiepileptics (sodium channel blockers), antiarrhythmics, corticosteroids, beta-blockers; or were allergic to mexiletine (1).

Subjects were randomly assigned (1:1) to a sequence of treatment (mexiletine/placebo or placebo/mexiletine). Diagnosis was balanced by stratification within both sequences. Mexiletine hydrochloride treatment was started at 200 mg per day (equivalent to 167 mg mexiletine) and up titrated in 200 mg increments every 3 days to reach a maximum total dose of 600 mg mexiletine hydrochloride per day (equivalent to 500 mg mexiletine) in one week, administered as 200 mg mexiletine hydrochloride three times daily (TDS).

The cross-over study design is shown in Figure 10. After a baseline period (four–eight days) to eliminate residual mexiletine from any previous treatment, patients were randomised and received either mexiletine or placebo for 18 days (maximum 22 days; period 1). After a wash-out period of at least four days (maximum eight days), patients switched study drug for a period of 18 days (maximum 22 days, period 2).

Figure 10: MYOMEX Study Design (1)



R: randomisation; V1: screening visit (Day -4); V2: baseline visit (Day 1; start of Period 1); V3: visit 3 (Day 18; end of Period 1); V4: visit 4 (Day 22; start of Period 2); V4: visit 5 (Day 39; end of Period 2); WO: washout;

The primary efficacy endpoint was the change in stiffness as self-reported by patients on a visual analogue scale (VAS). The VAS was constructed as an absolute measure, with a 100 mm straight horizontal line having the endpoints 'no stiffness at all' and 'worst possible stiffness'. The patients' responses were scored on the line to the nearest millimetre (a 100-point scale). A 50% reduction of the primary outcome (VAS) was postulated to be a clinically significant goal.

The secondary efficacy endpoints focused on:

- 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 with the Individualised Neuromuscular Quality of Life (INQoL) scale
- Clinical Global Impression (CGI) Efficacy index
- Preference between the 2 treatment periods and willingness to continue the treatment
- Number of intolerable increases in myotonia severity necessitating withdrawal
- Measure of the compound muscle action potential (CMAP) amplitude decline recorded from the abductor digiti minimi muscle after repeated short exercise test at room temperature and after cooling
- Score of a CMS. This scale comprises two 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 endpoints included adverse event (AE) frequency and severity; changes in clinical laboratory values; changes in vital signs; ECG and CGI Tolerability index.

Note that this study was not powered for subgroup analysis of myotonia congenita and paramyotonia congenita and not pre-specified in the statistical analysis plan.

Additional long-term follow-up after study completion

After completion of the MYOMEX study, patients had the opportunity to immediately continue treatment with mexiletine at a dosage adapted to their clinical response and tolerance to the drug. Long-term data on the patients treated at site 01 (Hôpital La Pitié Salpêtrière Paris), has been collected for up to 94 months after the completion of the study (50).

Table 8: MYOMEX Study design (NCT02336477) (1)

Study Acronym/ I.D.	MYOMEX, NCT02336477
Primary study reference	Clinical Study Report: Efficacy and safety of mexiletine in non-dystrophic myotonias. Data on file (1).
Trial design	A multi-centre, randomised, double-blind, placebo-controlled, crossover (two treatment periods of 18 days with washout period), phase III study
Participants (Key Inclusion criteria)	• Genetically definite MC and PC • Male and female participants, age between 18 and 65 who are able to comply with the study conditions • Participants who experience myotonic symptoms severe enough to justify treatment
Participants (Key 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 will contraindicate mexiletine or interfere with clinical evaluation • Use of any of the following medications that can interfere with muscle function: diuretics, antiepileptics (sodium channel blockers), antiarrhythmics, corticosteroids, beta-blockers, • Allergy to mexiletine
Settings and locations	Secondary care. Six centres in France (Paris, Lyon, Marseille, Nice, Nantes, Anger)

Trial drugs, n, dose, duration, timing	Drug: Mexiletine Blisters of 10 capsules of 200 mg mexiletine hydrochloride. Mexiletine was started at 200 mg / day (1 capsule to be taken at the beginning of the meal) and increased by 200mg every 3 days to reach a maximum of 600mg / day in 3 taken in 1 week. The duration of each treatment period was 18 days minimum (maximum 22 days). Drug: placebo
Concomitant medications	Six patients were on paracetamol, opioids
Primary efficacy outcomes	Score of stiffness severity on a self-assessment scale (100 mm VAS)
Secondary efficacy outcomes	• Standardized EMG measures after repetitive short exercise test at cold and long exercise test [Time Frame: 18 days] • Chair test: time needed to stand up from a chair, walk around it and sit down again [Time Frame: 18 days] • Severity and disability scale of myotonia to be validated [Time Frame: 18 days] • Quality of life scale (INQoL) [Time Frame: 18 days] • CGI efficacy (Clinical Global Impression- Efficacy index)
Safety outcomes	• Adverse event (AE) frequency and severity • Changes in clinical laboratory values • Changes in vital signs • ECG • CGI Tolerability index
Pre-planned subgroups	There were no pre-planned subgroups.
Duration of follow-up / loss to follow-up / cross over	After a baseline (wash-out) period (4-8 days) to eliminate residual mexiletine for patients who have received any previous treatment, patients were randomised and received either mexiletine or a placebo for 18 days (maximum 22 days; period I). Following a second wash-out period of minimum 4 days (maximum 8 days), patients received the study product they did not receive during period I for 18 days (maximum 22 days; period II).

	Additional follow-up after study completion After completion of the MYOMEX study, patients had the opportunity to immediately continue treatment with mexiletine at a dosage adapted to their clinical response and tolerance to the drug. Follow-up data, collected for up to 94 months are available for the patients treated at site 01 (Hôpital La Pitié Salpêtrière Paris). The available information was provided to the EMA in a narrative format.

Statland et al (NCT00832000) (47)

This was a randomised, double-blind, placebo-controlled crossover phase II study, conducted at seven neuromuscular referral centres in four countries – USA, Canada, England, and Italy and included participants with genetically confirmed NDM or patients who had clinical features of NDM but negative myotonic dystrophy DNA testing. The objective was to determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDM.

Patients already taking anti-myotonic treatments were first required to complete a washout period. Participants were randomised to mexiletine hydrochloride 200 mg capsules (corresponding to 167 mg mexiletine) three times a day (TID) or placebo capsules TID for four weeks. After a one-week washout period, they were placed on the opposite intervention for four weeks. Patients were randomly assigned the order of the two treatments in a 1:1 ratio, stratified by institution.

The study inclusion and exclusion criteria were that eligible participants should be at least 16 years of age; patients should have clinical symptoms or signs of NDM and myotonic potentials on electromyography; discontinuation of anti-myotonic agents medications for a wash-out period equal to seven times the half-life of elimination prior to their baseline visit; patients who do not have specific contraindications to taking mexiletine (cardiac conduction defects, hepatic or renal disease, or heart failure).

Patients were randomly assigned in a 1:1 ratio to 200 mg mexiletine hydrochloride or placebo three times per day for four weeks, followed by the opposite intervention for four weeks, separated by a 1-week wash-out period.

Eligible participants were aged at least 16 years, had genetically confirmed NDM or clinical symptoms or signs of NDM but negative myotonic dystrophy DNA testing, and had myotonic potentials on EMG. Patients taking anti-myotonic agents were required to discontinue medications for a washout period equal to seven times the half-life of elimination before their baseline visit.

The primary endpoint was stiffness severity score reported by patients 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 symptoms were assigned a score of 0 for analysis).

The secondary endpoints required participants to assess symptoms were:

- Patient-reported pain, weakness, tiredness
    - Measured daily over the 3rd and 4th weeks of treatment period using the IVR
- Clinical myotonia bedside assessment of eyelid and fist function measured five times in sequence at each clinic visit using a stopwatch to measure response times, participants were asked to:
- Squeeze their eyes closed for 5 seconds then rapidly open them
    - Make a tight fist for 5 seconds then rapidly open
    - Handgrip myotonia
- Using a commercially available grip dynamometer and computerised capture system, the maximum voluntary contractions 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
    - The maximal post-exercise decrement in CMAP after short and long exercise
- Myotonia on needle electromyography was graded on a 1+ to 3+ scale in the right abductor digiti minimi (hand muscle) and right tibialis anterior (lower leg muscle)
- Health-related quality of life using the SF-36 and the INQoL

The safety endpoint was the number of adverse events.

Table 9: Statland et al Study design (NCT00832000) (47)

Study Acronym/ I.D.	NCT00832000
Primary study reference	Statland et al. Mexiletine for symptoms and signs of myotonia in non-dystrophic myotonia: a randomized controlled trial. JAMA. 2012 Oct 3;308(13):1357-65. doi: 10.1001/jama.2012.12607.
Trial design	Randomised, double-blind, placebo-controlled crossover phase II study
Participants (Key Inclusion criteria)	• Aged at least 16 years • Clinical symptoms or signs suggestive of myotonic disorders • Presence of myotonic potentials on electromyography (EMG) • Participant in the Non-Dystrophic Natural History study (RDCRN 5303)‡ or a new patient with confirmed non-dystrophic myotonia ‡ Only one publication (15) reported data from this natural history study

Participants (Key Exclusion criteria)	• Other neurological conditions that might affect the assessment of the study measurements • Genetic confirmation of DM1 (more than 50 repeats of CTG) or DM2 • Existing cardiac conduction defects, as evidenced on EKG, including but not limited to the following conditions: malignant arrhythmia or cardiac conduction disturbances (e.g., second degree AV block, third degree AV block, or prolonged QT interval) • Existing permanent pacemaker • Current use of any of the following antiarrhythmic medications for a cardiac disorder: flecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone, or mexiletine • Use of medications for myotonia, such as phenytoin and flecainide acetate, within 5 days of study entry; carbamazepine and mexiletine within 3 days of study entry; or propafenone, procainamide, disopyramide, quinidine, and encainide within 2 days of study entry • Use of medications that produce myotonia, which may include fibrate acid derivatives, hydroxymethylglutaryl CoA reductase inhibitors, chloroquine, and colchicine • Kidney or liver disease • Heart failure • Seizure disorder • Pregnant or breastfeeding
Settings and locations	Neuromuscular referral centres in four countries – USA, Canada, England, and Italy
Trial drugs, n, dose, duration, timing	• Participants will receive mexiletine for 4 weeks, then no intervention for 1 week, and finally placebo for 4 weeks. Drug: Mexiletine hydrochloride • 200 mg three times a day; in pill form Drug: Placebo • Placebo three times a day; in pill form
Concomitant medications	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.
Primary efficacy outcomes	Patient-reported Stiffness on the IVR

Secondary efficacy outcomes	• Patient Reported Pain on the IVR • Patient Reported Weakness on the IVR • Patient Reported Tiredness on the IVR • Quantitative Measure of Hand Grip Myotonia (Seconds) • Compound Motor Action Potentials After Short Exercise Test • Graded Myotonia by Needle Electromyography - Right Abductor Digiti Minimi [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Clinical Hand Grip Myotonia Evaluation (Seconds) [Time Frame: The end of period 1 (week 4) and the end of period 2 (week 9)] • Clinical Eye Closure Myotonia Evaluation (Seconds) [Time Frame: The end of period 1 (week 4) and the end of period 2 (week 9)] • Graded Myotonia by Needle Electromyography - Right Tibialis Anterior [Time Frame: The end of period 1 (week 4) and period 2 (week 9)] • Compound Motor Action Potentials After Long Exercise Test [Time Frame: The end of period 1 (week 4) and period 2 (week 9)]
Safety outcomes	• Adverse events
Pre-planned subgroups	None
Duration of follow-up / loss to follow-up / cross over	Treatment periods were 4 weeks in duration, separated by a 1-week washout period.

Stunnenberg et al. (NCT02045667) (48)

This series of aggregated, double-blind, randomised, placebo-controlled N-of-1 trials, performed in a single academic referral centre in adults with clinical phenotype and genetically confirmed diagnosis of NDM, without cardiac or psychiatric comorbidity or comedication, selected from the Dutch neuromuscular database. Details of the inclusion and exclusion criteria are provided in Table 10.

Table 10: Inclusion and exclusion criteria (48)

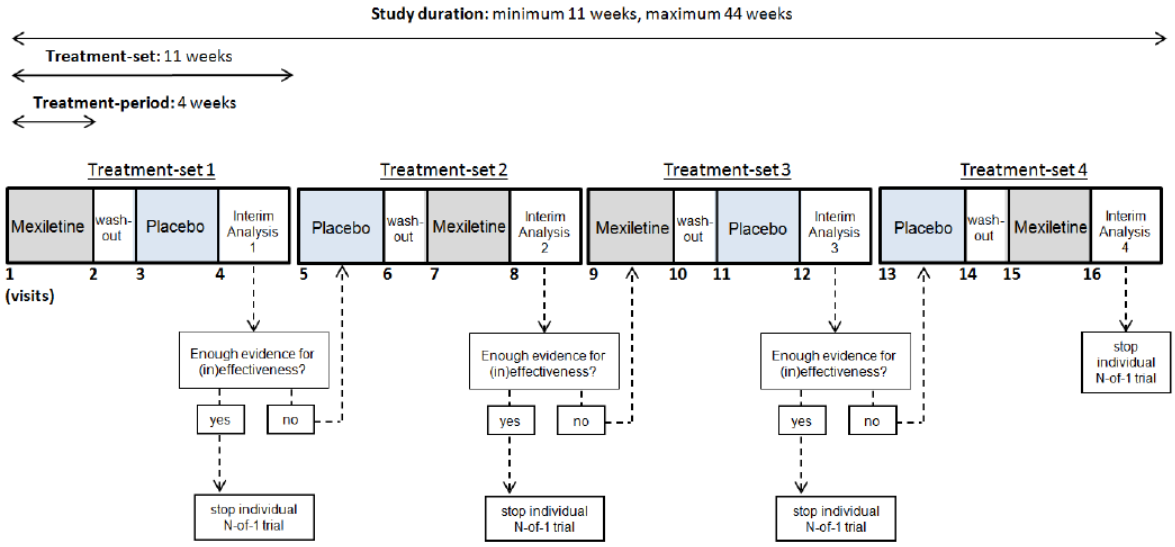
Inclusion criteria	Exclusion criteria
At least 18 years of age	Inability or willingness to approve to provide informed consent

Genetically confirmed diagnosis of NDM	Other neurological conditions that might affect the assessment of the study measurement
	Genetically confirmed myotonic dystrophy
	Existing cardiac conduction defects, evidenced on ECG including but not limited to the following conditions: malignant arrhythmia or cardiac conduction disturbance (such as second-degree AV block, third-degree AV block, or prolonged QT interval >500ms or QRS duration >150msec)
	Current use of the following antiarrhythmic medication for a cardiac disorder: flecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone or mexiletine
	Women who are pregnant or lactating
	Currently on medication for myotonia such as phenytoin and flecainide acetate within 5 days of enrolment, carbamazepine and mexiletine within 3 days of enrolment, or propafenone, procainamide, disopyramide, quinidine and encainide within 2 days of enrolment
	Renal or hepatic disease, heart failure, history of myocardial infarction, or seizure disorders

Patients were randomly assigned to receive mexiletine hydrochloride 200 mg capsules (equivalent to mexiletine 167 mg), or placebo capsule, three times per day. Those receiving anti-myotonic treatment underwent a 2-week washout period before baseline. Patients had four to 16 study visits, depending on the number of treatments sets necessary to draw conclusions regarding the treatment effect exceeding the clinically meaningful difference, with a probability greater than 0.80 (Figure 11).

Each N-of-1 trial consisted of one to four treatment sets, comprising 11 weeks each; a four-week period of mexiletine and a four-week period of placebo treatment, block-randomised, with a one-week washout in between and two weeks for statistical interim analysis at the end (Figure 11).

Figure 11: Study Design - Stunnenberg et al. 2018 (48)



The primary outcome measure was the mean daily self-reported stiffness severity score reported with an IVR diary. Patients noted if they experienced symptoms during the previous 24 hours and rated the severity of the symptoms on an ordinal scale (1-9, with 9 being the worst ever experienced). Based on clinical experience (consensus meeting with 3 clinical experts), a 0.75-point difference was considered a clinically meaningful difference for all four interactive voice response (IVR) scores.

Secondary outcomes included mean daily self-reported (using the IVR) severity scores for pain, weakness, and tiredness; the INQoL questionnaire composite score (0-100 scale; a higher score indicates greater disease severity) and 36-Item Short-Form Health Survey (Dutch version) mental and physical component scores (both 0-100 scales; lower score indicates greater disease severity) the first, fifth, and mean of five attempts of myotonic bedside tests: eyelid closure and handgrip muscle relaxation times after forceful muscle contraction for 5-seconds; and the Timed Up & Go test, which measures the time in which the patient rises from a chair, walks three metres, turns around, walks back, and sits down again, at a self-selected speed.

Table 11: Stunnenberg et al Study design (NCT02045667) (48)

Study Acronym/ I.D.	NCT02045667
Primary study reference	Stunnenberg et al. Effect of Mexiletine on Muscle Stiffness in Patients With Nondystrophic Myotonia Evaluated Using Aggregated N-of-1 Trials. JAMA. 2018 Dec 11;320(22):2344-2353. doi: 10.1001/jama.2018.18020. (50, 51).
Trial design	A double-blind, randomized and placebo-controlled combined N-of-1- trial using a Bayesian statistical approach.

Participants (Key Inclusion criteria)	• At least 18 years of age • Genetically confirmed diagnosis of NDMs • Participation in the "Genetical variability of the Non-dystrophic Myotonia" study of J. Trip or a new patient with genetically confirmed NDM.
Participants (Key Exclusion criteria)	• Inability or unwillingness to provide informed consent. • Other neurological conditions that might affect the assessment of the study measurements. • Genetic confirmed Myotonic Dystrophy type 1 (DM1) (CTG > 50 repeats), or Myotonic Dystrophy type 2 (DM2). • Patients with existing cardiac conduction defects, evidenced on ECG including but not limited to the following conditions: malignant arrhythmia or cardiac conduction disturbances (such as second-degree AV block, third degree atrioventricular (AV) block, or prolonged QT interval >500 ms or QRS duration > 150 msec). • Current use of the following antiarrhythmic medication for a cardiac disorder: flecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone or mexiletine. • Women who are pregnant or lactating. • Patients currently on medications for myotonia such as phenytoin and flecainide acetate within 5 days of enrolment, carbamazepine and mexiletine within 3 days of enrolment, or propafenone, procainamide, disopyramide, quinidine and encainide within 2 days of enrolment. • Patients with renal or hepatic disease, heart failure, history of myocardial infarction, or seizure disorders.
Settings and locations	Nijmegen, the Netherlands
Trial drugs, n, dose, duration, timing	Interventions: • Drug: Mexiletine hydrochloride • Drug: Placebo Placebo Comparator: Placebo • Placebo tablets three times daily orally Active Comparator: Mexiletine • Mexiletine hydrochloride 200 mg three times daily orally

Concomitant medications	
Primary efficacy outcomes	Severity score of stiffness reported by participants during the third and fourth week of each treatment period via the IVR diary.
Secondary efficacy outcomes	• Change in Individualized Neuromuscular Quality of Life Scale - Summary Score • Change in Short Form 36 - Physical Composite Score • Change in Clinical myotonia bedside-tests • Change in Muscle relaxation times measured with quantitative grip myometry • Change in Graded Myotonia by Needle Electromyography • Change in Mexiletine serum plasma concentration levels • Change in Patient-reported Pain on the IVR • Change in Patient-reported Weakness on the IVR • Change in Patient-reported Tiredness on the IVR • Change in Short Form 36 - Mental Composite Score
Safety outcomes	Adverse events were ascertained by active surveillance during trial visits and passive surveillance. Determination of the relationship between an adverse event and mexiletine treatment was performed by a data and safety monitoring board together with the trial pharmacologist
Pre-planned subgroups	Statistical analysis plan included the aggregation (analyses of prespecified genotype subgroup and total NDM patient groups) to obtain patients' mean effect sizes which were modelled, assuming a normal distribution around the genotype subgroups
Duration of follow-up / loss to follow-up / cross over	Each N-of-1 trial consisted of 1 to 4 treatment sets, comprising 11 weeks each: a 4-week period of mexiletine and a 4-week period of placebo treatment, block-randomised, with a 1-week washout in between and 2 weeks for statistical interim analysis at the end

B.2.3.2 Baseline characteristics

MYOMEX study (NCT02336477) (1)

An overview of patient disposition is shown in Figure 12 a total of 26 patients, 13 diagnosed with myotonia congenita and 13 diagnosed with paramyotonia congenita, were recruited. Of the 26 patients enrolled in the study, one withdrew consent prior to treatment and did not receive any study treatment. This patient was included in the intention-to-treat (ITT) population

but excluded from the modified ITT (mITT) and safety populations. The definition of mITT was all randomised patients with at least one available evaluation pertaining to the primary criterion or with a VAS value at V3 or V5 i.e. had to complete at least one treatment period. In addition, three patients were excluded from the per-protocol (PP) population due to treatment discontinuation, an intercurrent event unrelated to treatment and non-compliance.

Figure 12: MYOMEX patient disposition (1)

Baseline characteristics of the study population are shown in Table 12 and representative of the expected population that would be treated in practice (see Section B.2.13.2). Both treatment sequence groups were comparable on baseline characteristics including age, gender and blood pressure measurements. There was a numerical difference in the proportion of mexiletine naïve patients who received the placebo-mexiletine treatment sequence, compared to the mexiletine-placebo treatment sequence.

Table 12: MYOMEX demographics and baseline characteristics (mITT population) (1)

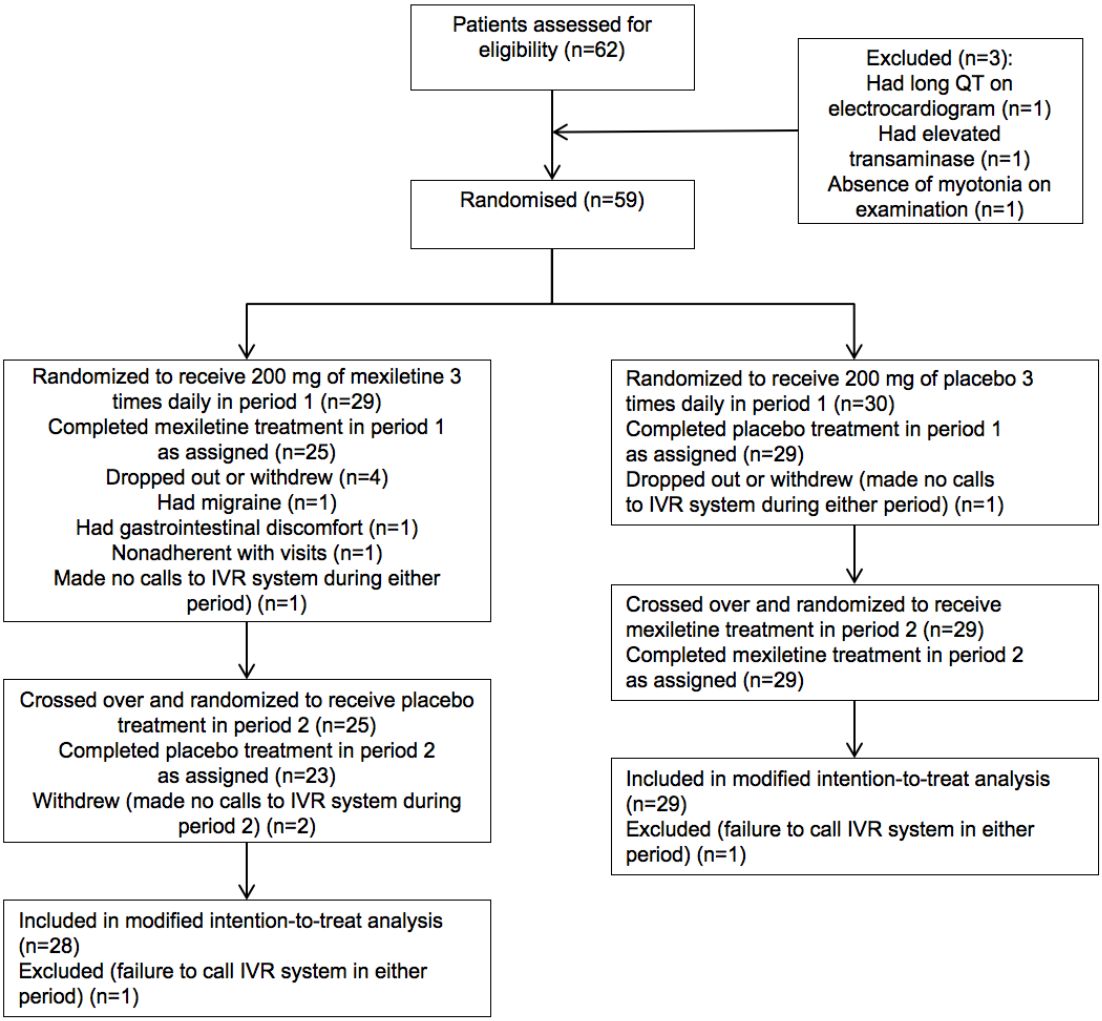
Demographics/ characteristics	**Treatment sequence**		**All patients**
	Placebo-mexiletine (n=13)	**Mexiletine-placebo (n=12)**	**(n=25)**
Mean (SD) age, years	[redacted]	[redacted]	[redacted]
Diagnosis, n (%)			
Myotonia congenita	[redacted]	[redacted]	[redacted]

Paramyotonia congenita	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Mean (SD) BMI, kg/m^2	[redacted]	[redacted]	[redacted]
Mean (SD) SBP (mmHg)	[redacted]	[redacted]	[redacted]
Mean (SD) DBP (mmHg)	[redacted]	[redacted]	[redacted]
Mexiletine treatment, n (%)			
Treated at screening	[redacted]	[redacted]	[redacted]
Previously treated (before screening)	[redacted]	[redacted]	[redacted]
Treatment naïve	[redacted]	[redacted]	[redacted]
BMI: body max index; mITT: modified intention-to-treat; SD: standard deviation			

Statland et al. (NCT02045667) (47)

A total of 62 eligible patients were recruited, of which three were ineligible and excluded at screening (Figure 13). Therefore, 59 patients were randomised patients were randomised to the mexiletine then placebo group and 30 patients to the placebo then mexiletine treatment group.

Figure 13: Patient disposition



IVR indicates interactive voice response

Of the 59 patients randomised, there were 33 men and 26 women, with a mean age of 42.9 years (Table 13). Patients were predominantly white and non-Hispanic. Thirty-four participants had chloride channel mutations, 21 had sodium channel mutations, and four 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.

Table 13: Demographics and baseline characteristics (47)

Demographics/ characteristics	**Mexiletine – placebo (n=29)**	**Placebo – mexiletine (n=30)**
Mean (range) age, years	41.10 (16–66)	44.70 (22–68)
Gender, n (%)		
Male	13 (44.8)	20 (66.7)

Female	16 (55.2)	10 (33.3)
Race, n (%)*		
White	28 (96.6)	29 (100.0)
Mutation, n (%)		
Chloride channel	17 (58.6)	17 (56.7)
Sodium channel	10 (34.5)	11 (36.7)
None identified	2 (6.9)	2 (6.7)
Medication, n (%)		
Mexiletine	7 (24.1)	6 (20.0)
Other	3 (10.3)	1 (3.3)
Mean (SD) IVR diary stiffness score†	3.89 (2.39)	4.63 (2.99)
Mean (SD) SF-36 score‡		
Physical, norm-based	38.70 (9.65)	40.80 (11.00)
Mental component	44.50 (13.30)	47.60 (9.80)
Mean (SD) INQoL QoL score§|	14.00 (9.03)	15.90 (12.50)
Geometric-like mean (pseudo SD) clinical hand-opening time, seconds	1.11 (0.90–3.48)	0.605 (0.51–1.84)
Geometric-like mean (pseudo SD), clinical eye-opening time, seconds	0.51 (0.49–2.42)	0.47 (0.46–2.3)
Geometric-like mean (pseudo SD) quantitative handgrip myotonia, seconds¶	0.65 (0.29–0.52)	0.51 (0.21–0.36)
EMG grade ≥3, n (%)**		
Abductor digiti minimi|	18 (62.1)	18 (62.1)
Tibialis anterior|	20 (69.0)	19 (65.5)
Mean (SD) short exercise test, % of baseline|	78.70 (24.50)	80.80 (28.70)

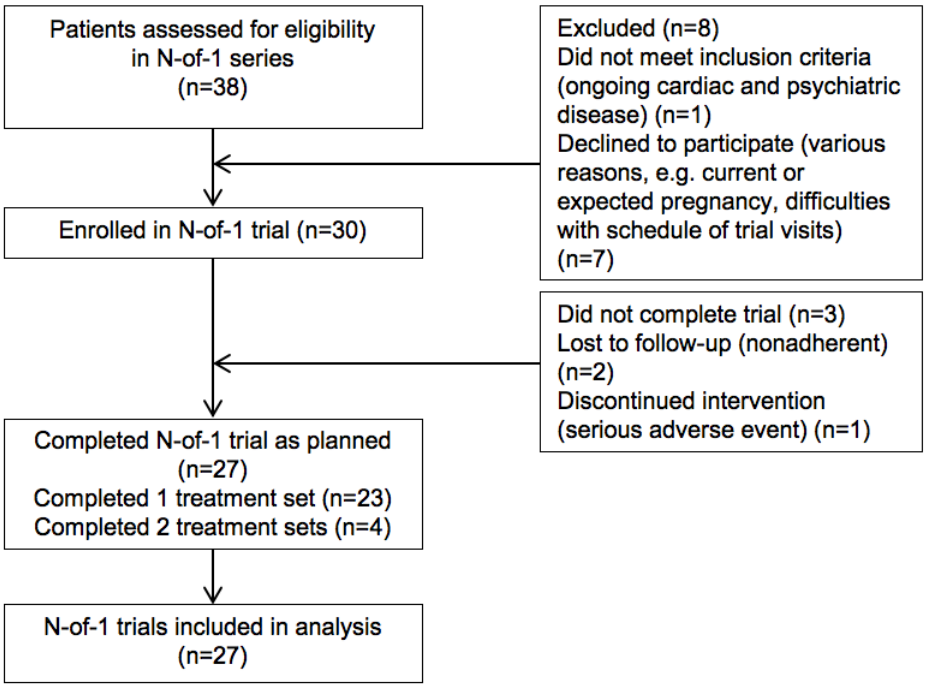
EMG: electromyography; INQoL: Individualised Neuromuscular Quality of Life; IVR: interactive voice response; QoL: quality of life; SD: standard deviation; SF-36: 36-Item Short-Form Health Survey.

*One patient did not report race (other races were not reported); †0 = no symptom, 1 = minimal, 9 = worst ever experienced. Eight patients had a true baseline stiffness severity score; day 1 score was used for 40 patients and day 2 score used for 10; ‡ Lower score = greater impact; § Higher score = greater impact; | One patient was missing; ¶ Eight patients did not have baseline quantitative handgrip myotonia test results; ** 0 = no myotonia, ≥1 = minimal electrographic criteria for myotonia to ≥3 = myotonia in every needle position

Stunnenberg et al (NCT02045667) (48)

Of the 38 patients contacted and recruited, one was ineligible (because of ongoing cardiac and psychiatric disease) and seven declined participation for a variety of reasons (current or expected pregnancy, difficulties with schedule of trial visits). Thirty patients were randomised and received study medication (Figure 14). There were three dropouts: two patients did not complete study visits, and for one patient the individual N-of-1 trial was stopped because of a serious adverse reaction.

Figure 14: Patient disposition



Twenty-two men and eight women with a mean age of 43.4 years (standard deviation (SD), 15.24; range, 19–65 years) were enrolled. Nineteen patients had a mutation in the skeletal muscle chloride channel gene (CLCN1), and 11 patients had a mutation in the skeletal muscle sodium channel gene (SCN4A). IVR stiffness scores (higher in patients with CLCN1 genotype), IVR pain scores (higher in patients with SCN4A genotype), and eyelid closure action myotonia scores (higher in patients with SCN4A genotype) differed between the two genotype subgroups at baseline (Table 14).

Of the 27 patients who completed their individual N-of-1 trial, 23 underwent a single treatment set and four completed a second treatment set; thus, in total, 31 treatment sets from 27 patients were analysed. For the outcome assessments, 773 of 868 (89%) telephone calls to assess the primary outcome were completed and 2,676 of 2,728 (98%) possible outcome measures for the secondary outcomes were collected at the in-person visits. Since the amount of missing data was relatively small and assumed missing at random, multiple imputation was not performed.

Table 14: Baseline patient characteristics by Genotype subgroups (48)

Characteristic	*CLCN1* (N=16)	*SCN4A* (N=11)	p-value[a]
Age, mean (range), y	50 (24–65)	38 (19–64)	0.09
Men, No. (%)	13 (81)	7 (64)	0.39
Pretrial anti-myotonic medication, No. (%)			
Mexiletine	2 (13)	0	0.50
Other	7 (44)	5 (46)	0.62
IVR score, median (IQR)[b]			
Stiffness	6.7 (6.0–7.0)	4.7 (3.3–5.1)	0.002
Pain	0 (0–1.1)	3.4 (2.3–5.5)	0.002
Weakness	3.8 (1.1–5.0)	0.5 (0–6.1)	0.06
Tiredness	3.4 (1.4–6.0)	5.1 (3.9–6.1)	0.16
Handgrip action myotonia, median (IQR), s[c,d]	1.1 (0.9–2.0)	1.5 (1.0–6.4)	0.40
Eyelid closure action myotonia, median (IQR), s[c,d]	1.2 (0.6–2.9)	4.0 (1.3–11.2)	0.01
Timed Up & Go, median (IQR), s[c,e]	9.7 (8.8–11.0)	9.5 (8.3–10.3)	0.49
INQoL composite score, median (IQR)[f]	84.0 (74.5–110.3)	98.0 (56.0–120.0)	0.82
SF-36 score, median (IQR)[g]			
Physical component	40.8 (37.7–46.6)	38.7 (33.6–40.0)	0.11
Mental component	52.1 (44.7–57.1)	55.0 (37.2–59.1)	0.88

CLCN1: skeletal muscle chloride channel gene; INQoL: individual neuromuscular quality of life questionnaire, IQR: interquartile range, IVR: interactive voice response; SCN4A: skeletal muscle sodium channel gene; SF-36: short form 36-item health status survey

a) Nonparametric test of differences between genotype disease subgroups using the Mann-Whitney U test.

b) Baseline IVR scores derived from a two-week period before the start of the trial. IVR scores represent the severity of daily-reported symptoms (stiffness, pain, weakness, and tiredness) on an ordinal scale (1–9, with 9 being the worst ever experienced).

c) represents the median (IQR) across all patients, with each patient contributing his or her median score on 5 trials of the measure.

d) Handgrip and eyelid closure action myotonia represent muscle relaxation times after forceful muscle contraction for five seconds (relaxation time increase with increasing myotonia).

e) Time Up & Go test measures the time in which the patient rises from a chair, walks 3 metres, turns around, walks back and sits down again in a self-selected speed (test time increase with increasing myotonia).

f) scale, 0 to 100; a higher score indicates greater disease severity.

g) scale for each component, 0 to 100 scales; a lower score indicates greater disease severity.

Suetterlin et al. 2015 (49)

Study design

This retrospective review of a large skeletal muscle channelopathy patient cohort in the United Kingdom assessed all patients with genetically confirmed NDM prescribed mexiletine hydrochloride with a minimum of 6 months follow-up. Doses were titrated weekly until symptoms resolved, or a total daily dose of 600 mg was reached. The mean daily dose was 416.7 mg of mexiletine hydrochloride, reflecting real world data of average dosing.

Baseline characteristics

A total of 122 patients were identified, and 63 met inclusion criteria. The mean length of follow-up was 4.8 years (range 6 months - 17.8 years).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 15: MYOMEX Statistical analysis plan (1)

Trial number (acronym)	**NCT02336477 (MYOMEX)**
Objectives	The main purpose of this randomised study was to evaluate the efficiency and tolerance of mexiletine in the symptomatic treatment of non-dystrophic Myotonia. Secondary objectives include the evaluation of the electromyographic tests as a tool for standardised evaluation of the response to therapeutics used in Myotonia and the reliability and validity of a new quantitative scale of the severity of Myotonia.

Statistical analysis	The main analysis was done on the mITT population. This analysis was supplemented by a per protocol analysis. All analyses were performed according to randomization. The statistical analysis followed the statistical analyses plan (SAP) for study NCT02336477 (v5.1 dated 27 July 2015). Descriptive statistics was calculated according to the nature of the variable studied – whether a continuous or qualitative variable. For continuous variables, the number of observed values, number of missing data, mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum and maximum values were calculated. For qualitative variables, the frequency and associated percentages of the different modalities observed were reported. The Fisher-exact test informed the comparison of categorical variables whilst the test of the sum of Wilcoxon ranks informed the comparison of continuous variables. Correlation between 2 parameters was informed by the Spearman coefficient. Efficacy analyses: Absolute changes on the primary criterion (the score of stiffness severity) from baseline (V2 and V4) at end of period (V3 or V5) were assessed for each period by treatment and by diagnosis. Difference between treatment 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 The model allowed testing if a carry-over effect was present: • 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 as above • 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 analysed by period. Treatments were compared using a Wilcoxon test independently for each diagnosis. If the p-value associated with the diagnosis-treatment interaction was significant (≤ 0.05), a complementary analysis was performed to test the treatment effect in each diagnosis.

	1. In the absence of carry-over effect, the tested model was to include: • Treatment and study period as factors. • Patient as random effect. • Baseline value as covariate. 2. In case of carry-over effect, the data were described and analysed 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. 1. Change from baseline (V2) in chair tests were calculated and treatments were compared using Wilcoxon test. 2. Changes from baseline (V2) for INQoL scores at V2, V3 and V5 were calculated and the treatment effect was assessed for each item using a mixed effect linear model which included treatment, study period, and treatment sequence as fixed effects, patient as random effect and baseline value as co-variable. The proportion of patients with no symptoms was evaluated and patients who did not report any symptoms were included in the analysis. 3. The efficacy of the treatment (the CGI-efficacy index as evaluated by the investigator at V3 and V5) was on a 4-point scale. Collected data were transformed as binary variables (efficient [good and fair]/not efficient [poor and none]) and efficacy between treatments was compared using the McNemar test. 4. Comparisons for patient's preference for one or the other period (as well as patient willingness to continue mexiletine) at V5 were performed using a binomial test. The following analyses were performed in the mITT population only: 5. Measurement of the CMAP amplitude decline (recorded from the ADM muscle after repeated short exercises and cold exposure at V2, V3 and V5) for each test (room temperature, cold exposure) and for each assessment time (before, immediately after short exercise) was provided. In addition, the presence or absence of repetitive discharges (post-exercise myotonic potentials [PEMPs]) after each test was documented. Values after short exercise(s) were compared to values before first exercise at room temperature and after cold

	exposure; values after cold exposure were compared to values before cold exposure. 6. CMS scores (evaluated at V2, V3 and V5) were assessed by two independent investigators or designees at baseline. Values were assessed by the same investigator who had followed-up the patient throughout the study were considered as baseline values. The other values were used to assess inter-productivity of the tests. Intra- and inter-rater reliability were analysed with weighted kappa coefficients for each individual item. Intraclass coefficients were calculated for summary scores. Changes from baseline (V2) were calculated and treatments were compared using the same methodology as for the primary criterion. Correlations with the quality of life and the stiffness score (VAS) were assessed using the Spearman coefficient. 7. Differences in the number of premature discontinuations between treatments for each period were assessed using the Fisher's exact test. Correlations with CMS, INQoL, and stiffness scores for mexiletine plasma concentrations at V2, V3 and V5 were assessed using the Spearman coefficient for the mITT population. Safety analyses: 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 post-randomisation, with, 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.

Sample size, power calculation	Sample size was calculated according to clinical experience. This identified 40 to 50% of patients require symptomatic treatment for myotonia. Two hundred patients were identified across the 7 centres that took part in this study (114 with myotonia congenita and 86 with paramyotonia congenita). The aim was to recruit 24 patients (12 of each diagnosis), representing 25% of the overall population that required symptomatic treatment. 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.
Changes to the SAP	The study protocol was amended 4 times. All statistical analyses were described in the last version of the SAP with minor modifications. Study was unblinded after a blind review of the data, locking database and the validation of the SAP. The definition of the PP population was revised after the unblinding. In the original protocol, the PP had been defined as “all randomised 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”. After revision of the definition, the PP population included “all randomised patients who did not have any major protocol deviation and who completed the 2 study periods”. The following secondary analyses were added after unblinding: • The evolution of the score of stiffness severity as a function of time for the mITT and PP populations. In addition to the evaluation of the stiffness VAS score at baseline and Day 18, patients recorded at home the stiffness VAS score in the morning when the drug dose was changed (Day 4 and Day 7). • The percentage of patients with an absolute VAS change from baseline ≥ 50mm for the mITT and PP populations. • The evaluation of mexiletine levels (C2h) as a function of stiffness VAS score for the mITT population • The evaluation of mexiletine levels (C2h) as a function of mexiletine dose per body weight for the mITT population.

Interim analysis	No interim analyses were performed.
Outcome populations, **Imputing of missing data**	The following subject population were evaluated and used for presentation and analysis of the data: • Intention-to-treat population (ITT): All randomised patients that have received a randomisation number at V2 • Modified intention-to-treat population (mITT): All randomised 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 randomised 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. As described in the study disposition for the included population the mITT and the SAF populations are the same (N = 25; MC = 13; PC = 12)

Table 16: Statland et al. (2012) Statistical analysis plan

Trial number (acronym)	**NTC00832000**
Objectives	To determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDMs
Statistical analysis	All treatment effect analyses used a linear mixed-effects model (random effect for participant, independent and identically distributed random errors with participant) to adjust for any period effect and included data for patients that dropped out. 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 carry-over effect. With regards to assumptions: • One assumption required valid Wald tests and the residuals normally distributed. The individual interactive voice responses (IVRs) severity scores (stiffness, pain, tiredness, and weakness) were replaced with the weekly means to fulfil the assumptions. QQ plots satisfied the assumption. • When modelling cross-over study data and including only the main effects for period and treatment, the treatment effect was assumed the same across period (carry-over effect). Efficacy analyses: For the primary endpoint the Wald test was used, Most confidence intervals (CIs) were calculated using the standard error of the estimate taken from the model results. Exception to this were the end points requiring a log transformation for which a bootstrap CI was calculated. The effect size was the treatment effect estimated divided by the within-participant standard deviation (SD). Overall treatment effect variance was validated using log likelihood test. The paired Wilcoxon test was used to test the treatment effect hypothesis. The following transformations were used to fulfil the normality assumption: • log (t_i + 0.1) for the handgrip and eye closure times • log (t_i) for the quantitative handgrip myometry.

Sample size, power calculation	The aim was to recruit 54 patients with available primary end point measurements for nine weeks (four weeks on mexiletine/placebo and four weeks on the opposite treatment with one-week intermission). The sample size was determined by Monte Carlo simulations which 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 $\alpha = 0.5$.
Changes to the SAP	None reported.
Interim analysis	Random drug levels were collected before study visits at baseline and the end of the weeks 4, 5 and 9 (end of study).
Outcome populations, **Imputing of missing data**	The study used the intention-to-treat principle modified to remove missing values that were assumed to be missing at random.

Table 17: Stunnenberg et al. (2018) Statistical analysis plan

Trial number (acronym)	**NTC02045667**
Objectives	To determine the probability of clinical effectiveness of mexiletine when used in patients with NDM.
Statistical analysis	A Bayesian analysis was used on multiple N-of-1 trials that enable answering the objective on an individual as well as on the population level. This would help obtaining posterior distribution for the treatment effect in both population level and between-patient variation. A hierarchical (multi-level) model was used, with the IVR measure for stiffness as the dependent variable. Patient, subgroup of patients and centre were used as the structural grouping factors. Patient was treated as a random effect (for both intercept and slope). Centre and subgroup of patients were treated as fixed effects. A common within person residual was assumed. All p-values were 2-sided and $p < 0.05$ was considered statistically significant for all tests. Primary and secondary endpoints were analysed in the same way. Two types of priors were used; non-informative and 'clinical priors'. Normal and gamma distributions were used for said priors.

	To check for robustness with respect to prior distributions, the elicited prior distributions would be replaced with non-informative priors in the analyses. To estimate simulation-based type I error and bias attributable to an observed-response-base stopping rule, a post hoc simulation-based sample size calculation was performed.
Sample size, power calculation	Thirty out of thirty-eight patients were recruited.
Changes to the SAP	None reported.
Interim analysis	After treatment pair 1, 2 and 3 of each N-of-1 trial it would be investigated whether the existing evidence at that moment were sufficient to be able to conclude that one of the two treatments was more effective for that particular individual. Two stopping criteria had been defined based on the posterior probability of treatment effects larger than 0.75 (cut-off of substantial effect. Only non-informative priors were used for the interim analyses.
Outcome populations, **Imputing of missing data**	Not reported.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A complete quality assessment for each trial is provided in Appendix D (Section D 1.3).

As there were no parallel group RCTs included, the quality assessment checklist suggested in the user guide was replaced with the following checklist, "Revised Cochrane risk of bias tool for randomised trials (RoB 2.0). Additional considerations for cross-over trials" (52) For the N-of-1 trial (48) a quality assessment was performed following the CENT 2015 checklist, which is based on the CONSORT 2010 checklist items with modifications or additions for individual or series of N-of-1 trials (53).

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 MYOMEX study (NCT02336477) (1)

Significant improvements were observed across diagnosis in all efficacy endpoints when mexiletine was compared to placebo.

Primary efficacy endpoint

Score of stiffness severity on a self-assessment scale (100 mm VAS)

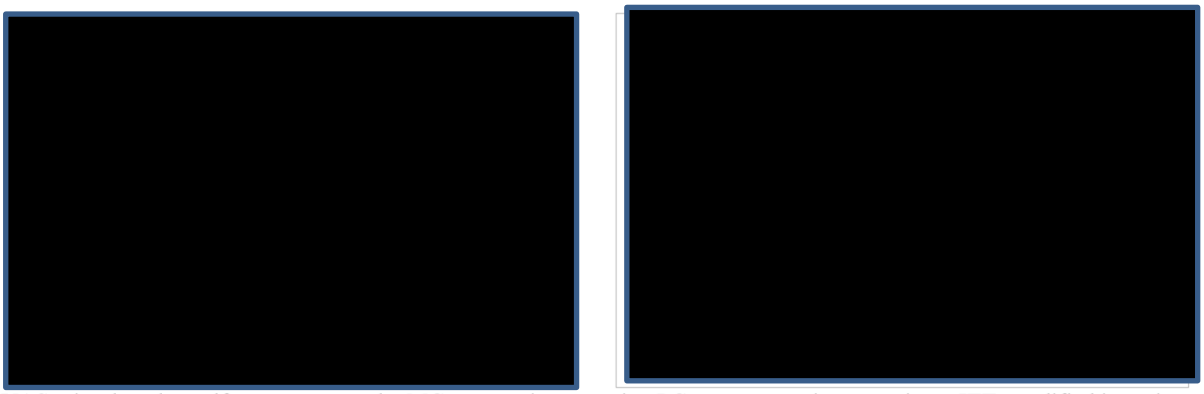
The primary efficacy criterion of this study was the stiffness as assessed by the patient on a visual analogue scale (VAS). The primary analysis was performed in the modified intention to treat (mITT) and per protocol (PP) populations, see Figure 16 and Figure 17. Absolute changes from baseline at the end of each period were assessed by treatment and by diagnosis. Difference between treatments was evaluated using a mixed effect linear model on ranks.

Treatment with mexiletine led to a significant improvement in the primary endpoint, stiffness. The individual stiffness VAS score for patients receiving placebo generally remained stable. The median stiffness VAS scores for patients receiving mexiletine in the 25 participants in the modified intent-to-treat (mITT) population were [redacted] at baseline and decreased to [redacted] at the end of the treatment period, while those on placebo did not change ([redacted] vs [redacted] at baseline and end of treatment, respectively) – see Figure 15. This represents a median change of [redacted]% of the stiffness VAS score compared to baseline for subjects under mexiletine (vs. a [redacted]% median change for placebo).

Figure 15: Median evolution of stiffness using the visual analogue score

Figure 16 for mITT and Figure 17 for PP populations clearly show 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.

Figure 16: Stiffness VAS Score by Treatment Sequence, mITT (A = Mexiletine – Placebo, B = Placebo – Mexiletine)



VAS: visual analog self-assessment scale; MC: myotonia congenita; PC: paramyotonia congenita; mITT: modified intention-to-treat

Figure 17: Stiffness VAS Score by Treatment Sequence, PP (A= Mexiletine - Placebo, B: Placebo – Mexiletine)

VAS: visual analog self-assessment scale; MC: myotonia congenita; PC: paramyotonia congenita;

According to the mixed effect linear model, mexiletine treatment allowed a highly significant stiffness improvement regardless of the subjects' diagnosis ([redacted]), i.e. MC or PC. The mixed effect linear model evidenced no carry-over effect (treatment sequence effect, [redacted]). Therefore, the hypothesis of a carry-over effect was rejected and consequently the data from the two periods were combined.

The model showed a significant effect of the treatment ([redacted]) and baseline value ([redacted]) in the mITT (Table 18). As the diagnosis-treatment interaction effect was not significant ([redacted]), the linear model was not computed by diagnosis.

Table 18: Mixed Effect Linear Model for the Stiffness VAS absolute Change from Baseline – mITT Population

Diagnosis	Parameter	p-value
Total population	Diagnosis	[redacted]

	Treatment	[redacted]
	Period	[redacted]
	Treatment-diagnosis interaction	[redacted]
	Baseline value	[redacted]

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 18 and Figure 19 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 with patients achieving clinical benefit by Day 7 on the 400 mg dose.

Figure 18: Stiffness VAS score as a Function of Time by Treatment and Treatment Sequence – mITT population

Figure 19: MEX-PLA: sequence mexiletine-placebo; PLA-MEX: sequence placebo-mexiletine

Descriptive analysis of the percentage of patients with an absolute VAS change from baseline ≥ 50 mm at Day 4, Day 7 and Day 18 in the mITT population found that 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 (1). On Day 18, [redacted]% and [redacted]% of the patients had an absolute VAS change from baseline ≥ 50 mm in the mexiletine and placebo treatments, respectively.

Long-term follow up data from MYOMEX from site 01 (Hôpital La Pitié Salpêtrière Paris) (50)

In order to collect-long-term data on the patients treated at the lead investigator site 01 (Hôpital La Pitié Salpêtrière Paris), informed consent had to be obtained as it was not stipulated in the initial informed consent form that follow-up data collected after completion of the study would be used for further investigation. The lead investigator could only follow up patients on their site and not other sites. Out of the 12 patients enrolled at Site 01, informed consent was collected in 8 subjects (32% of the total mITT study population). The reasons for not gathering consent in the remaining 4 patients was that they could not be reached because they were being treated at another site for three patients and as one of the patients died from an ear nose and throat cancer.

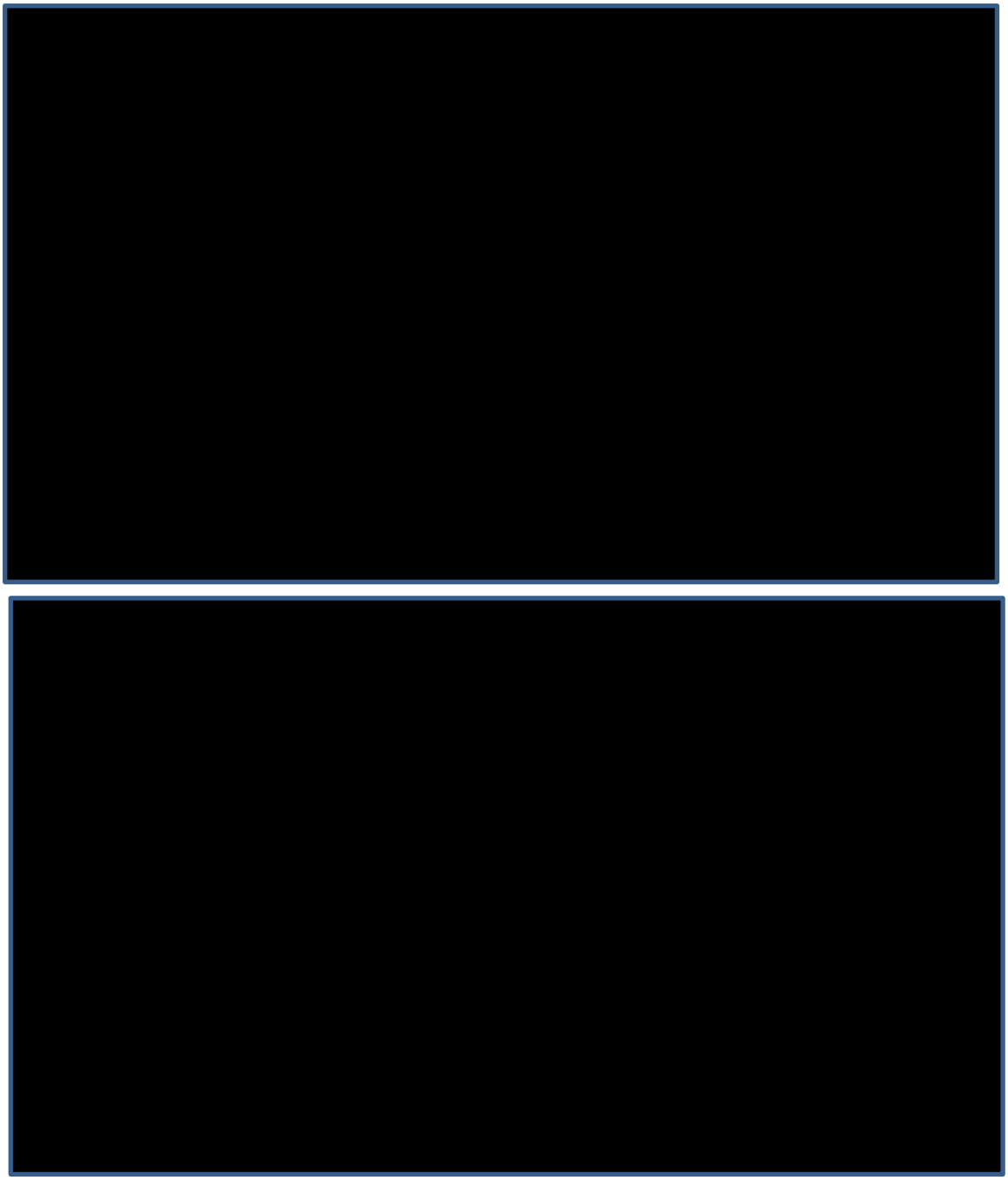
During the follow-up visits, patients were asked about:

- their mexiletine dosing regimen
- the efficacy of the treatment using the visual analogue scale (VAS) stiffness score (0-100 mm, with 0 mm = “no myotonia” and 100 mm = “most severe myotonia”), as during the MYOMEX study, or using the patient’s impression on efficacy (0-100%, with 0% = no efficacy, 100% = no symptoms at all)
- the safety of the treatment (reported adverse events)

Mexiletine treatment was associated with a clear long-term benefit for all 8 patients, who reported improved stiffness scores as determined on a VAS and/or perceived efficacy after several years of treatment. All patients wished to continue their mexiletine treatment.

The stiffness scores reported for the 8 patients who had a mean follow up period of 48 months (range 3 – 94 months) demonstrate that the reduction in stiffness scores achieved with mexiletine at the end of the MYOMEX trial were least maintained (Figure 20) as there was a further 7% reduction in the average in the VAS stiffness score at the last data point for each patient at follow-up, compared to that recorded at the end of the original MYOMEX study period versus baseline (50). The mean mexiletine hydrochloride dose at the time of the last measurement was 400 mg daily (equivalent to 2 capsules of Namuscla 167mg).

Figure 20: VAS scores on long-term follow up (mean 48 months) for 8 patients in the MYOMEX study



Secondary efficacy endpoints

INQoL

After treatment with mexiletine, all the indicators of the QoL domains of INQoL improved, with greatest impact observed in patient activity. The results for the INQoL scores are shown in Figure 21 and Figure 22 show the changes in symptoms related to NDM and the impact on daily living, respectively for all patients included in the study. Detailed results for the INQoL scores before and after treatment for the mITT population are shown in Table 19 below.

Figure 21: Scores for INQoL symptom subdomains before study initiation and in treatment and no treatment arms of study (mITT)

Figure 22: Scores for INQoL impact of daily living domains before study initiation and in treatment and no treatment arms of study (mITT)

Table 19: Individualized Neuromuscular Quality of Life (INQoL) Before and After Treatment – mITT Population

			Absolute values			Absolute changes from baseline	
Domain	Diagnosis		Before treatment	Placebo	Mexiletine	Placebo	Mexiletine

Weakness	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Locking	Total (N=25	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Activities	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independence	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social relationship	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emotions	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body image	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall quality of life	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perceived treatment effects	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Expected treatment effects	Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

End of treatment period values were collected at Visit 3 (Day 18) and Visit 5 (Day 39).

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 QoL, 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.

INQoL: individualized neuromuscular quality of life; Med: median; mITT: modified intention-to- treat; SD: standard deviation.

** N=24: Baseline value was missing for one patient

The mixed effect linear model showed a significant improvement in the total population (treatment effect for each domain of the INQoL questionnaire, [redacted]), when patients were on mexiletine (Table 20).

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

- A treatment effect for each domain of the INQoL questionnaire ([redacted]) except for the expected treatment effect ([redacted])
- An effect of baseline values for all domains ([redacted]) except for muscular locking, body image, perceived treatment effect and expected treatment effect
- A period effect for fatigue, overall quality of life, social relationship, emotions, independence, and activities ([redacted])

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

Table 20: Mixed Effect Linear Model for Each Domain of the Individualised Neuromuscular Quality of Life Questionnaire (INQoL) – mITT Population

Domain	Parameter	p-value
Weakness	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Locking	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Pain	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Fatigue	Treatment	[redacted]

	Period	[redacted]
	Baseline value	[redacted]
Activities	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Independence	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Social relationship	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Emotions	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Body image	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Overall quality of life	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Perceived treatment effect	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Expected treatment effect	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]

Clinical Global Impression of Efficacy

Overall, mexiletine treatment was considered as efficient by both the patients ([redacted]%) and the investigators ([redacted]%) – see **Error! Not a valid bookmark self-reference.**. Patients clearly preferred the mexiletine treatment period over the placebo period ([redacted]%, p=[redacted]) and only [redacted] patients were not willing to continue mexiletine treatment after the study (including the one who prematurely discontinued the study following an AE and one who did not consider the treatment as efficient).

Table 21: Clinical Global Impression of Efficacy – mITT Population

	Placebo	**Mexiletine**	**McNemar, p-value**
CGI as judged by the investigators	N=25	N=24	

Efficient	[redacted]	[redacted]	[redacted]
Not efficient	[redacted]	[redacted]	
CGI as judged by the patients	N=25	N=25	
Efficient	[redacted]	[redacted]	[redacted]
Not efficient	[redacted]	[redacted]	

Efficient = good or fair reported in the case report form
Not efficient = poor or none reported in the case report form

Mexiletine plasma concentrations after 18 days of treatment (200 mg three times a day) were within the therapeutic range usually described for mexiletine (0.5 to 2.0 µg/mL). Mexiletine was not detected in the plasma of any patient during the placebo period at any timepoint. Before first mexiletine intake, plasma concentration was null or below the detection threshold for all patients in both periods (V2 or V4 depending on the treatment sequence), regardless of treatment sequence, meaning that the wash-out period was sufficient.

Clinical myotonia rating scale (CMS) scores

The severity and disability global scores before and after treatment are presented in The global severity score after placebo showed little improvement whilst all patients treated with mexiletine showed an improvement in their severity score (mean change [redacted] for placebo vs. [redacted] for mexiletine).

Similar observations can be made for the disability global score:

- After treatment with placebo, mean absolute change from baseline was [redacted] (SD [redacted]) for the total population.
- After treatment with mexiletine, the mean absolute improvement was [redacted] (SD [redacted]) for the total population.

Table 22. 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.

The global severity score after placebo showed little improvement whilst all patients treated with mexiletine showed an improvement in their severity score (mean change [redacted] for placebo vs. [redacted] for mexiletine).

Similar observations can be made for the disability global score:

- After treatment with placebo, mean absolute change from baseline was [redacted] (SD [redacted]) for the total population.
- After treatment with mexiletine, the mean absolute improvement was [redacted] (SD [redacted]) for the total population.

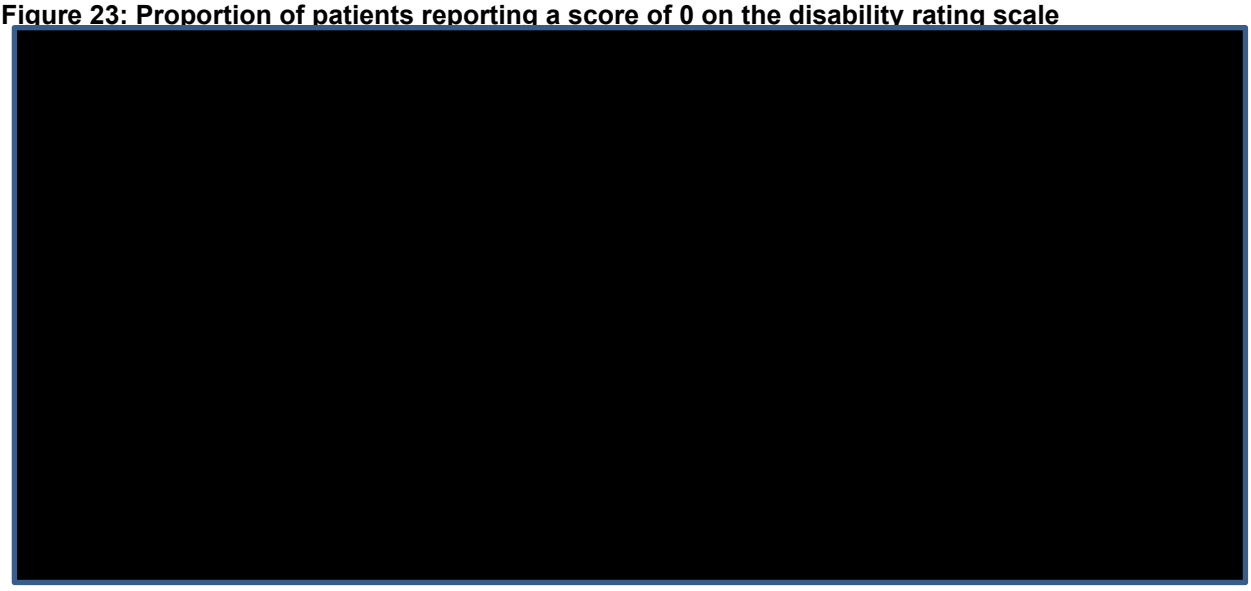
Table 22: Severity and Disability Global Scores Before and After Treatment – mITT Population

		Absolute values			Absolute changes from V2	
Items		Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
Severity global score*	N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disability global score**	N	25	25	25	25	25
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

End of treatment period values were collected at V3 and V5.
* 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
mITT: modified intention-to-treat population; SD: standard deviation

More patients reported a normal score of '0' on the disability rating scale after treatment with mexiletine compared to placebo, demonstrating that mexiletine improved patient's ability to undertake daily activities (Figure 23).

Figure 23: Proportion of patients reporting a score of 0 on the disability rating scale



Each domain was rated 0-4 with 0 = normal. NB. Few scores of 3 or 4 were observed

The decrease observed in the disability score for the total study population was significant ([redacted]) with no significant diagnosis-treatment interaction effect ([redacted]) (Table 23). Therefore, mexiletine significantly decreased the disability score in the overall population.

Table 23: Mixed Effect Linear Model for the CMS Severity and Disability Global Score – mITT Population

Diagnosis	Parameter	p-value
CMS – Global Severity Score	Diagnosis	[redacted]
	Treatment	[redacted]
	Period	[redacted]
	Treatment-diagnosis interaction	[redacted]
	Baseline value	[redacted]
CMS – Global Disability Score	Diagnosis	[redacted]
	Treatment	[redacted]
	Period	[redacted]
	Treatment-diagnosis interaction	[redacted]
	Baseline value	[redacted]

Correlations between CMS, INQoL, and stiffness VAS scores assessed using the Spearman coefficient are provided in Table 24.

The global score of severity was strongly correlated with the disability score ([redacted]), the stiffness score ([redacted]) and the quality of life ([redacted]). It was also inversely related to the perceived and expected treatment effects [redacted] and [redacted] respectively.

Similarly, the global score of disability was strongly correlated with the severity score ([redacted]), the stiffness score ([redacted]) and moderately correlated with the quality of life ([redacted]). It was also inversely related to the perceived and expected treatment effects [redacted] and [redacted] respectively.

Table 24: Correlations between Clinical Myotonia Scale, Quality of Life, and Stiffness Scores assessed using the Spearman Coefficient– mITT Population

	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disability global score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Chair test

Chair test results are provided in Table 25 and Table 26 for the values collected in the mITT population at baseline (V2) and after treatment, respectively. The chair test was performed at baseline (V2) and at the end of each treatment period (V3 or V5). At baseline no marked differences were observed between treatment sequences.

Table 25: : Chair Test Results at Baseline – mITT Population

	Chair test (seconds)		
	Placebo-mexiletine	**Mexiletine-placebo**	**Total**
N	13	12	25
Mean	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]

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 26. 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) [redacted]). The time taken to perform the chair test significantly improved at the end of the mexiletine treatment period compared to placebo, regardless of the patients' diagnosis. Median duration to stand up, turn around the chair and sit down was around [redacted] seconds after placebo and around [redacted] seconds after mexiletine.

Table 26: Chair Test Before and After Treatment – mITT Population

		Chair test (seconds): Absolute values			Chair test (seconds): Absolute changes from V2	
		Before treatment (V2)	**Placebo**	**Mexiletine**	**Placebo**	**Mexiletine**
Total (N=25)	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	p value*				[redacted]	

*Wilcoxon signed-rank test p value

CMAP amplitude

In patients with MC, the mean CMAP amplitude decreased after the first short exercise but returned to normal values after exercise cessation. At room temperature, the CMAP amplitudes recovered with repeated exercise and approached normal values (warm-up phenomenon) whereas after cold exposure, decrease in CMAP amplitudes remained more pronounced (cold-aggravated myotonia). Overall, the decrease in CMAP amplitude was less pronounced in subjects receiving mexiletine than in those receiving placebo. In patients with

PMC, the expected patterns were observed, i.e. an aggravation of myotonia with repeated exercises and with cold. Additionally, the decrease in CMAP amplitudes was less pronounced in subjects receiving mexiletine than in those receiving placebo.

B.2.6.2 Statland et al (NCT00832000) (47)

It should be noted that unfortunately, up to 25% of outcome data for the IVR, nearly 50% for some domains of the INQoL and around 10% of SF-36 data were missing, but it was not reported how these missing data were interpreted.

Primary efficacy endpoint

Both treatment periods showed a significant improvement in stiffness as reported on the IVR diary when patients were on mexiletine compared to placebo (Table 27).

As explained in Section B.2.3.1, treatment effect was estimated separately for each period. Change in treatment effect in period 1 was highly significant (P <.001) at 2.53 for mexiletine and 4.21 for placebo, a difference of −1.68 (95% CI, −2.66 to −0.706) and significant in period 2, 1.60 for mexiletine vs 5.27 for placebo (difference, −3.68; 95% CI, −3.85 to −0.139; P=.04).

Table 27: Mixed Model Results for IVR stiffness - Includes Mean Estimate Under Both Treatments, the Difference of Treatments (Mexiletine Minus Placebo), Effect Size, and Significance Level (47)

End Point	No. of Participant	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
Interactive voice response						
Stiffness, first period	57	2.53 (1.80 to 3.17)	4.21 (3.40 to 5.20)	-1.68 (-2.66 to -0.706)	-1.36	<.001
Stiffness, second period	57	1.60 (1.04 or 2.20)	5.27 (4.44 to 6.27)	−3.68 (−3.85 to −0.139)	-2.97	0.04

Secondary efficacy endpoints

The significant improvement seen in IVR stiffness was repeated in IVR assessment of pain, weakness and tiredness with a treatment effect of -1.63 (-2.00 to -1.26), -1.26 (-1.67 to -0.861) and -0.918 (-1.30 to -0.532), respectively (Table 28). Patients who received mexiletine showed significant improvements in most other outcomes in the study, including patient-reported outcomes, QOL scales, and quantitative measures of myotonia.

Table 28: Mixed Model Results for IVR Pain, Weakness and Tiredness; Exercise and Needle electromyography - Includes Mean Estimate Under Both Treatments, the Difference of Treatments (Mexiletine Minus Placebo), Effect Size, and Significance Level

End Point	No. of Participant	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
Interactive voice response						
Stiffness, first period	57	2.53 (1.80 to 3.17)	4.21 (3.40 to 5.20)	-1.68 (-2.66 to -0.706)	-1.36	<.001
Stiffness, second period	57	1.60 (1.04 to 2.20)	5.27 (4.44 to 6.27)	−3.68 (−3.85 to −0.139)	-2.97	0.04
Pain, overall	48	1.54 (0.924 to 2.13)	3.17 (2.43 to 3.93)	-1.63 (-2.00 to -1.26)	-1.36	<.001
Weakness, overall	44	1.96 (1.43 to 2.63)	3.22 (2.52 to 3.98)	-1.26 (-1.67 to -0.861)	-0.994	<.001
Tiredness, overall	49	2.9 (2.12 to 3.68)	3.82 (3.03 to 4.53)	-0.918 (-1.30 to -0.532)	-0.709	<.001
Exercise (% baseline)						
Short, overall	56	83.1 (77.5 to 88.4)	78.6 (71.9 to 84.7)	4.54 (-0.680 to 9.75)	0.347	.09
Prolonged, overall	56	81.8 (76.8 to 87.0)	80.1 (74.7 to 86.4)	1.69 (-3.34 to 6.73)	0.134	.50
Needle, electromyography						
RADM, overall	56	2.05 (1.75 to 2.33)	2.62 (2.39 to 2.86)	-0.568 (-0.812 to -0.325)	-0.947	<.001
RTA, overall	56	2.07 (1.73 to 2.37)	2.54 (2.28 to 2.76)	-0.464(-0.675 to -0.254)	-0.900	<.001

The results of SF-36 showed variation across the dimension with regard to significance levels (Table 29). The overall scores for physical function, role physical, bodily pain and social function showed a significant improvement in addition to the physical composite score which improved in the presence of mexiletine by 5.58 (mexiletine, 44.8 vs placebo, 39.2; difference, 5.58; 95% CI, 3.44-7.72; P < .001).

Table 29: Mixed Model Results of SF-36 (47)

End Point	No. of Participant	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
SF-36						

Physical function, overall	57	42.8 (40.1 to 46.1)	37.8 (34.9 to 41.3)	5.00 (2.81 to 7.20)	.904	<.001
Role physical, overall	57	46.5 (43.6 to 49.2)	39.2 (35.7 to 42.6)	7.23 (4.55 to 9.92)	1.07	<.001
Bodily pain, overall	57	49.8 (46.4 to 52.6)	42.0 (38.6 to 45.5)	7.78 (5.08 to 10.5)	1.14	<.001
General health, overall	57	45.5 (41.9 to 48.7)	44.5 (41 to 47.7)	0.977 (−0.659 to 2.61)	0.240	.24
Vitality, first period	57	45.5 (41.1 to 49.6)	43.7 (39.7 to 48.1)	1.76 (−4.34 to 7.85)	0.211	.57
Vitality, second period	57	51.9 (48.1 to 55.5)	40.0 (35.1 to 45.0)	11.9 (−0.307 to 20.5)	1.43	.06
Social function, overall	57	47.1 (44.4 to 49.8)	41.9 (38.5 to 44.9)	5.27 (2.69 to 7.85)	0.809	<.001
Role emotional, first period	57	46.2 (42.0 to 50.3)	45.5 (41.2 to 49.4)	0.764 (−5.68 to 7.21)	0.102	.81
Role emotional, second period	57	49.9 (46.2 to 53.1)	39.1 (33.5 to 45.0)	10.8 (−1.51 to 21.6)	1.45	.09
Mental health, first period	57	47.3 (43.6 to 51.0)	47.3 (43.7 to 50.6)	0.016 (−5.24 to 5.27)	0.00258	.99
Mental health, second period	57	53.3 (50.2 to 56.2)	44.4 (39.8 to 48.7)	8.84 (−0.572 to 18.2)	1.42	.07
Physical composite, overall	57	44.8 (41.9 to 47.4)	39.2 (35.9 to 41.9)	5.58 (3.44 to 7.72)	1.04	<.001
Mental composite, first period	57	47.4 (44.0 to 50.2)	47.7 (44.2 to 51.3)	−0.351 (−5.87 to 5.17)	-0.0539	.90

Mental composite, second period	57	53.1 (50.3 to 55.8)	42.7 (36.8 to 48.3)	10.4 (0.941 to 20.6)	1.60	.03

All dimensions in the INQOL questionnaire showed significant improvement in the presence of mexiletine, with the exception of weakness, overall. The summary QoL score shows a significant improvement (mexiletine, 14.0 vs placebo, 16.7; difference, −2.69; 95% CI, −4.07 to −1.30; P < .001), Table 30.

Table 30: Mixed Model Results for INQoL (47)

End Point	No. of Participants	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
INQOL						
Weakness, overall	35	45.7 (37.7 to 52.6)	49.3 (41.7 to 57.3)	-3.56 (−9.54 to 2.43)	-0.290	.24
Muscle locking, overall	43	40.0 (33.1 to 46.7)	53.8 (46.4 to 61.1)	−13.7 (−20.4 to −7.03)	-0.888	<.001
Pain, overall	32	39.9 (30.6 to 49.0)	48.2 (39.2 to 57.1)	−8.32 (−13.8 to −2.87)	-0.782	.004
Fatigue, overall	35	48.4 (40.9 to 56.6)	58.3 (50.6 to 66.0)	−9.96 (−17.0 to −2.93)	-0.678	.007
Activity, overall	51	34.2 (26.7 to 43.0)	47.1 (40.1 to 55.5)	−12.9 (−18.3 to −7.43)	-0.950	<.001
Independence, overall	51	17.8 (12.3 to 23.3)	22.5 (17.2 to 28.1)	−4.74 (−8.14 to −1.35)	-0.561	.007
Social relations, overall	51	18.9 (13.5 to 24.5)	25.9 (18.0 to 35.2)	−7.02 (−13.4 to −0.671)	-0.440	.03
Emotions, overall	51	27.7 (22.0 to 34.4)	33.8 (27.1 to 41.5)	−6.13 (−10.1 to −2.15)	-0.619	.003
Body image, overall	51	24.2 (17.3 to 31.0)	29.4 (22.0 to 36.5)	−5.27 (−10.4 to −0.105)	-0.408	.05
QOL, overall	51	14.0 (11.6 to 16.5)	16.7 (14.0 to 19.4)	−2.69 (−4.07 to −1.30)	-0.780	<.001
Perceived treatment effect, overall	51	36.6 (27.1 to 45.8)	21.7 (12.7 to 31.1)	14.9 (7.43 to 22.3)	0.797	<.001

Expected treatment effect, overall	51	36.1 (26.9 to 47.0)	23.1 (14.5 to 33.6)	13.0 (4.18 to 21.8)	0.585	.005

Table 31 shows significant improvements in all clinical assessments carried out in this clinical trial. 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<.001) and overall QMA hand-grip 90% to 5% relaxation times (mexiletine, 0.321 seconds vs placebo, 0.429 seconds; difference, −0.109; 95% CI, −0.177 to −0.0560; P <.001). Electrophysiological measures of myotonia showed a mixed response. Mexiletine significantly improved the severity of graded myotonia on electromyography (right abductor digiti minimi: difference, −0.568; 95% CI, −0.812 to −0.325; P < .001). There was no statistically significant association with mexiletine and electrophysiological exercise testing.

Table 31: Mixed Model Results for clinical assessments (47)

End Point	No. of Participant	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
Clinical assessment, overall, seconds						
Eye closure	57	0.161 (0.0704 to 0.314)	0.474 (0.261 to 0.871)	−0.313 (−0.602 to −0.149)	-0.888	<.001
Handgrip	57	0.164 (0.0858 to 0.294)	0.494 (0.281 to 0.872)	−0.330 (−0.633 to −0.142)	-0.748	<.001
QMA handgrip	54	0.321 (0.274 to 0.370)	0.429 (0.365 to 0.517)	−0.109 (−0.177 to −0.0560)	-0.518	<.001

B.2.6.3 Stunnenberg et al (NCT02045667) (48)

Primary efficacy endpoint

The Bayesian analysis of the individual N-of-1 trial data showed the predefined clinically meaningful effectiveness of mexiletine in 24 of the 27 patients (89%). This enabled the N-of-1 trial to be stopped for these patients and treatment was continued in a normal clinical care setting. Predefined clinical ineffectiveness was shown in 3 patients (11%) with Bayesian analysis. Their individual N-of-1 trials were stopped and mexiletine treatment was discontinued. These three non-responders were found to have an SCN4A genotype.

Bayesian-aggregated N-of-1 trials analysis showed a 100% posterior probability of reaching a clinically meaningful difference for the NDM group overall and for the CLCN1 genotype subgroup; this probability was 93% for the SCN4A genotype subgroup. In the total non-dystrophic myotonia group, the median muscle stiffness score was 6.08 (interquartile range, 4.71-6.80) at baseline and was 2.50 (95% credible interval [CI], 1.77-3.24) during the mexiletine period and 5.56 (95% CI, 4.73-6.39) during the placebo period – see Table 32

where mean results are reported within genetic subgroup. This corresponded with a mean reduction of IVR stiffness score of 3.06 (95% CI, 1.96 to 4.15) for the NDM group (n = 27), 3.84 (95% CI, 2.52 to 5.16) for the CLNC1 genotype subgroup (n = 16), and 1.94 (95% CI, 0.35 to 3.53) for the SCN4A genotype subgroup (n = 11).

Table 32: Primary and Secondary Outcome Measures - IVR measures for total population (N = 27) (48)

Outcome Measure	Baseline Score, Mean (SD)	Placebo Period, Mean (SD)	Mexiletine Period, Mean (SD)	Treatment Effect, Mean (95% CI)	P-value
IVR score					
Stiffness	5.65 (1.78)	5.55 (2.09)	2.42 (1.81)	3.12 (2.46 to 3.78)	<.001
Stiffness CLCN1	6.45 (1.71)	6.46 (1.71)	2.60 (1.50)	3.82 (3.10 to 4.54)	<.001
Stiffness SCN4A	4.34 (2.02)	4.22 (1.93)	2.16 (2.24)	1.89 (1.01 to 2.76)	.002
Genotype × treatment interaction					.004
Pain	1.95 (2.09)	2.08 (2.10)	1.37 (2.13)	0.70 (0.18 to 1.23)	.01
Weakness	2.84 (2.54)	2.96 (2.75)	1.49 (1.66)	1.56 (1.05 to 2.06)	<.001
Tiredness	4.28 (2.28)	3.65 (2.51)	2.41 (2.53)	1.27 (0.58 to 1.95)	.001

The claim that mexiletine reduces myotonia with a meaningful difference (with >95% probability) was already reached after aggregating results from the first 11 consecutive patients with NDM. No significant randomisation order effect (P = .85) or period effect (P = .22) were found.

Secondary efficacy endpoints

Results of the additional secondary outcomes based on frequentist analysis are presented in Table 33. Secondary objective clinical and electrophysiological outcome measures that showed a statistically significant (frequentist) treatment effect at NDM group level included the SF-36 survey (Dutch version) physical and mental component scores, INQoL questionnaire composite score, mean of handgrip and eyelid closure action myotonia bedside tests, walking speed, handgrip dynamometry peak force, and the myotonic discharges grade on needle electromyography.

Table 33: Secondary Outcome Measures - quality of life and handgrip measures for total population (N = 27) (48)

Outcome Measure	Baseline Score, Mean (SD)	Change Placebo	Change Mexiletine	Treatment Effect (Placebo-	P-value

		Period, Mean (SD)	Period, Mean (SD)	Mexiletine), Mean (95% CI)	
HRQoL measure					
SF-36 Physical component score	38.26 (7.81)	1.04 (−0.60 to 2.96)	8.66 (5.94 to 11.38)	7.81 (4.72 to 10.88)	<.001
SF-36 Mental component score	50.29 (9.67)	−1.85 (−4.81 to 1.11)	4.77 (0.67 to 8.48)	6.78 (1.64 to 11.92)	.001
INQoL composite score	96.89 (38.49)	−7.22 (−14.5 to −0.29)	−21.44 (−30.90 to −11.95)	−14.22 (−24.71 to −3.74)	.01
Handgrip action myotonia					
First attempt	3.33 (5.00)	0.46 (−0.30 to −1.23)	−2.39 (−4.22 to −0.55)	−2.85 (−5.28 to −0.42)	.02
Fifth attempt	1.36 (1.25)	0.28 (−0.43 to 0.99)	−0.69 (−1.18 to −0.19)	−0.97 (−2.03 to 0.09)	.07
Fifth attempt CLCN1	0.93 (0.41)	−0.01 (−0.21 to 0.18)	−0.30 (−0.42 to −0.18)	0.04 (−1.11 to 1.19)	.95
Fifth attempt SCN4A	2.59 (3.00)	0.71 (−1.17 to 2.60)	−1.24 (−2.48 to −0.02)	−1.96 (−3.41 to 0.51)	.009
Genotype × treatment interaction					.04
Mean	2.02 (2.33)	0.29 (−0.17 to 0.76)	−1.14 (−1.95 to −0.34)	−1.44 (−2.66 to −0.22)	.02

The INQoL composite score, though significant, was not as highly significant as the split component scores of SF-36 suggesting a need to review the impact of other dimensions of the measure in this study population. The timed tests presented in Table 34 varied in significance across the number of attempts, however, mean attempts show significance with regard to the reduction in time taken to carry out the activities whilst on mexiletine in comparison to placebo.

Table 34: Secondary Outcome Measures - timed tests for total population (N = 27) (48)

Outcome Measure	Baseline Score, Mean (SD)	Placebo Period, Mean (SD)	Mexiletine Period, Mean (SD)	Treatment Effect, Mean (95% CI)	P-value

Eyelid closure action myotonia					
First attempt	6.70 (7.38)	−0.74 (−2.49 to 1.01)	−4.99 (−8.25 to −1.73)	−4.25 (−8.45 to −0.05)	.05
Fifth attempt	2.24 (3.23)	−0.44 (−1.24 to 0.36)	−1.39 (−2.57 to −0.21)	−0.95 (−2.25 to 0.35)	.14
Mean	3.50 (4.15)	−0.43 (−1.24 to 0.37)	−2.54 (−4.15 to −0.93)	−2.11 (−3.94 to −0.28)	.03
Timed Up & Go					
First attempt	10.10 (2.38)	−0.15 (−0.99 to 0.68)	−1.41 (−1.96 to −0.85)	−1.25 (−2.23 to −0.28)	.01
Fifth attempt	8.91 (1.52)	0.29 (−0.45 to 1.03)	−0.70 (−1.13 to −0.27)	−1.00 (−2.01 to 0.03)	.06
Mean	9.51 (1.77)	0.07 (−0.67 to 0.01)	−1.05 (−1.48 to −0.62)	−1.12 (−2.07 to −0.18)	.02
Handgrip dynamometry relaxation time (90%-5%)					
First attempt	0.84 (1.81)	−0.10 (−0.87 to 0.67)	−0.10 (−0.22 to 0.01)	−0.02 (−0.86 to 0.82)	.96
Fifth attempt	0.31 (0.23)	0.00 (−0.12 to 0.13)	−0.02 (−0.07 to 0.03)	−0.01 (−0.16 to 0.14)	.87
Mean	0.48 (0.70)	−0.07 (−0.33 to 0.19)	−0.05 (−0.10 to 0.00)	−0.02 (−0.28 to 0.25)	.91
Handgrip dynamometry peak force (Number)					
First attempt	344.07 (173.56)	−7.81 (−39.39 to 23.77)	18.92 (−6.53 to 44.37)	32.92 (−5.10 to 70.94)	.09
Fifth attempt	321.41 (150.51)	6.15 (−14.99 to 27.30)	27.96 (5.27 to 50.65)	24.08 (−5.22 to 53.39)	.10
Mean	336.85 (157.85)	−3.85 (−25.84 to 18.14)	29.90 (5.74 to 54.05)	37.23 (10.19 to 64.28)	.009
Handgrip dynamometry transient paresis, %					
First attempt	29.19 (27.65)	0.69 (−7.68 to 9.07)	−2.4 (−11.55 to 6.75)	−3.7 (−15.10 to 7.68)	.51
Fifth attempt	20.30 (18.75)	0.73 (−3.63 to 5.09)	−8.56 (−17.26 to 0.14)	−12.25 (−22.04 to −2.47)	.02
CLCN1	24.35 (23.11)	4.31 (−1.32 to 9.94)	−18.75 (−28.59 to −8.91)	−23.85 (−32.45 to −15.24)	<.001
SCN4A	9.12 (10.33)	−5.00 (−11.32 to 1.32)	9.56 (1.24 to 17.87)	13.71 (−1.96 to 25.47)	.02

Genotype × treatment interaction					<.001
Mean	24.11 (20.13)	−0.08 (−4.84 to 4.68)	−6.38 (−10.81 to −1.95)	−7.34 (−13.45 to −1.24)	.02
CLCN1	32.56 (22.35)	1.53 (−5.70 to 8.75)	−11.26 (−16.83 to −5.69)	−12.37 (−18.35 to −6.38)	<.001
SCN4A	8.10 (7.40)	−2.64 (−8.50 to 3.22)	2.31 (0.10 to 4.52)	4.46 (−3.85 to 12.76)	.28
Genotype × treatment interaction					.002

B.2.6.4 Suetterlin et al. 2015 (49)

Efficacy endpoints

This retrospective review of a large skeletal muscle channelopathy cohort (n=63) had a mean length of follow-up of 4.8 years (range, 6 months to 17.8 years).

Efficacy was based on subjective patient report, documented by the clinician where the mean effective daily dose of mexiletine across the study population was 416.7 mg. Twelve patients were refractory to mexiletine treatment.

B.2.6.5 Conclusions – efficacy of mexiletine

Well conducted randomised clinical studies have demonstrated mexiletine's efficacy and well tolerated profile as an anti-myotonic intervention that and significantly improved myotonia, pain, weakness and tiredness (1, 47, 48) and long-term use is supported with observational data of up to 17.8 years of follow-up which in the context of a rare disease is unusual and significant (49). Health-related quality life was consistently and significantly improved in the disease specific instrument INQoL and also to some degree with SF-36. However, as discussed in section 3a and 6f and Appendix B the SF-36 is not an appropriate quality of life instrument to measure myotonia, and therefore unable to capture the full treatment benefits of mexiletine. Accordingly, INQoL measures are mapped directly to EQ-5D in the health economic evaluation.

B.2.7 Subgroup analysis

No sub-group analyses are presented as per NICE scope.

B.2.8 Meta-analysis

A meta-analysis of the mexiletine trials was not considered feasible and any results would be highly uncertain. See Section B.2.9 below for further details regarding the challenges in conducting such analysis which apply equally to the mexiletine trials as well as the lamotrigine trial considered for an indirect treatment comparison.

A summary of challenges of a meta-analysis for this indication are:

- Patients across studies differed in disease diagnosis, for example, patient population in Statland et al did not have to be genetically confirmed NDM patients and the number who had are not reported (47).
- Clinical exchangeability of the primary endpoints of stiffness for VAS and IVR used in the mexiletine trials (see Appendix M).
- Clinical endpoints such as eyelid closure action myotonia and handgrip relaxation time were not measured in MYOMEX and in the Statland trial a geometric mean for the time was recorded. Additionally, these endpoints have a narrow focus that are not necessarily descriptive of the impact of myotonia across all types of NDM. In the assessment of these endpoints, there are potential issues such as interobserver variability and selection of points for assessment (see Appendix M).
- Which version of the INQoL questionnaire was used – in MYOMEX it is version 1.2; Statland et al version 1.0 and it is not reported in Stunnenberg et al. Different versions have slightly different questions and the scores reported could be different. In addition, Stunnenberg et al report only a composite score for INQoL and no results for the domains.
- In the Statland trial, up to 25% of outcome data for the IVR, nearly 50% for some domains of the INQoL and around 10% of SF-36 data were missing, but it was not reported how these missing data were interpreted.
- Ideally patient level data would have helped address some of the above issues and the authors of the Statland and Stunnenberg trials were approached for patient level data without success.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Feasibility assessment for conducting an indirect or mixed treatment assessment of mexiletine vs. lamotrigine

Lupin does not believe that lamotrigine is a relevant or appropriate comparator as specified in the NICE Final Scope. Reasons for this are described in Decision Problem – Section B1.1. and Section B.1.3.7. and it does not represent established use in the NHS.

A systematic literature review was conducted including lamotrigine as well as mexiletine to identify any randomised controlled trials. As described in detail in Appendix D four trials were found (three for mexiletine and one for lamotrigine). Table 35 lists the trials that were found. The quality assessment of these studies are provided in Appendix D. Apart from the Andersen (lamotrigine) trial (8), which has some concerns, the trials were well conducted. The patients treated with lamotrigine were provided with mexiletine as escape medicine during the trial while in the mexiletine trials no escape medication was allowed.

Table 35: Summary of the randomised controlled trials found from the SLR and used to assess feasibility of performing an indirect or mixed treatment comparison

References of trial	Mexiletine	Lamotrigine	Placebo
Andersen (2017) (8)		Yes	Yes
MYOMEX (2017) (1)	Yes		Yes
Statland (2012) (47)	Yes		Yes
Stunnenberg (2018) (48)	Yes		Yes

The authors of the lamotrigine trial and also the other mexiletine trials (Statland et al, and Stunnenberg et al) were contacted to see if patient level data could be obtained to support any potential ITC without success. Therefore, only Lupin's own trial (MYOMEX) has patient level data available.

A feasibility analysis was undertaken to assess the possibility of conducting an indirect or mixed treatment comparison of mexiletine versus lamotrigine. Lupin also consulted with clinical experts regarding the trial endpoints and their exchangeability (Appendix M).

A summary of the baseline demographics and disease characteristics across these studies are presented in Table 36. The trial populations are broadly similar in terms of age and all required genetic confirmation of NDM in the inclusion criteria apart from the Statland trial. In the Statland trial, the inclusion criteria stated eligible patients could have genetically confirmed NDMs, or clinical features of NDMs but negative myotonic dystrophy DNA testing. This could introduce some uncertainty that all the patients recruited into the trial definitely had NDM. Based on the VAS scales used in the mexiletine trials the Statland population may have been a milder population compared to the one recruited by Stunnenberg et al. but this is difficult to fully determine in the absence of patient level data and also from the fact that there were missing data from the Statland et al trial and slightly different inclusion criteria. MYOMEX also

used a VAS where patients marked between 0-100 mm the level of stiffness whilst in the other two mexiletine trials patients used an interactive voice response (IVR) diary to report stiffness (1=minimal to 9=worst ever experienced).

Table 36: Trial, Baseline Demographic and Disease Characteristics

Characteristic	Andersen 2017(8)	MYOMEX 2017(1)	Statland 2012(47)	Stunnenberg 2018(48)
Trial design type	Double blind, cross-over RCT	Double blind, cross-over RCT	Double blind, cross-over RCT	Double blind, cross-over RCT[3]
Study treatments	Lamotrigine Placebo	Mexiletine 600mg/day Placebo	Mexiletine 600mg/day Placebo	Mexiletine 600mg/day Placebo
Treatment duration	8 weeks	18 days	4 weeks	4 weeks
Trial conduct period	2013-2015	2011-2014	2008-2011	2014-2015
Countries	Denmark	France	USA, Canada, UK, Italy	Netherlands
Number of patients analysed	26	25	59	27
Patient level data available?	N	Y	N	Y[2]
Genetically confirmed NDM	Y	Y	Y/N[9]	Y
Efficacy subgroups	None	MC/PC	None	Genotype
Age (years)[1]	45	43	43	43
Male (%)	61	[redacted]	56	73[8]
BMI (kg/m^2) [1]	28	[redacted]	NR	NR
MC (%)	54	[redacted]	NR	NR
PC (%)	46	[redacted]	NR	NR
Stiffness assessment type[4]	MBS (0-5)	VAS (0-100)	VAS (0-9)	VAS (0-9)
Baseline stiffness[5]	3.2 (1.2)	[redacted] ([redacted])	4.26 (2.71)	6.65 (1.78)

Eyelid closure action myotonia (s)	4.8	NR	0.49[7]	3.50
Hand grip relaxation time (s)[7]	4.3	NR	0.86[7]	2.02

[1]Mean/median. [2]IPD available for limited baseline and primary endpoint (mean daily stiffness severity score). [3]Aggregate N-of-1 design, multiple period per patient. [4]Patient self-reported. [5]Mean(SD). [7]Geometric mean. [8]Incorreclty reported as 22% in the abstract of the publication. [9] Inclusion criteria stated patients could have genetically confirmed NDMs, or had clinical features of NDMs but negative myotonic dystrophy DNA testing

Table 37 lists all the outcomes measures across all relevant trials.

Table 37: Outcome measures across trials for indirect comparison feasibility analysis

Outcome Measures	Outcome	Andersen (2017)(8)	MYOMEX (2017)(1)	Statland (2012)(47)	Stunnenberg (2018)(48)
STIFFNESS					
Score of stiffness severity on a self-assessment scale (100 mm VAS)	Primary		x		
Patient-reported Stiffness on the interactive voice response (IVR) diary (experience in last 24 hours recorded daily, on a scale of 1 to 9)	Primary			x	x
Myotonia Behaviour Scale (MBS), change from baseline	Primary	x			
PAIN					
Patient Reported Pain on the IVR diary (experience in last 24 hours recorded daily)	Secondary			x	x
WEAKNESS					
Patient Reported Weakness on the IVR (experience in last 24 hours recorded daily)	Secondary			x	x
TIREDNESS					
Patient Reported Tiredness on the IVR (experience in last 24 hours recorded daily)	Secondary			x	x
DISEASE SEVERITY					
Clinical Myotonia Scale (CMS) comprising 2 sections: myotonia severity scale (examination of patient) and disability scale (patient's view of disability in activities of daily living)	Secondary		x		

Clinical Global Impression (CGI) efficacy index	Secondary		x		
Average in use of mexiletine as escape medicine*	Secondary	x			
CLINICAL MYOTONIA OF THE EYE					
Eyelid muscle relaxation time after 5 secs maximal contraction (repeated 5x)	Secondary	x		x	x
CLINICAL MYOTONIA OF THE HAND					
Hand Grip relaxation time after 5 seconds maximal contraction (repeated 5x) - dynamometry, electrophysiological tests	Secondary	x		x	x
CLINICAL MYOTONIA OF THE LEG					
TUG-test (time up and go) 10 minutes of rest in the chair, walk 3m and then return to sitting	Secondary	x			x
14-step-stair-test, walk up 14 stairs and return to base	Secondary	x			
Electromyography (EMG)					
Electromyography (EMG) – myotonic discharge grading performed in left rectus femoris muscle at rest (10 insertions, with 30 seconds of evaluation per insertion)	Secondary			x	x
GENERAL TIMED EXERCISE TESTS					
Compound Motor Action Potentials (CMAP) after short exercise test	Secondary		x	x	x
Compound Motor Action Potentials (CMAP) after long exercise test	Secondary			x	x
Chair test: time needed to stand up from a chair, walk around it and sit down again	Secondary		x		

HEALTH RELATED QUALITY OF LIFE					
INQoL score	Secondary		x	x	x
SF-36 (mental and physical components)	Secondary	x		x	x

As can be seen from Table 37 above there are very few endpoints which have been used in the both the lamotrigine and mexiletine trials. The following outcomes were assessed in the lamotrigine trial and at least one of the mexiletine trials:

- Stiffness
- Clinical measures of myotonia of the eye, hand or leg
- Health related quality of life (HRQoL), namely SF-36

All were examined to see if they could form a clinically meaningful ITC, in particular the measures of stiffness and HRQoL that were used in the lamotrigine and mexiletine studies.

Measurement of stiffness

Three different measures of stiffness were used across the trials:

- The lamotrigine trial used the myotonia behaviour scale (MBS),
- MYOMEX used a VAS (0-100 mm)
- The Statland and Stunnenberg studies used an interactive voice response (IVR) diary (1=minimal to 9=worst ever experienced).

The Behaviour Rating Scale originally developed as pain measurement instrument (54), and was modified by Hammeren et al (55) in a study of six NDM patients. The MBS comprises of the following questions on a scale of 0 to 5 (Table 38).

Table 38: Myotonia Behaviour Scale (MBS)

Score	Description
0	No stiffness
1	Some stiffness exists, which can be ignored
2	Some stiffness exists, which can be ignored at times, but doesn't impair daily activities
3	Stiffness exists, which demands a higher level of mental awareness when performing **some** duties and activities
4	Severe stiffness exists, which impairs **every** duty and activity
5	Incapacitating stiffness exists, which demands constant moving not to be totally locked up, with regard to movement

Clinical experts were consulted regarding the possible clinical interchangeability of the MBS and VAS/IVR scales. All stated that the MBS was different to the VAS/IVR as it not only measured stiffness but also impact on function. Some also noted the scale had been developed in a very small study and had not been validated, see Appendix M.

Some experts also commented that the VAS and the IVR may not be wholly interchangeable either as it might depend on how the question was asked of participants; there could also be differences in that the VAS requires a line to be drawn between 0 and 100 mm whilst the IVR patients were asked to provide a score between 1 and 9. It should also be noted that there is no explanation provided for the existence of missing data in the Statland study (47).

Therefore, it was concluded that it would not be appropriate to conduct ITC of this outcome given the variability in the measures used to assess stiffness.

Clinical myotonia tests

The following tests were used in the lamotrigine trial and also on one or two of the mexiletine trials.

- Eyelid muscle relaxation time after 5 secs maximal contraction (repeated 5x)
- TUG-test (time up and go) 10 minutes of rest in the chair, walk 3m and then return to sitting
- Hand Grip relaxation time after 5 seconds maximal contraction (repeated 5x) - dynamometry, electrophysiological tests

Clinical experts consulted by Lupin, see Appendix M, stated such measures were used in the clinical diagnosis of myotonia such as the eyelid and hand-grip relaxation time but there would be issues in accurately determining the clinical effectiveness of a particular treatment and interpreting the results for the following reasons:

- Lack of a consensus on minimally clinically important difference for the tests
- Lack of precision
    - Observer bias
        - Impacted by observer reaction time and their judgement of fully open hands and stretched fingers/eyes; this is particularly difficult in the least affected patients who might be able to open their eyes or hands quite quickly
        - Times recorded for eyelid myotonia could be quite different according to the NDM genotype
    - Patient expectation bias
        - Patients slowing down opening their eyes because they misunderstood the doctor's instructions
    - Instrument used
        - How the time taken to open the eyes was recorded might impact the results – The Statland trial and the lamotrigine trial reported that a stopwatch was used to record the time, but the lamotrigine trial did not

state how this was done. The use of a stopwatch itself can be subject to variability.

Hammaren et al (55) report that normal values of TUG are not definitely set and they differ between investigators. The TUG can also be dependent on the height of the chair (neither the Andersen nor Stunnenberg trials where this test was used report the height of the chair used).

Therefore, it was concluded that it would not be appropriate to conduct an ITC of this outcome given the issues described above.

HRQoL instruments

The SF-36 was used in the lamotrigine trial and also two mexiletine trials. Both the Statland and Stunnenberg mexiletine trials reported the SF-36 physical and composite scores with Statland also reporting individual domains. However, compared to INQoL, SF-36 is not considered an appropriate tool for the assessment of quality of life in NDM patients (15, 36).

It should be noted that unfortunately in the Statland et al trial, up to 25% of outcome data for the IVR, nearly 50% for some domains of the INQoL and around 10% of SF-36 data were missing, but it was not reported how these missing data were interpreted. This makes it difficult to assess impact of mexiletine on QoL in the Statland study.

The lamotrigine trial appears to have only reported an overall score for the SF-36. The lamotrigine trial reported that the SF-36 overall health status in patients was 65±18 at baseline but the authors also stated that normal health, measured by SF-36, is defined as 50 which either means the population had very mild disease or it has not been reported correctly.

We note that the developers of the SF-36 (56) state that *"The components analyses showed that there are two distinct concepts measured by the SF-36 – a physical dimension and a mental dimension. Therefore, it is not appropriate to try and come up with one overall score; thus, instead the two summary scores are used"*.

Furthermore, in a systematic review, Lins et al (57) identified at least nine different ways of calculating a SF-36 Total Score and concluded that calculating a SF-36 Total/Global/Overall Score is a measurement bias (a systematic error) that can lead to a measure with poor validity. Therefore, the use of an overall score in the lamotrigine trial is considered inappropriate as well as there being insufficient data to inform a meaningful ITC for this outcome. A complete list of the what was reported by each trial is shown in Appendix D.

Conclusion

An ITC/MTC of the lamotrigine trial versus any of the mexiletine trials is not possible and lamotrigine is not established use in the NHS.

B.2.9.1 Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

B.2.10 Adverse reactions

B.2.10.1 MYOMEX Study (NCT02336477) (1)

In MYOMEX, 25 patients received at least one dose of mexiletine (safety population). The mean mexiletine treatment duration was 19.0 days (SD 2.4 days), representing an exposure of 1.4 patient-years (1). In MYOMEX, 25 patients received at least one dose of mexiletine (safety population). The mean mexiletine treatment duration was 19.0 days (SD 2.4 days), representing an exposure of 1.4 patient-years (1).

No patient withdrew due to intolerable increase in myotonia severity. Only one patient (4.0% of the total population) prematurely discontinued the study medication following occurrence of an adverse event (1).

The severity of the majority of adverse events was [redacted]% mild and [redacted]% moderate experienced by the participants receiving mexiletine. Only one adverse event in the mexiletine group was deemed to be severe (tachycardia), who discontinued treatment. The most frequent treatment-related adverse events were upper abdominal pain, vertigo and insomnia. While mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, no marked variations in ECG parameters were observed between baseline and the end of the treatment period when tested on NDM patients. An overview of adverse events are reported in Table 39 (1).

Table 39: Overview of adverse events in the safety population (1)

		Placebo (N = 25)		**Mexiletine (N = 25)**		**Total (N=25)**	
		Ev	Patient (%)	Ev	Patient (%)	Ev	Patient (%)
Total	Any AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Severe AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AE requiring concomitant medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = Number of patients
Patient = Number of patients with at least one AE
% = Percentage of patients with at least one AE
Ev= Number of events

In the MYOMEX study the most frequently reported events ([redacted] patients) during mexiletine treatment which were considered as related to mexiletine were abdominal upper pain ([redacted]

patients), nausea (patients), and insomnia (patients). Tachycardia in a context of anxiety led to mexiletine discontinuation in one patient. Abnormal ECG findings were reported for patients but were not considered by the investigator or cardiologist as a contraindication to initiate/continue mexiletine. No significant variations were observed in 12-lead ECG parameters or in the portable ECG device parameters between baseline and the end of the treatment period, either with placebo or mexiletine. No other safety signals were observed and overall, investigators as well as patients considered mexiletine tolerability as good.

Table 40: Adverse events by SOC and PT – SAF

		Placebo (N = 25)		**Mexiletine (N = 25)**		**Total (N=25)**
	Ev	Patient (%)	Ev	Patient (%)	Ev	Patient (%)
TOTAL POPULATION						
INFECTIONS AND INFESTATIONS						
Rhinitis						
Nasopharyngitis						
Gastroenteritis						
Influenza						
Sinusitis						
NERVOUS SYSTEM DISORDERS						
Headache						
Radicular pain						
Somnolence						
Paraesthesia						
Tremor						
GASTROINTESTINAL DISORDERS						
Abdominal pain						
Nausea						
Abdominal pain upper						
Diarrhoea						
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Fatigue						

Chest pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphadenopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CARDIAC DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAR AND LABYRINTH DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EYE DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MUSCOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle contracture	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSYCHIATRIC DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]		[redacted]	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysmenorrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VASCULAR DISORDERS	[redacted]	[redacted]	[redacted]		[redacted]	
Flushing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = Number of patients
Patient = Number of patients with at least one AE
% = Percentage of patients with at least one AE
Ev= Number of events

Table 41: Drug-related adverse events by SOC and PT – SAF

Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal Pain Upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General Disorders And Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chest Discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, Thoracic And Mediastinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ear And Labyrinth Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision Blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal And Connective Tissue Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain In Extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin And Subcutaneous Tissue Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Flushing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = Number of patients
Patient = Number of patients with at least one AE
% = Percentage of patients with at least one AE
Ev= Number of events

B.2.10.2 Statland et al NCT00832000 (47)

In this phase II, double-blind, placebo-controlled crossover study, 58 patients received at least one dose of mexiletine. Overall, mexiletine was well tolerated. There was one serious adverse event determined to be not study-related (narcotic withdrawal). The most common adverse event was gastrointestinal in nine participants receiving mexiletine and one receiving placebo. There were two reported cardiac adverse events both found incidentally on electrocardiogram at the end of week 4: one patient had bradycardia (mexiletine) that resolved on follow-up electrocardiogram; the other had premature ventricular complexes (placebo). Neither necessitated stopping the study. All the reported adverse events are listed in Table 42 (47).

Table 42: Reported adverse events in clinical trial of mexiletine in sodium channel and chloride channel mutations (47)

Category	Mexiletine	Placebo
Cardiac	1	1
Constitutional	3	0
Dermatology/Skin	1	2
Gastrointestinal	9	1
Infection	1	3
Lymphatics	0	1
Musculoskeletal/Soft Tissue	0	2
Neurologic	5	1
Pain	4	0
Total	24	11

B.2.10.3 Stunnenberg et al NCT02045667 (48)

In this series of aggregated, double-blind, randomised, placebo-controlled N-of-1 trials, performed in a single academic referral centre, the most common adverse event was gastrointestinal discomfort [21 mexiletine (70%), 1 placebo (3%)]. These symptoms were controlled in most patients with lifestyle advice. All 24 mexiletine responders continued mexiletine treatment during the follow-up period that was completed on September 10, 2016 (range, 18-31 months), without adverse events that occasioned discontinuation.

One serious adverse event was reported during mexiletine treatment; with one patient developing an allergic skin reaction (3%) resulting in treatment discontinuation.

No clinically relevant electrocardiographic rhythm abnormalities or cardiac conduction interval changes were observed during the course of the trial.

B.2.10.4 Suetterlin et al., 2015 (49)

In this retrospective review of 63 patients treated for 6 months or greater with mexiletine, a total of 33 of 63 patients (52.4%) reported 1 or more adverse events. Sixteen of the 23 patients (69.6%) who reported dyspepsia required dyspeptic therapy, despite which four stopped taking mexiletine. Eight of 11 patients (72.7%) who stopped mexiletine previously because of inefficacy or intolerable adverse events found it effective and tolerable on retrial.

No serious adverse events were reported. Further, paired assessment of ECG parameters while not taking mexiletine and at the highest dose at which an ECG was recorded for each individual revealed no significant change in heart rate (71 beats per minute vs 71 beats per minute; p=0.97), PR interval (154 milliseconds vs 166 milliseconds; p=0.23), QRS duration (89 milliseconds vs 89 milliseconds; p=0.52), automatically calculated QTc (406 milliseconds vs 405 milliseconds; p=0.88), or manually calculated QTc (386 milliseconds vs 392 milliseconds; p=0.30). All 16 patients referred to cardiology because of cardiac concern were advised it was safe to start or continue mexiletine.

The authors concluded that the absence of any significant change in ECG parameters or serious adverse events within a total of 302.4 years of patient follow-up demonstrates the long-term safety of mexiletine and suggests that frequent routine ECG monitoring of patients on maintenance dose may not be necessary.

B.2.10.5 Post-marketing safety

As mexiletine has been approved since 1975 as an antiarrhythmic and since 2010 in France for the symptomatic treatment of myotonic disorders, periodic safety update reports (PSURs) provide long-term safety information supporting the use of mexiletine for the treatment of chronic conditions. Safety data presented in this section are based on:

Four PSURs (2010–2012) related to the approved indication in myotonic syndromes in France (58-61)

One French PSUR for the period between the withdrawal of mexiletine (2008) and its approval in the myotonia indication (2010), during which time Boehringer Ingelheim France provided mexiletine for an off-label indication with no alternative available therapy (myotonia) (62)

One international PSUR (2005–2008) related to the antiarrhythmic indications and covering the last period (2005–2008) before mexiletine production ended (63)

Following the approval in 2010 of mexiletine for the symptomatic treatment of myotonic disorders in France, four PSURs have summarised the long-term safety and tolerability of mexiletine (Mexiletine hydrochloride AP-HP 200 mg capsules) in patients with myotonic disorders (58-61).

Between November 2010 and October 2012, 18 treatment-related adverse events were reported over 2 years of treatment with mexiletine in France, including the MYOMEX study (15 treatment-related adverse events). Treatment-related adverse events reported outside of the MYOMEX study were drug exposure during pregnancy and foetal exposure during pregnancy (59-61).

In addition to the 25 patients treated in the MYOMEX study, a mean number of 372 patients with myotonic disorders were treated with mexiletine (based on a posology of two capsules per day, with 407,300 capsule units for treatment over the period). During the period covered by these PSURs, there were no reported serious adverse events, no dose modifications and no modifications of the formulation for safety reasons (58-61).

The analysis of safety data collected between 2010 and 2012 did not reveal evidence of any new safety issues with the use of mexiletine in France. As such, the benefit-risk profile was considered favourable (58-61).

Between 2008 and 2010, mexiletine (Mexitil®, mexiletine hydrochloride 200 mg capsules) was imported by Boehringer Ingelheim France for off-label usage by French patients with myotonic disorders, while a long-term solution was investigated. During this period, total exposure to mexiletine was 285.1 patient-years. Three health-professional confirmed cases were reported in patients with myotonia, two of which (in the same patient) were serious (62):

- Malaise without prodrome and syncope in a 19-year old female patient treated with mexiletine for myotonia
- Dyspnoea on exercise in a 20-year old female patient, requiring hospitalisation, about 40 days after the start of mexiletine for myotonia. Mexiletine was discontinued and the patient recovered. Co-suspect drugs included metoprolol, desloratadine and hydroxyzine
- The third case was a non-serious occurrence of somnolence in a 20-year old male patient (63). Somnolence was also reported in the MYOMEX study and is listed as a common adverse drug reaction (ADR) in the mexiletine summary of product characteristics (1, 39).

Pre-2008

The last international PSUR published by Boehringer Ingelheim covered the period 2005–2008 and was related to the use of mexiletine (Mexitil®, mexiletine hydrochloride 200 mg capsules) in cardiac indications. During this period, exposure to mexiletine was approximately 7,740 patient-years in clinical trials and 486,077 patient-years in clinical practice (62).

During the PSUR period, the total number of health-professional confirmed cases was 258 and the total number of adverse drug reactions was 411 (Table 43) (62). During this period, no new issues or safety concerns were identified. Of the 258 cases, there were two health-professional confirmed case reports classified as off-label use in patients with myotonia, neither of which was serious. One case was the occurrence of nausea, vomiting, constipation and confusion requiring discontinuation of mexiletine in a 42-year old male patient, treated

with mexiletine (200 mg TDS) for paramyotonia congenita. The second non-serious case was diffuse mild dysesthesia in a 48-year old female patient while on treatment with mexiletine (Mexitil®, mexiletine hydrochloride 200 mg) for Becker myotonia congenita (62).

Table 43: Health-professional confirmed case reports and ADRs (PSUR 2005–2008) Boehringer Ingelheim. Periodic safety update report. Mexitil. October 2005-October 2008

Cases	**n**
Health-professional confirmed case reports	258
Serious	110
Non-serious	148
Fatal	13
ADRs	411
Serious	178
Non-serious	178
Seriousness not reported	55
ADRs: adverse drug reactions; PSUR: periodic safety update report	

Post-launch of NaMuscla (December 2018 onwards)

Safety data are now available since the marketing authorisation of NaMuscla for NDM for the period 18 December 2018 to 17 June 2019 (64). No new risk has been identified during the review period. The signals of drug interaction between sacubitril/valsartan and mexiletine causing proarrhythmogenic effect, fatal Drug Reaction and Eosinophilia with Systemic Symptoms (DRESS), fatal Pulmonary fibrosis were identified, which will be subject for close monitoring and discussion in future PSUR. In all cases mexiletine had been prescribed for a cardiac indication rather than for NDM.

B.2.10.6 Conclusions – safety and tolerability of mexiletine

Mexiletine has been approved initially for ventricular arrhythmia since 1975 in a similar posology as for the treatment of myotonia and is still in use in countries like US, Canada and Japan for this indication. Thus, there are extensive post-marketing safety data available from its past and current use for the treatment of arrhythmia spanning several thousand patient-years. In addition to this, there is post-marketing safety data available from its use in the treatment of myotonic disorders from France where the drug is approved for the symptomatic treatment of myotonic disorders since 2010.

In randomised controlled trials of mexiletine for the treatment of NDM, mexiletine was found to be well tolerated, with gastrointestinal discomfort being the most common adverse event. There were no treatment-related serious adverse events. Post-marketing safety data are also available, covering the periods 2008–2012 (myotonia indication) and 2005–2008 (mostly cardiac indications) and since the launch of NaMuscla. The analysis of post-marketing safety data did not reveal evidence of any new safety issues with the use of mexiletine in myotonic

disorders (58-61, 63, 64). Thus, there is substantial safety data for a medicine being assessed in such a rare disease.

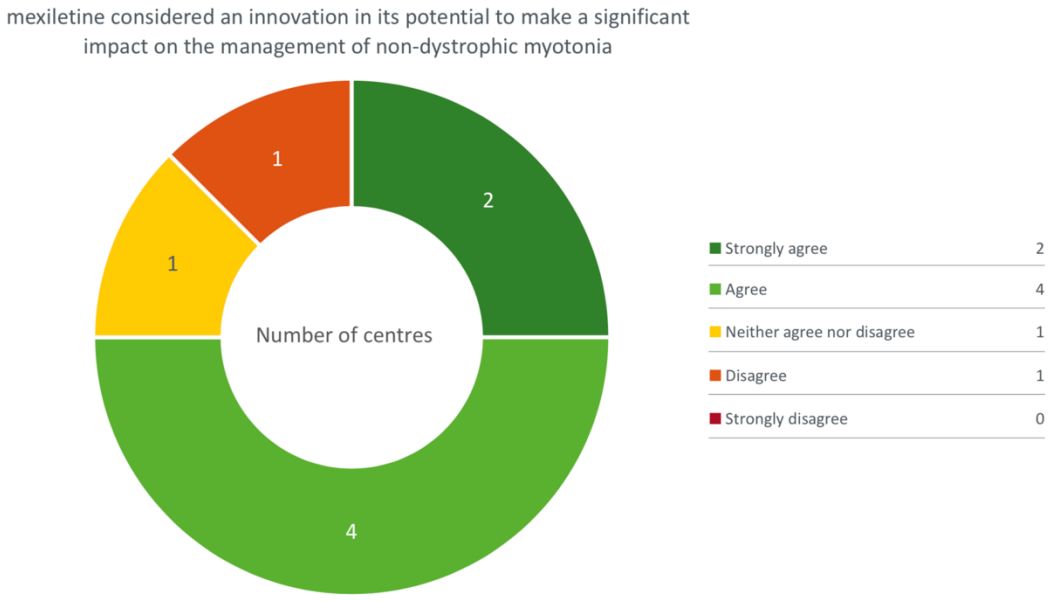
B.2.11 Ongoing studies

There are no known ongoing studies. However, Lupin continues to collate clinical and patient opinion of the impact of mexiletine in the treatment of NDM patients.

B.2.12 Innovation

NaMuscla is the first licensed medicine for NDM that brings access for patients to a highly effective treatment which can dramatically improve HRQoL. From recent market research (3) out of eight neuromuscular centres in England & Wales, responsible for circa 393 patients with NDM, six centres strongly agreed or agreed that mexiletine was an innovation in the treatment of NDM (Figure 24). These 6 centres collectively accounted for 93% of the patients who were currently being treated.

Figure 24: Mexiletine as an innovation in the management of NDM (3)



Mexiletine is an established first choice treatment for NDM. For many patients, treatment with mexiletine is transformational and effectively a step-change in their life. Many patients may prefer to try and manage their condition themselves, avoiding trigger factors such as cold, stressful situations (e.g. presenting at meetings), anxiety about going to new places where may need to walk up or down stairs or avoiding such places where there may be many stairs. stressful situations. Feedback from interviews with clinical experts indicate that patients express the view that once they have tried mexiletine they wished they had taken it sooner

(Appendix M). Conversely, patients who have been on mexiletine but stop due to a lack of access to mexiletine supply, notice a significant difference after stopping mexiletine and then re-starting it (Appendix M).

A patient survey (MyoPath) has highlighted the dramatic impact mexiletine had on symptoms and how their condition greatly worsened as a result of not being treated with mexiletine (27). Unlike the UK, most countries in Europe have not had the ability to obtain mexiletine via importation. Despite this patients have experience difficulties in obtaining special imported mexiletine due to supply disruption and shortages (see Appendix L and (27)). NaMuscla offers offer a guaranteed supply of mexiletine through usual channels of supply in the UK. The pan-European MyoPath survey found that the ability to access mexiletine 'drastically' or 'substantially' reduced frequency of falling in 77% of patients and disruption in mexiletine treatment harmed 85% of patients (27, 38). Another survey found that 26.9% of patients found it hard to find employment that accommodates issues caused by stiffness and 65.4% having anxiety related to negative experiences (falling, shaming, bullying) (2). Patient interviews found that because of restrictions in their condition patients lead a more sedentary lifestyle (Appendix L) which could potentially have wider public health issues.

In the MyoPath survey respondents reported a significant or drastic improvement in the following as a result of mexiletine:

- 72% of patients in the ability to work
- 75% in ability to exercise or play sports
- 85% in overall mobility (e.g. leaving house or taking public transport)
- 82% ability to drive car
- 80% ability to take care of my child
- 77% ability to socialise and communicate with others (e.g. speaking in public, shaking hands)
- 66% ability to do tasks independently (e.g. dress, brush hair, brush teeth, tie shoes, feed myself)
- 91% emotional well-being

As NDM is a hereditary condition some patients decide never to have children for the fear of passing on a condition which may severely affect the quality of life (Appendix L), so this will be an aspect that is not captured in the QALY.

Thus, the availability of licensed mexiletine (NaMuscla) brings assurance for patients to obtain a highly effective treatment. The psychological and social impact of NDM itself should not be underestimated and the availability of clinically effective treatment for NDM together with the assurance of mexiletine supply, without possible delays or interruption associated with uncertainty of importation of medicines, will not necessarily be captured in the QALY.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Key findings of the clinical evidence

Mexiletine (NaMuscla®) is a non-selective voltage-gated sodium channel blocker that exerts its potent anti-myotonic effect by blocking muscular sodium channels. Clinical studies have demonstrated that mexiletine significantly improves myotonia, pain, weakness and tiredness in patients with NDM. Health-related quality of life improved significantly in mexiletine-treated patients, measured primarily using the disease specific instrument the Individualised Neuromuscular Quality of Life (INQoL) Questionnaire.

MYOMEX – pivotal registrational phase III trial results(1)

Myotonia "Stiffness" improvements

The primary endpoint of this study was stiffness as assessed by the patient on a VAS. The median stiffness VAS scores for patients receiving mexiletine in the mITT population were of [redacted] at baseline and decreased to [redacted] at the end of the treatment period, while those on placebo did not change ([redacted] vs [redacted] at baseline and end of treatment, respectively). This represents a median change of [redacted]% of the stiffness VAS score compared to baseline for subjects under mexiletine (vs. a [redacted]% median change for placebo). According to the mixed effect linear model, mexiletine treatment allowed a highly significant stiffness improvement regardless of the subjects' genotype ([redacted]). The mixed effect linear model evidenced no carry-over effect (treatment sequence effect, [redacted]). Long-term data from the MYOMEX trial for the 8 patients who had a mean follow up period of 48 months (range 3 – 94 months) demonstrate that the reduction in stiffness scores achieved with mexiletine at the end of the MYOMEX trial were least maintained, as there was a further 7% reduction in the average in the VAS stiffness score. The mean mexiletine hydrochloride dose at the time of the last measurement was 400 mg daily.

QoL improvements

In addition to the stiffness improvement, an improvement in quality of life was observed in every domain of the INQoL. The mixed effect linear model showed that this improvement with mexiletine was significant for the total population demonstrating a treatment effect for each domain of the INQoL questionnaire, [redacted]).

Patient and investigator reported outcome of change

Overall, mexiletine treatment was considered as efficient by both the patients ([redacted]%) and the investigators ([redacted]%). Patients clearly preferred the mexiletine treatment period over the placebo period ([redacted]%, [redacted]) and only [redacted] patients were not willing to continue mexiletine treatment after the study (including the one who prematurely discontinued the study following an AE and one who did not consider the treatment as efficient).

Clinical Myotonia Scale (CMS)

An improvement in the severity and disability scores of the newly developed CMS was also observed after mexiletine treatment for both diagnoses. The decrease observed in the disability score for the total study population was significant ([redacted]) with no significant diagnosis-treatment interaction effect ([redacted]).

The global score of severity was strongly correlated with the disability score ([redacted], [redacted]), the stiffness score ([redacted], [redacted]) and the quality of life ([redacted], [redacted]). It was also inversely related to the perceived and expected treatment effects [redacted], [redacted] and [redacted], [redacted] respectively. Similarly, the global score of disability was strongly correlated with the severity score ([redacted], [redacted]), the stiffness score ([redacted], [redacted]) and moderately correlated with the quality of life ([redacted], [redacted]). It was also inversely related to the perceived and expected treatment effects [redacted], [redacted] and [redacted], [redacted] respectively.

Supportive evidence for the clinical effectiveness of mexiletine (47, 48)

Further evidence for the clinical effectiveness of mexiletine comes for the Phase II trial by Statland et al and an aggregated N-of-1 trial by Stunnenberg et al.

In the Statland trial mexiletine significantly improved the primary endpoint of patient-reported severity score stiffness on the IVR diary compared to placebo (47). Because of a statistically significant interaction between treatment and period for this outcome, treatment effect was estimated separately for each period. Change in treatment effect in period 1 was highly significant (P <.001) at 2.53 for mexiletine and 4.21 for placebo, a difference of −1.68 (95% CI, −2.66 to −0.706) and significant in period 2, 1.60 for mexiletine vs 5.27 for placebo (difference, −3.68; 95% CI, −3.85 to −0.139; P=.04). The significant improvement seen in IVR stiffness was repeated in IVR assessment of pain, weakness and tiredness. For the HRQoL the results of SF-36 showed variation across the dimension with regard to significance levels. The overall scores for physical function, role physical, bodily pain and social function showed a significant improvement in addition to the physical composite score which improved in the presence of mexiletine by 5.58 (mexiletine, 44.8 vs placebo, 39.2; difference, 5.58; 95% CI, 3.44-7.72; P < .001). Assessment of all dimensions in the INQOL questionnaire showed significant improvement in the presence of mexiletine, with the exception of weakness, overall. The summary QoL score shows a significant improvement (mexiletine, 14.0 vs placebo, 16.7; difference, −2.69; 95% CI, −4.07 to −1.30; P < .001), suggesting that the INQoL measure is more capable of detecting changes in health-related quality of life in this population.

Similarly the aggregated N-of-1 trials by Stunnenberg et al where in the total population, the median muscle stiffness score was 6.08 (interquartile range, 4.71-6.80) at baseline and was 2.50 (95% credible interval [CI], 1.77-3.24) during the mexiletine period and 5.56 (95% CI, 4.73-6.39) during the placebo period (48). This corresponded with a mean reduction of IVR stiffness score of 3.06 (95% CI, 1.96 to 4.15) for the NDM group (n = 27). Statistically significant changes in INQoL composite score and the physical and mental composite SF-36 scores were also seen with mexiletine.

The retrospective review of a large UK skeletal muscle channelopathy cohort with a mean length of follow-up of 4.8 years (range, 6 months to 17.8 years) provides evidence that in

clinical practice the effective dose is 416.7 mg daily of mexiletine hydrochloride (49). IT also provides evidence of the long-term safety of mexiletine in an NDM population and the authors suggest that frequent routine ECG monitoring of patients on maintenance dose may not be necessary.

Safety and tolerability

Mexiletine is well tolerated with the most common adverse event being gastrointestinal (GI) affecting up to [redacted] of patients in the MYOMEX (1) and Statland et al. trials (47) with a similarly frequency reported from long-term use based on observational data of up to 17.8 years of follow-up from a retrospective chart review (49), Further extensive safety data comes from post-marketing surveillance data from its use as an antiarrhythmic prior to its withdrawal from Europe and from its use in the treatment of myotonic disorders from France where the drug is approved for the symptomatic treatment of myotonic disorders since 2010 and now recent PSUR data since the launch of NaMuscla in December 2018. The information from the substantial patient exposure to mexiletine in the clinical setting for the antiarrhythmic indications was extrapolated to that of the NDM population by the EMA and was considered to result in a positive benefit/risk balance that supported the approval of marketing authorisation for symptomatic management of myotonia in patients with NDM .

B.2.13.2 Strengths and limitations of the clinical evidence

The development of medicinal products intended for the treatment, diagnosis or prevention of rare diseases, including NDM, can be very challenging due to distinct rare disease features, such as small patient populations, low event rates, incomplete understanding of disease natural course, and a lack of previous clinical trials. In addition, there are no longitudinal data capturing the natural history of NDM to either understand disease progression nor resource use which Lupin considers require further research.

Strengths

Evidence of mexiletine's clinical effectiveness from three trials including real-world long-term data

The most obvious challenge in rare disease trials is the recruitment of the right patients in adequate numbers (65). Despite this and unusually for a very rare disease, there are three randomised controlled mexiletine trials that enrolled a total of 115 patients and demonstrated a significant treatment effect for mexiletine compared to placebo (1, 47, 48).

In clinical practice patients will generally be titrated until symptomatic relief is achieved and thus lower doses are used in practice. In the MYOMEX study 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 with patients achieving clinical benefit by Day 7 on the 400 mg dose. This is supported by the long-term follow up (mean 48 months) data from MYOMEX where the mean dose of mexiletine hydrochloride was 400 mg daily to at least maintain the improvements seen in VAS stiffness scores seen at the end of the study

period. In addition, the real-world UK data (mean length of follow-up was 4.8 years (range, 6 months to 17.8 years) from Suetterlin et al reported the average dose of mexiletine prescribed was 416.7 mg mexiletine hydrochloride per day and corroborated from input by clinical experts (Appendix M). Thus, in the health economic analysis a dose of mexiletine 400 mg daily is used in the base case.

Long-term safety data available

Mexiletine well tolerated, with gastrointestinal discomfort being the most common adverse event. There are extensive post-marketing safety data from mexiletine's previous antiarrhythmic indication and now current NDM indication. In addition real-world UK data for mexiletine in NDM has also been reported.

Key endpoints reported are clinically meaningful and relevant

The primary endpoint of a change in stiffness was a patient reported outcome, either as a VAS (MYOMEX) or IVR (Statland and Stunnenberg trials. Patient-reported outcome measures (e.g. through a VAS) have the advantage of recording the patient experience as it occurs, without the bias of interpretation by an interviewer. Moreover, the efficacy evaluation of antimyotonic treatment in clinical practice is mainly based upon subjective statements of the patients about the improvement in their stiffness and activities of daily living, with measures such as hand grip relaxation time, electromyography, chair tests not used as confirmed by clinical experts (Appendix M).

Statistically significant improvements in stiffness were seen in all the mexiletine trials. A 50% reduction of VAS score is often used as a minimally clinically important difference (MCID), notably in the assessment of pain (66-68). In response to an EMA question during the marketing authorisation process analyses were provided for a 50% decrease in VAS score (69). Overall, in the MYOMEX trial [redacted]% of subjects in the mexiletine group compared to [redacted]% in the placebo group reported a ≥ 50% decrease in VAS score in the mITT population ([redacted]) ([redacted]% and [redacted]%, respectively, in the PP population, [redacted]). Additional analyses for the EMA also included the presentation of very stringent decrease of at least 50 mm on the 100 mm VAS scale (absolute reduction) and another of ≥ 25 mm absolute decrease. In pain a ≥ 25 mm absolute decrease was the most accurate in predicting a successful pain reduction after a given treatment (67).

For the decrease of at least 50 mm on the 100 mm VAS scale (absolute reduction), this was achieved by [redacted]% of subjects in the mexiletine group compared to [redacted]% in the placebo group in the mITT population ([redacted]) ([redacted]% and [redacted]%, respectively, in the PP population, [redacted]). An absolute decrease of 25 mm in VAS stiffness score was achieved by [redacted]% of subjects in the mexiletine group compared to [redacted]% in the placebo group in the mITT population ([redacted]% and [redacted]%, respectively, in the PP population). Only subjects with a VAS baseline value ≥ 25 mm were taken into account for this calculation.

All three trials also demonstrated a statistically significant difference in a secondary endpoint of quality of life as measured by the validated INQoL instrument. None of the trials were powered for this endpoint, but this is not surprising considered the rarity of the disease and

challenges in recruiting large numbers of patients to power multiple endpoints. MYOMEX a significant treatment effect for mexiletine was seen in the domains of locking, weakness, pain, fatigue, activities, independence, social relationship, emotions, body image and overall quality of life of the INQoL questionnaire ([redacted]). Significant differences in the SF-36 were also seen in the Statland and Stunnenberg trials where this instrument was used but as described in Section 1.3.5 the SF-36 in not the most sensitive instrument to capture a difference in HRQoL compared to the INQoL.

Patient population broadly generalisable to England and Wales

The three mexiletine studies were conducted in France (MYOMEX) (1), the Netherlands (Stunnenberg) (48) and in the USA and Europe with England included in the Statland study (47). The mean age of patients in the studies ranged between 40-50 years old; this is in line with that reported in other observational studies. Patients with both sodium and chloride channelopathies were included in the studies and patients with a range of stiffness severity at baseline were recruited.

A feature of MYOMEX is that the inclusion criteria used ensured that a relatively homogenous patient population was enrolled with respect to myotonia symptoms for the comparison of mexiletine to placebo. This was a discussion point with the EMA during NaMuscla's marketing authorisation review. The criterion specified that to be included 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. This does not necessarily mean these patients suffered from "severe myotonia"; rather, they had clinical symptoms of myotonia that were severe enough to justify treatment with mexiletine. There is no generally recognised and agreed upon definition of myotonia severity; symptoms may show a high inter- and intraindividual variability. Clinical findings span a continuum from mild to severe, not only between individuals but also, within the same patient, from day to day and even within the same day, depending on factors such as the outside temperature, the level of physical activities, stress, and the diet. Only patients with myotonia symptoms interfering with their daily life will receive treatment which was accepted by the EMA and hence NaMuscla is indicated for symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders.

There is no reason to believe that the results seen in the MYOMEX, Statland and Stunnenberg studies would not be broadly generalisable in England and Wales.

Crossover design

Whilst the crossover design of the MYOMEX study could raise the potential of overestimation of the treatment effect, it can equally be argued that the cross-over design offers advantages over a parallel study in the evaluation of treatments for NDM. Most notably, the use of a crossover design means that possible confounders between treatment groups do not need to be considered as patients are in fact their own control. MYOMEX could not be restricted to mexiletine-naïve patients; patients already receiving mexiletine were hesitant to stop treatment for a long period. As such, a crossover design with two short periods of treatment

was chosen, rather than a parallel group design. Furthermore, at first mexiletine intake, plasma concentration was null or below the detection threshold for all patients in both periods (baseline or at Visit 4 (Day 22) depending on the treatment sequence), regardless of treatment sequence, meaning that the wash-out period was sufficient. Finally, the Mixed Effect Linear Model did not show a difference in treatment effect for treatment periods with no evidence of a carry-over effect (treatment sequence effect).

Weaknesses

Short trial durations

Study durations of the prospective, randomised, controlled trials were short, and this may also be considered a limitation to the evidence base. However, a longer study duration would not be ethical in keeping patients off an acknowledged therapy in NDM and where the treatment effect is seen within a short space of time. There are however long-term data for mexiletine as described above.

Dosing regimen titration in the trials may not reflect clinical practice

The doses used in the mexiletine studies were in line with the Summary of Product Characteristics of NaMuscla. However, in all the trials patients were force titrated to achieve the maximum dose of 600 mg mexiletine hydrochloride daily at which point efficacy was assessed. As discussed above this is addressed with the follow-up data from the MYOMEX study and real-world data from Suetterlin et al.

Inclusion criteria and missing data in Statland et al

In the MYOMEX and Stunnenberg studies all participants had to have genetically confirmed NDM; in the Statland trial participants with genetically confirmed NDM or patients who had clinical features of NDM, but negative myotonic dystrophy DNA testing could be included which is a weakness of the study. It should also be noted that up to 50% of endpoint data is missing in the presentation of the results by Statland et al. which is not discussed in the publication.

Lack of head to head studies for mexiletine vs. lamotrigine as defined in the NICE Scope and inability to conduct an indirect treatment comparison or meta-analysis

At the time of the initiation of the MYOMEX, Statland and Stunnenberg studies, there was no identified standard of care in the literature, and hence the use of a placebo-control was most appropriate.

Lamotrigine has been specified as a comparator in the NICE scope for the appraisal of mexiletine. Lupin does not consider lamotrigine an appropriate comparator as it is only very rarely used as a second-choice agent whilst mexiletine is the first-choice agent for the treatment of NDM in the UK, and in Lupin's opinion cannot possibly be described as an established treatment in practice in the NHS. Feedback on the NICE draft scope, from the

NHNN, Queens Square Centre for Neuromuscular Diseases, London stated mexiletine is first-choice, with lamotrigine as a second-choice option. German guidelines also confirm this positioning.. Lupin has also consulted with experts in England to confirm this as well (see Section B.1.3.7 for further details). Additional data from market research involving 8 neurology centres in the England and Wales (including the NHNN) shows that lamotrigine is not established in practice with less than 3% of patients currently on or having ever received lamotrigine (see Section B.1.3.7.) and this result was confirmed in a UK patient survey (2).

A systematic literature review was conducted including lamotrigine as well as mexiletine to identify any randomised controlled trials. As described in detail in Appendix D one trial for lamotrigine was found that was published in 2017 by Andersen et al (8). The quality assessment of the lamotrigine study revealed that data are incompletely reported and, in some cases, such as the SF-36, incorrectly reported thus questioning the validity and strength of this study.

A feasibility assessment for conducting a meta-analysis of the mexiletine trials and an indirect treatment comparison with lamotrigine was performed and it was concluded that for key outcome measures neither were possible as no overlapping outcome measures as reported could be identified and reasonably be included in an ITC (Section B.2.9.1). Patient level data would have helped address some of the above issues and the authors of the trials were approached for patient level data without success.

B.2.13.3 End-of-life criteria

Mexiletine for the treatment of NDM does not meet the criteria for ‘life-extending treatment at the end of life'.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted using a single search strategy to identify cost-effectiveness, health-related quality-of-life (HRQoL), and cost and resource use studies (see Section B.3.5). No studies containing economic evaluations or cost and resource use data were identified (see Appendix G). There were also no studies identified with utility data (see Appendix H).

B.3.2 Economic analysis

As no cost-effectiveness studies were identified, a *de novo* model was created to evaluate the treatment of symptomatic myotonia in adults with non-dystrophic myotonia (NDM) and a valuation study was carried out to generate utility data to assess changes in HRQoL between mexiletine and its comparators. Due to the short duration of the MYOMEX study, extrapolation

of the clinical effectiveness and impact on QoL to a longer time horizon was informed by additional sources including long-term follow up data from MYOMEX (50), clinical and patient expert advice (39) (Appendix L, Appendix M) and data from Suetterlin et al (49) a retrospective review of a large UK muscle channelopathy patient cohort.

B.3.2.1 Patient population

The patient population is as per the marketing authorisation of NaMuscla and the NICE final scope. Patients entering the model are adults with NDM who require symptomatic treatment of myotonia. Patient-level data from the MYOMEX study provided evidence of treatment impact and benefit. The 25 genetically identified NDM adults aged 18–65 years recruited to the MYOMEX study had a mean age of 44 years.

B.3.2.2 Intervention technology and comparators

The cost-effectiveness model compares treatment of NDM with NaMuscla against no treatment (i.e. no pharmacological treatment). It is assumed that all patients also receive best supportive care (BSC) regardless of treatment choice. Once the diagnosis is made, mexiletine treatment is invariably initiated by a neurologist after discussion with the patient at either the National Hospital for Neurology and Neurosurgery in Queen Square, London or one of the neurology centres commissioned by NHS England as a specialised service (6, 22). By this stage patient's symptoms will be severe enough that any strategies they have developed to cope with their condition, such as avoiding triggers or performing muscle warming routines (effectively best supportive care), will not be sufficient and the patient will require treatment. Patients entering the MYOMEX trial had disease severe enough to warrant drug therapy, as described in section B.2.3.1, hence the placebo arm of the study is effectively BSC.

A systematic literature review (SLR) was conducted to identify randomised controlled trials of interventions used for the treatment of myotonic symptoms in NDM. The SLR identified four randomised placebo-controlled trials, the details of which are presented in Appendix D. Three RCTs compared mexiletine to placebo whilst one RCT compared lamotrigine to placebo. Table 44 lists the four trials identified.

Table 44: Summary of the randomised controlled trials found from the SLR

References of trial	Mexiletine	Lamotrigine	Placebo
Andersen (2017) (8)		Yes	Yes
MYOMEX (2017) (1)	Yes		Yes
Statland (2012) (47)	Yes		Yes
Stunnenberg (2018) (48)	Yes		Yes

The results of an indirect treatment comparison (ITC) feasibility assessment is presented in Section B.2.9.1. which concludes that an ITC/MTC is not possible between mexiletine and

lamotrigine, in addition to lamotrigine not being an established treatment for NDM under the NHS (see Section B.1.3.7.).

For the patient population defined in the NICE scope, evidence from direct treatment comparison of mexiletine to placebo in the MYOMEX trial is used in this economic evaluation.

B.3.2.3 Perspective

The model perspective on costs is that of the National Health Service (NHS) and Personal Social Services (PSS), in line with the NICE reference case.

The NICE reference case also indicates that the perspective on outcomes should focus on the patient and caregivers. Patient and clinical expert elicitation suggests substantial societal costs for both the patient and family members, which are not incorporated when only considering the NHS perspective. This includes the ability to work with patients and clinicians alike specifying the impact of myotonic symptoms in the workplace (Appendix L, Appendix M and (27)) – see Section B.1.3.5 and B.2.1.2.

Since no information could be obtained for caregivers, the model solely captures patient outcomes. As a consequence, costs which fall outside of the NHS and PSS perspective have not been incorporated in this evaluation, hence, there is a possibility the economic model underestimates the potential value of NaMuscla for patients and their families.

B.3.2.4 Discount rate

The discount rate is set at 3.5% for both cost and outcomes as per NICE reference case. A lower discount rate (1.5% rather than 3.5%) which is aligned with the most recent UK HM Treasury Green Book is used in the scenario analysis (70), as the All-Party Parliamentary Group on Access to Medicines recently recommended that NICE adopts the HM Treasury Green Book rate of 1.5%.

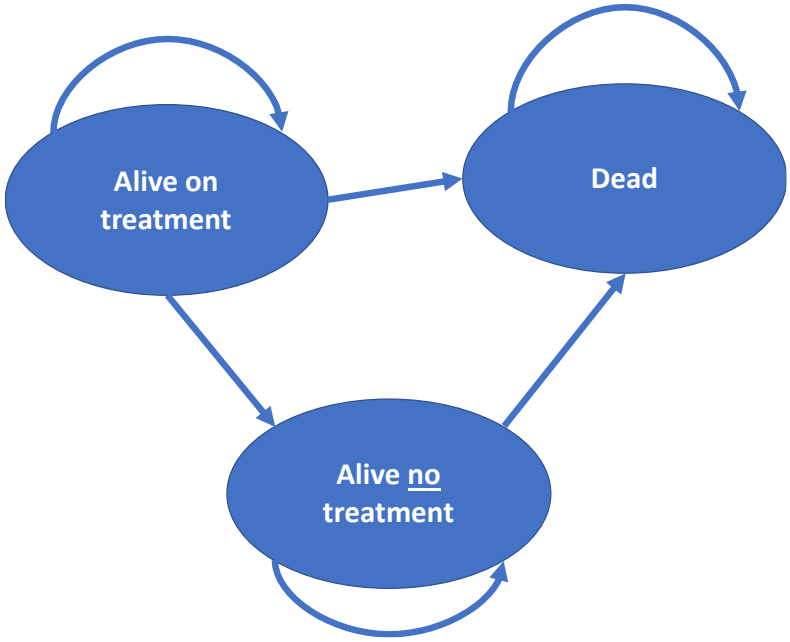
B.3.2.5 Model structure

Due to the heterogeneity of the presentation of myotonic symptoms in NDM disease (described in section B.1.3.3), clinical experts agreed there were no validated cut-offs to enable the segmentation of the population defined in the NICE final scope. A patient level analysis was considered a more appropriate method to gather the differences in outcomes upon mexiletine treatment in an NDM population.

A Markov cohort simulation model was created within Microsoft Excel® to evaluate the cost-effectiveness of NaMuscla for the treatment of patients with NDM. The Markov model was built in line with the NICE Reference Case and enabled the extrapolation of costs and benefits across the lifetime of an NDM cohort. All model inputs and calculations are set out in tables within the model which can be modified to incorporate new data and enable scenario analyses. The goal of the model was to assess benefits and costs associated with the treatment of myotonic symptoms in NDM patients with mexiletine in comparison to best supportive care.

A lack of evidence of the natural history of the disease in the literature and from clinical experts when questioned (Appendix M and (39)) led to the use of a simple Markov model where patients could be in one of two health states, 'alive on treatment' (AOT) or alive with no treatment (ANT), with the final absorbing state 'death', as illustrated in Figure 25.

Figure 25: Markov model structure



A cycle length of one year was considered appropriate to capture changes in treatment benefit and costs based on the typical follow-up period by neurology specialists (see Appendix M), with a half-cycle correction also applied. The model assumes that once a patient discontinues treatment, they cannot return to treatment and may only move onto the absorbing state of death. This is a conservative assumption as Suetterlin and colleagues found that many patients who discontinued treatment reinitiated treatment (49). As the length of time to re-initiation was not reported by Suetterlin et al (2015), it was assumed the mean discontinuation rate obtained from this study incorporates re-initiation rates.

Patient level analysis of the MYOMEX patient population provided evidence of the clinical effectiveness with and without mexiletine treatment. This was extrapolated to one year and enabled the calculation of cost of treatment and utilities associated with each Markov state. There is no evidence or clinical rationale to inform the impact of NDM on mortality, hence, survival was assumed the same as that of the general UK population (71). A variety of sources (1, 3, 39, 49, 50) (see also Appendix M for clinical expert input) including long term data from the MYOMEX trial and real world data were used to provide evidence of the clinically effective treatment dose for long term therapy, frequency of adverse events, mexiletine discontinuation rates and disease progression enabling the extrapolation of treatment benefit in the modelled population to a longer time horizon. The features of the model are detailed in Table 45.

The model structure and approach were reviewed and validated by two third-party health economic consultancies (see Section B.3.10).

Table 45: Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	A lifelong time horizon, capping the maximum survival at age 100 years	The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared (46). Therefore, a lifetime horizon was chosen to model the accumulation of differential costs and QALYs until death. The mean age of patients in the MYOMEX population was 44 years (1). Patients in the model were assumed not to survive past 100 years, hence the time horizon of the model was 56 years. The impact of time horizon has been assessed in scenario analysis.
Cycle length	1 year	A Markov model was used in order to capture the effects of NDM. As per current clinical practice the condition of the patients is measured on an annual basis (Appendix M). A half cycle correction was incorporated due to the long-time horizon of the model, see Section B.3.6.2.
Discount rate	3.5% for health effects and costs	NICE reference case. The impact of alternative discount rate of 1.5% has been tested in sensitivity analyses.
Perspective (NHS/PSS)	NHS in England and Wales	NICE reference case.
Source of utilities	As generated in preference-based valuation of INQoL outputs obtained during MYOMEX study	The INQoL measure collected during the MYOMEX study is the best measure for capturing the impact of NDM on patients QoL. Relevant mapping was conducted to derive utility weights from EQ-5D. See section B.3.4.2
Source of healthcare resource use	According to disease severity proxy, see section B.3.5	Healthcare resource use was not collected directly during the MYOMEX study. A disease severity proxy was generated to approximate healthcare resource use according to subjective assessment of disability using the disability scale of the Clinical Myotonia Scale used in

		MYOMEX, clinical expert advice was also used to assign resource use. Genetic testing is included in the base case as requested by the NICE Final Scope. A conservative assumption that all patients receive the test is based on market research carried out by Lupin that confirms 87% of patients with NDM have been tested (3).
Source of costs	BNF 2019 (11), NHS Reference costs (72), PSSRU (73)	Costs were obtained from UK national resources to reflect the UK NHS/PSS perspective.

B.3.3 Clinical parameters and variables

A summary of key data sources for the clinical parameters and variables for the cost effectiveness model are presented in Table 46 and a detailed description of model inputs and sources follow.

Table 46: Overview of key data sources

Model Section	Parameter	Data source
Patient population	Demographic characteristics (age, gender)	MYOMEX study population in both the base case and scenario analyses (1)
Clinical inputs for NaMuscla	Clinically effective dose in long term use	MYOMEX long term efficacy corroborated by clinical experts in the base case (Appendix M and (39, 50)) and Suetterlin et al (49)
	Treatment compliance	MYOMEX population in base case (1)
	Treatment discontinuation	Suetterlin et al (49)
	Adverse events (GI) of mexiletine	Suetterlin et al (2015) (49) in the base case. MYOMEX (1), Statland et al (2012) (47) and Stunnenberg et al (2018) (48) inform scenario analyses.
	Disease severity proxy or healthcare resource use	Clinical Myotonia Scale (CMS) disability scale as reported in MYOMEX study population in the base case and scenario analysis (1) supported by patient and expert advice (Appendix L, Appendix M and (39))

	Disease progression differential	Assumption supported by the literature (17), clinical expert elicitation (Appendix M) and long-term follow-up of MYOMEX study population (50).
	Likelihood of falls resulting in fracture	Assumption informed by the Lupin Advisory Board (39) and supported by patients (2, 27), Appendix L.
Clinical inputs for best supportive care	Disease severity proxy for healthcare resource use	Clinical Myotonia Scale (CMS) disability scale as reported in MYOMEX study population in the base case and scenario analysis (1).
	Disease progression differential	Assumption supported by clinical expert elicitation (Appendix M) and patients ((2, 27), Appendix L).
	Healthcare resource use multiplier	Assumption of a multiple of 3 (i.e. x3) due to likely underestimation of healthcare resource use in the absence of treatment.
	Likelihood of falls resulting in fracture	Assumption informed by Lupin Advisory Board (39), and supported by patients (2, 27), Appendix L.
Mortality	All-cause mortality rates	Life tables for England

B.3.3.1 Population Baseline Characteristics

The model simulates individual patients from the MYOMEX study. The baseline characteristics of the modelled population, in terms of age and gender, is informed by the modified intention to treat (mITT) population of the MYOMEX study (n=25). Of the modelled population, [redacted]% were male and the mean age was 44 years. The gender distribution informed the survival calculations of the modelled population only. Some clinical experts consulted pointed out that there was no difference in age distribution in NDM so that a higher percentage of a males might not reflect the UK population (Appendix M) .

The population is assumed to have received a genetic test to confirm the disease diagnosis as requested in the NICE final scope. Genetic testing is already provided as a highly specialised service by the National Hospital for Neurology and Neurosurgery (NHNN), Queens Square Centre for Neuromuscular Diseases – a part of University College London and the national diagnostic centre for NDM (22). Thus, the infrastructure is already in place for the diagnosis of NDM and funded by NHS England. Additionally, clinical experts confirm that treatment is driven by clinical diagnosis and a negative genetic test would not always lead to treatment being discontinued or not initiated (6).

Therefore, the eligible population that are genetically diagnosed with NDM nor the availability of NaMuscla will drive diagnosis. Only clinically diagnosed patients are offered the option of treatment if symptoms impact quality of life. Once a clinical and/or genetic diagnosis is made, mexiletine treatment is invariably initiated after discussion with the patient. By this stage patient's symptoms will be severe enough that any strategies they have developed to cope with their condition such as avoiding triggers or performing muscle warming routines (effectively best supportive care) will not be sufficient and the patient may benefit from treatment.

Although the genetic test should not be incorporated in the base case it has been included as per NICE final scope. A scenario analysis is presented without the cost of the genetic test.

B.3.3.2 Clinically effective dose

In the base case drug costs are determined by a daily mean effective dose of mexiletine of 400 mg daily (14 capsules per week) based on the MYOMEX trial including long-term follow-up data, and expert advice (see Appendix M and (1, 39, 50)). A UK real world retrospective study from Suetterlin et al reported that the mean clinically effective dose of mexiletine used was 416.7 mg daily (49). This dose derived from Suetterlin et al (2015) data does not equate to a specific number of capsules, a scenario analysis conservatively rounded the daily dose to 429 mg daily, which equates to 15 capsules per week, to represent 'wastage' as presented in Table 47.

Table 47: Calculation of mean effective dose

Daily dose	Number of capsules per day	Equivalent weekly number of 200 mg capsules	Role in model
400 mg	2.00	14 capsules	Base case
429 mg	2.15	15 capsules	Scenario analysis

The use of the 400 mg daily dose as the base case is supported by the MYOMEX study (1) where the clinical benefit was achieved by Day 7 (i.e. during the dose titration period) when patients were on 400 mg dose (see Figure 18 and Figure 19), Section B.2.6.1.) and long-term follow-up data (mean (48 months) for a small group of patients where the mean dose was 400 mg daily (50) (see Section B.2.6.1. Figure 20). As highlighted in Section B.2.3.2 patients in all the mexiletine trials were force titrated to achieve a dose of 600 mg mexiletine hydrochloride daily at which point efficacy was assessed and so represents an artificial situation rather than what will happen in clinical practice where patients are titrated until symptoms and QoL are improved as reported by the patient. The effective dose used in the base case was also confirmed by clinical experts, all of whom agreed that patients in the real world tend to be 400 mg daily (Appendix M and (39)). An effective dose of 429 mg informed the scenario analysis.

B.3.3.3 Disease progression differential

A differential effect is assumed to exist in NDM such that quality of life decreases over time in the absence of treatment for myotonic symptoms.

The detailed natural history and determinants of morbidity have yet to be prospectively studied (13) and so the underlying disease progression is unknown but data suggests that disease severity worsens over time. In one study 58% of patients reported that the severity of their myotonia had increased since the onset of symptoms (17). A UK patient survey found that 87.3% of patients reported their stiffness and 70.8% reported their weakness had worsened since diagnosis (2). Such a scenario has been confirmed in patient elicitation interviews where symptoms are seen to worsen in the absence of treatment (Appendix L). Feedback from two German clinical experts support that in the absence of an effective treatment a decline in QoL over time occurs, as imported mexiletine has not been an option (Appendix M). Long-term data from MYOMEX shows the clinical benefit of mexiletine is at least maintained and this is supported by clinical experts (Appendix M). In the base case it was assumed there was a differential effect between mexiletine treatment and no treatment over the lifetime of an NDM patient of 15%. Different differential effects were explored between mexiletine and no treatment in various scenario analyses.

B.3.3.4 Treatment compliance

In the MYOMEX study, two compliance rates were calculated:

- Number of patients who took treatment according to protocol
- Number of capsules taken by individual during the mexiletine phase of the study

Mean compliance was calculated according to the number of capsules taken by each individual during the mexiletine arm of the MYOMEX study, [redacted]% in the base case. This was used to calculate the annual number of capsules taken by an individual in the model which in turn informed mexiletine drug cost calculations. Compliance only informed drug cost calculations within the model. The impact of other sources of compliance that were assessed in the compliance was assessed in the Mexiletine clinical trials identified in the SLR compliance informed scenario analyses as presented in Table 48.

B.3.3.5 Treatment discontinuation

The transition probability of moving from the AOT health state to the ANT health state in the Markov model were informed by the discontinuation rate of patients whilst in the mexiletine arm of the MYOMEX study. Due to the short duration of the MYOMEX study (mean duration in each treatment arm was 19 days), the retrospective analysis by Suetterlin et al, with its mean follow-up of 4.8 years and where 15 out of 63 patients discontinued treatment, was considered the best source for the probability of discontinuation. The probability of discontinuation in this study was converted to an annual discontinuation rate using the equation below resulting in an annual discontinuation rate of 5.15% (49).

$$Annual\ rate\ of\ treatment\ discontinuation = \frac{-ln(1-p)}{t}$$

This transition probability informed the movement of patients from alive with treatment to alive without treatment.

Table 48: Sources of mexiletine compliance and discontinuation probabilities

Study	Compliance rate	Discontinuation rate
MYOMEX study (1)	[redacted]% (base case)	[redacted]%
Statland et al (2012) (47)	90.2%	7%
Stunnenberg et al (2015) (51)	94%	3%
Suetterlin et al (2015) (49)	Not reported	5.15% (base case)

B.3.3.6 Adverse events

The probability of the modelled population having an adverse event was informed by the joint probability of suffering a gastrointestinal (GI) disturbance whilst on mexiletine and being treated for dyspepsia associated with this GI disturbance. The base case probability of having a GI disturbance was informed by long term data from Suetterlin et al (49), see Table 49. The probability of GI disturbance from MYOMEX, Statland, and Stunnenberg were used in scenario analysis. The forced titration in these trials to a dose of mexiletine hydrochloride 600 mg daily make the frequency of adverse events more difficult to interpret and hence it was more appropriate to use the real-world data from Suetterlin et al in the base case.

Table 49: Adverse event probabilities incorporated into economic model

Study	Probability	
	GI disturbance	**Treatment for dyspepsia**
MYOMEX study (1)	[redacted]	Not reported
Statland et al (2012) (47)	0.32	Not reported
Stunnenberg et al (2015) (51)	0.70	Not reported
Suetterlin et al (2015) (49)	0.33	0.70

Another adverse event incorporated into the model is the risk of fractures following a fall for patients whilst taking mexiletine or no treatment. This was not quantified by any degree of severity as patients with severe disease may compensate by being more careful in avoiding the risk of falls and so the difference was simply defined as that being on mexiletine or not. Injuries from falls were reported by 69.2% of patients in a recent survey of UK patients (2) and

is therefore an important adverse event to capture in the health economic model despite the lack of data for this rare disease. The likelihood of such events, as informed by clinical experts in the advisory board (39), are summarised in Table 50. However, these may be underestimated based on patient insights (Appendix L and (2) but cannot be quantified.

Table 50: Probability of falls resulting in a fracture, as informed by the UK advisory board

	Mexiletine	Placebo	Source
Probability of falls resulting in a fracture	0.1	0.2	UK Advisory Board (39)

B.3.3.7 Mortality

As there is little evidence (due to a lack of natural history studies) that NDM patients have a reduced life-expectancy compared to the general population, no assumptions have been made in the model and modelled patients are assumed to have the same survival as the general population (71).

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

As illustrated in section B.1.3.5, the INQoL measure is the most appropriate validated measure of HRQoL in NDM patients. Availability of patient level data from MYOMEX enabled the assessment of quality of life changes for each individual within the study population and the direct elicitation of utilities changes associated with myotonic symptoms when a patient is treated with mexiletine or not receiving a pharmacological treatment. The advantage of the MYOMEX dataset is that the HRQoL impact of treatment and no treatment is observed in each member of the study population due to the cross-over study design. This ensures the unique presentation of myotonia in an individual is appropriately captured in the assessment of health-related quality of life, better assessing the HRQoL impact of mexiletine in this heterogenous population. This is particularly important in NDM as a lack of understanding of the natural history of the disease makes it difficult to identify discrete health states for the assessment of treatment impact.

The NICE reference case prefers the assessment of HRQoL to be directly elicited from patients, or individuals acting as their carers when this is not possible informed by the generic measure, and the preferred measure is EQ-5D. The EQ-5D was not collected in any of the clinical trials identified during the systematic literature review (see section B.2.6.1-B.2.6.4). This submission utilises the condition-specific preference-based measure, INQoL. At the time the MYOMEX study was carried out, the INQoL questionnaire was, and still is, the only validated QoL questionnaire that referred specifically to the presence and impact of myotonic

symptoms (33). Therefore it was the preferred measure to capture changes in HRQoL for the mITT and PP populations in the MYOMEX study.

Sansone and colleagues compared the effectiveness of the neuromuscular disease-specific measure, INQoL, to the generic measure SF-36 in assessing QoL in patients with skeletal muscle channelopathies. Myotonia was found to be the most disabling symptom in the population assessed as well as the symptom with the highest impact on NDM patients' QoL perception. A conclusion of the study was that myotonia should be the treatment target for NDM patients. Muscle weakness, fatigue and pain were also found to have significant impact on NDM patients' QoL perception.

No generic measure was collected during the MYOMEX study. To obtain utility values that describe quality of life during the MYOMEX study, the QoL measured by the INQoL instrument had to be valued.

With regards to the correct QoL measure for NDM, Sansone and colleagues concluded that INQoL was an appropriate measure because *"…it can quantify the impact of muscle symptoms that are specific to this group of patients (e.g. myotonia, muscle pain).*" (33). Trivedi and colleagues described INQoL as "*a more relevant instrument for determining symptom impact on quality of life in non-dystrophic myotonia compared with the generic SF-36*" (15).

The inability of SF-36 to assess myotonia is particularly important as Sansone and colleagues state that "*…myotonia should be the treatment target for patients…and improvement of myotonia should be the primary outcome measure …*" (33).

With regards to sensitivity of a QoL measure, some SF-36 items are considered not relevant to muscle disease and could easily be influenced by other factors (34). Sansone and colleagues concluded that INQoL was more capable of capturing the "*physical limitations owing to the muscle condition*" than SF-36. INQoL also assesses "*the extent by which [myotonia] has a detrimental effect on QoL perception. This [enabled the authors] to pick out differences amongst the channelopathies that are not captured by SF-36 alone.*" (33).

Due to the aforementioned limited amount of data in this disease; lack of common outcomes to enable assessment across trials; small population size heterogenous population with regards to symptom presentation, intensity and duration; and lack of natural history data, the decision was taken to carry out patient level assessment of an NDM cohort to inform the economic model. Patient level data was available from the MYOMEX population who completed the INQoL questionnaire during the study. Due to the publication of limited quality of life data in other mexiletine studies, Lupin has approached authors of other mexiletine studies to obtain patient level data in order to assess quality of life in the NDM population without success. Due to a lack of mapping algorithms for INQoL, the valuation was based on public preferences from a representative sample of the UK population using a choice-based method, a discrete choice experiment (DCE).

B.3.4.2 Mapping

A discrete choice experiment is a quantitative stated preference survey method whereby health outcomes can be described in terms of discrete attributes and levels that are presented as scenarios for an individual to select their preferred option. For this submission a preference-based mapping approach to estimate the relationship between the INQoL and the EQ-5D was undertaken using the DCE. Selected items from the INQoL (based on their conceptual overlap with EQ-5D) were included in a DCE. The DCE derived preference data indicated the importance of each of the INQoL items. This allowed us to estimate the difference between participants' strength of preference for the best state defined by the INQoL and the worst state (extreme problems on each INQoL item). These preference weights from the DCE were then rescaled to fit the range of the EQ-5D (1.0 to -0.59).

The sole aim of this DCE survey was to understand how important differences in each of the mapped items from the INQoL were to the general public.

The process of generating health state utility values in this assessment has been published (74) and is described here in four parts:

- Conceptual mapping of INQoL to EQ-5D
- Development and application of the DCE scenarios
- Health state utility calculation
- Validation of methodology

Conceptual mapping of INQoL to EQ-5D

The conceptual mapping process was informed by one-to-one discussions with three clinical experts and a health economist expert. These experts were presented with assumptions and processes to enable the discussions, advice and validation (74, 75).

INQoL is a valid measure of quality of life or health status in patients with myotonia because it covers the different aspects of HRQoL that are affected in myotonia (content validity) and additionally the tool measures these concepts accurately (construct validity) (34). The EQ-5D is the preferred HRQoL measure for the assessment of QoL in the NICE Reference case (46).

The mapping process was made up of three main parts: the mapping of symptoms assessed by INQoL domains to appropriate EQ-5D domains; the identification of appropriate items within INQoL domains; and the mapping of response levels within INQoL items to response levels in EQ-5D domains.

Mapping of INQoL symptoms to EQ-5D domains

In total, six INQoL domains were identified for conceptual mapping. This was driven by INQoL domains that closely matched aspects of the five domains of the EQ-5D i.e. mobility; self-care (washing & dressing); usual activities (work, study, housework, family or leisure activities); pain or discomfort and anxiety or depression. Three INQoL domains were conceptually similar;

pain, emotions (anxiety & depression), and activities (daily activities such as washing & dressing, and leisure activities).

The three clinical experts in NDM who informed the mapping process reviewed the process of selecting items and response levels and provided feedback (74). In addition to these three domains, the three clinical experts agreed that muscle weakness and muscle locking, assessed by two separate INQoL domains, would be appropriate to be included in the mapping process. Clinicians advised that these domains conceptually mapped to the mobility domain of EQ-5D due to the impact muscle weakness and muscle locking have on an individual's mobility. Clinical experts considered weakness and locking to be independent of each other. For example, in younger patients' muscle locking can be a major feature whilst weakness is not. Whilst some older people are more affected by muscle weakness due to muscle ageing. Thus, very little muscle weakness combined with multiple problems with usual activities/leisure is entirely possible.

In addition, the literature identified fatigue as impairing subjective assessment of HRQoL in patients with NDM (15, 17, 20, 47, 76) and fatigue is among the most frequent complaints reported by patients with chronic illnesses (77-80). For this reason, and as validated by the experts, fatigue was included for conceptual mapping.

Identification of INQoL items

Each domain in INQoL has multiple items. Hence, the appropriate items within each domain were sought for mapping to EQ-5D. Items were selected which quantify the degree the respondent is affected. This is in keeping with the descriptive levels of the EQ-5D domains which aim to elicit the severity of each domain. Other items within each INQoL domain were excluded because they were designed to establish whether symptoms caused difficulties in the patients' life or rated how important such difficulties were. For example, below are the three questions of the weakness domain of INQoL:

- How much weakness would you say you have in the muscles affected by your condition?
- Does your muscle weakness cause difficulties in your life at the moment?
- How important to you are any difficulties caused by your muscle weakness?

The first question, and the equivalent item in all six domains, was chosen because it describes the severity of muscle weakness.

The process resulted in a decrease from 45 to 8 items. Table 51 sets out the justification for the included and excluded items of the INQoL questionnaire.

Table 51: Rationale for the inclusion and exclusion of INQoL items (version 1.2)(81)

INQoL item number	INQoL domain	INQoL items	Included/ Excluded	Justification
	[redacted]			
[redacted]	[redacted]	[redacted]	Included	Domain not present in EQ-5D but identified by clinical experts as a key aspect of physical function and mobility. Domain item selected as describes health and assesses severity of symptom. Supporting evidence of domain impact on QoL (15, 33).
[redacted]	[redacted]	[redacted]	Excluded	These items were excluded because the severity of symptom has been captured in part a of INQoL domain. The extent to which this symptom caused difficulties and the importance of those difficulties are outside QoL measurement scope, as informed by EQ-5D.
[redacted]	[redacted]	[redacted]	Excluded	
	[redacted]			
[redacted]	[redacted]	[redacted]	Included	Domain not present in EQ-5D, however, clinical experts suggested this should be included. It was considered as another aspect of physical function or mobility. Domain item selected as describes health and assesses severity of symptom. Supporting evidence of domain impact on QoL (15, 33).
[redacted]	[redacted]	[redacted]	Excluded	These items were excluded because the severity of symptom has been captured in part a of INQoL domain. The extent to which this symptom caused difficulties and the

[redacted]	[redacted]	[redacted]	Excluded	importance of those difficulties are outside QoL measurement scope, as informed by EQ-5D.
	[redacted]			
[redacted]	[redacted]	[redacted]	Included	Domain conceptually similar to EQ-5D domain. Domain item selected as describes health and assesses severity of symptom. Supporting evidence of domain impact on QoL (15, 33).
[redacted]	[redacted]	[redacted]	Excluded	These items were excluded because the severity of symptom has been captured in part a of INQoL domain. The extent to which this symptom caused difficulties and the importance of those difficulties are outside QoL measurement scope, as informed by EQ-5D.
[redacted]	[redacted]	[redacted]	Excluded	
	[redacted]			
[redacted]	[redacted]	[redacted]	Included	Domain not in EQ-5D but clinical experts identified it as an important symptom in NDM. Domain item selected as describes health and assesses severity of symptom. Supporting evidence of domain impact on QoL (15, 33).
[redacted]	[redacted]	[redacted]	Excluded	These items were excluded because the severity of symptom has been captured in part a of INQoL domain. The extent to which this symptom caused difficulties and the

[redacted]	[redacted]	[redacted]	Excluded	importance of those difficulties are outside QoL measurement scope, as informed by EQ-5D.
	[redacted]			
[redacted]	[redacted]	[redacted]	Included	Domain conceptually similar to EQ-5D domain.
[redacted]	[redacted]	[redacted]	Included	Domain conceptually similar to EQ-5D domain.
[redacted]	[redacted]	[redacted]	Excluded	Age related, so excluded. Assumption that partly considered in Daily Activities domain of INQoL.
[redacted]	[redacted]	[redacted]	Excluded	These items were excluded because the severity of symptom has been captured in part A of INQoL domain. The extent to which this symptom caused difficulties and the importance of those difficulties are outside QoL measurement scope, as informed by EQ-5D.
[redacted]	[redacted]	[redacted]	Excluded	
[redacted]	[redacted]	[redacted]	**Excluded**	Not assessed in EQ-5D.
[redacted]	[redacted]	[redacted]	**Excluded**	Not assessed in EQ-5D.

[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	Included	Assessed in EQ-5D and identified in literature as impacting QoL in NDM.
[redacted]	[redacted]	[redacted]	Included	Assessed in EQ-5D and identified in literature as impacting QoL in NDM.
[redacted]	[redacted]	[redacted]	Excluded	Not assessed in EQ-5D.
[redacted]	[redacted]	[redacted]	Excluded	Not assessed in EQ-5D.
[redacted]	[redacted]	[redacted]	Excluded	Not assessed in EQ-5D.
[redacted]	[redacted]	[redacted]	Excluded	Not assessed in EQ-5D.
[redacted]	[redacted]	[redacted]	**Excluded**	Not assessed in EQ-5D.
[redacted]	[redacted]	[redacted]	**Excluded**	Not assessed in EQ-5D.

An expert on utilities reviewed the proposed approach and analyses and suggested a sensitivity analyses should be undertaken to explore different assumptions regarding the value for the worst health state in the INQoL measure (74). All INQoL items were significant predictors of choice in the DCE indicating that they were all independently important (74).

Table 52 summarises the mapping of INQoL items that, from the process described above, have been conceptually mapped to the appropriate EQ-5D domains.

Table 52: Conceptual mapping of the INQoL questions to the descriptive system of EQ-5D-5L (74)

EQ-5D Domain	INQoL Item
Mobility	[redacted]
Self-care (washing & dressing)	[redacted]
Usual activities (leisure, work, social activities)	[redacted]
Pain/discomfort	[redacted]
Anxiety/ depression	[redacted]

The INQoL has been independently developed and validated and it has been assumed that all items have content and construct validity (34, 82).

It should be noted that more than one item could be mapped to EQ-5D domains due to multiple symptoms and functions being present in the majority of these five domains. For example, two separate INQoL items (Anxiety and Depression) were mapped to the single EQ-5D domain Anxiety/Depression. This resulted in three EQ-5D domains being mapped to two separate INQoL items.

Mapping of response levels

In order to develop a DCE survey that wasn't too large, and impractical, a decision was taken to reduce the number of response choices. Each INQoL item has a six or seven-point Likert response scale. Upon consultation with a clinical expert with experience in this area of research, four response level were included in the DCE (including the best level and the worst level). Keeping all seven response choices would have resulted in 144 choice questions in the survey, which from experience and advice from the experts would have been impractical for the respondents, increasing the risk of non-completion. Response options were chosen which

closely matched response levels in EQ-5D-5L, as this was considered a more appropriate tool to map response levels to. This enabled three response levels describing existing problems in addition to “not at all”. Use of response levels in EQ-5D-3L would have only enabled two levels of each Likert scale within INQoL items to be used.

It is worth noting that the upper (no problems) and lower (extreme problems) anchors were included for each item. Therefore, dropping some of the INQoL response levels did not impact on the alignment of the best or worst health state defined by INQoL and EQ-5D-5L.

Summary of the process and assumptions that inform the INQoL item selection

- The item reduction process was guided by the five dimensions of the EQ-5D. Items from INQoL which conceptually matched the content of EQ-5D as closely as possible were chosen. The selection of items which matched the EQ-5D was based on what was perceived as conceptual overlap rather than formal statistical work. The selection of items was also guided and confirmed by clinical experts ((74) and Appendix M) and literature (33).
- For the valuation exercise, it was decided, as informed by the experts ((74) and Appendix M), that neither all domains nor all of the six or seven response levels were necessary to appropriately assess quality of life in NDM patients.
- It is appropriate to map multiple INQoL items to EQ-5D domains containing two compound items e.g. pain or discomfort and anxiety or depression. Separate items are within the INQoL questionnaire to reflect these compound items and questions for each item within the compound item were added to the appropriate EQ-5D dimension as shown in Table 52.
- The reduction exercise was validated by clinical experts ((74) and Appendix M).

Development and application of the DCE scenarios

A published fractional factorial method informed the design of the DCE, minimising participant burden whilst representing INQoL items with different response levels in a balanced and statistically efficient manner. The eight conceptually mapped INQoL items were combined with the conceptually mapped response choices using an orthogonal design (83) to produce DCE scenarios. The orthogonal design combined questions and response choices with zero correlation. One implication of this is that conceptually related items were not related in the choice sets (e.g. no muscle locking was as likely to be paired with no muscle weakness as extreme muscle weakness). This assumption was later corroborated by patients who described heterogenous symptoms that reduced the chance of implausible states, see Section B.1.3.5 and Appendix L.

This choice method was justified as the items informing the choice sets were considered independent due to the developers of the INQoL items scoring domains describing these items separately.

The sample who informed the valuation exercise were the general public and they were not made aware of what is clinically realistic or unrealistic. Respondents were asked to consider the choice questions at face value.

The orthogonal design required 32 choice questions. The second choice in each question was determined by folding over the first choice. This is a simple method for producing efficient pairs of choices in main effects models described by Street and colleagues (84). The order of questions was randomised, and half of the participants completed questions 1-16 and the other half 17-32. An example of a choice question can be seen in Figure 26.

Figure 26: Example DCE scenario (74)

	Treatment A	Treatment B
*How much **muscle weakness** you would have*	A moderate amount	An extreme amount
*How much **'locking' (seizing up)** of your muscles you have*	A moderate amount	An extreme amount
*Your muscle condition affects your ability to do daily activities e.g. **washing, dressing & housework***	Moderately	Extremely
*Your muscle condition affects your **ability to do leisure activities***	Extremely	None at all
*How much **pain** you have*	Slight	Moderate
*How much **tiredness or fatigue** you have*	A moderate amount	An extreme amount
*Your muscle condition makes you feel **anxious***	Extremely	None at all
*Your muscle condition makes you feel **depressed***	Moderately	Extremely
Which treatment is best? *Please tick A or B*	A ❑	B ❑

It has been noted in the literature that measures like the EQ-5D make no attempt to control for apparently implausible states which have been reported to occur. In the design of EQ-5D-5L, implausible health states were not excluded due to a lack of an agreed measure of health state implausibility (85). In addition to this, a recent study by Yang et al concluded that implausible states could not be excluded due to a lack of agreement between respondents of what is implausible (86).

In conclusion, individuals within the MYOMEX study and in the real-world context, suggest that there are few implausible presentations of myotonic symptoms in NDM and there are no tools in the literature which enable the identification of implausible scenarios in the created DCE scenarios.

The survey was hosted online and a sample of 508 members of the UK general public were recruited to complete the questionnaire. Quota sampling was used to balance geographic distribution, gender, and ethnicity, see Table 53: Demographics of DCE survey participants (74). All participants were aged 18 or over and provided consent to take part. Non-UK residents were excluded from the sample.

Choice data were analysed using the conditional logit model to estimate a linear function. The resulting coefficient weights were then rescaled so that the maximum score was 1 and the minimum score was -0.594, anchored in line with UK valuation weights for EQ-5D-3L.

Table 53: Demographics of DCE survey participants (74)

Characteristic	[redacted]
Age (years)	
Mean (SD)	[redacted]
Min, Max	[redacted]
Gender, n (%)	
Male	[redacted]
Female	[redacted]
Ethnicity, n (%)	
White Caucasian	[redacted]
Black British	[redacted]
Black Caribbean	[redacted]
Black African	[redacted]
Black Other	[redacted]
Asian Indian	[redacted]
Asian Pakistani	[redacted]
Asian Bangladeshi	[redacted]
Asian Other	[redacted]
Chinese	[redacted]
Mixed - White and Black	[redacted]
Mixed - White and Asian	[redacted]
Mixed – Other	[redacted]
Prefer not to answer	[redacted]
Other	[redacted]
Education, n (%)	
No formal qualifications	[redacted]
Left school at 16	[redacted]
Left school at 18	[redacted]
University degree	[redacted]
Other	[redacted]
Prefer not to answer	[redacted]
Main activity, n (%)	
Paid employment	[redacted]
Looking after family/home	[redacted]
Retired	[redacted]

Seeking work, unemployed	[redacted]
Not working, health problems	[redacted]
In education or training	[redacted]
Other	[redacted]
Prefer not to answer	[redacted]
Geographic region, n (%)	
England	[redacted]
Scotland	[redacted]
Wales	[redacted]
Northern Ireland	[redacted]

The results of the conditional logit regression of choice set preferences are presented in Table 54.

Table 54: [redacted]

Attributes and levels	Coefficients	SE	z	P>|z|	95% CI	Odds ratios	95% CI
[redacted]							

Results indicate that each item in the INQoL questionnaire was a significant predictor of choice for responders. Given the orthogonal design of the questionnaire, each attribute can be interpreted independently. Additionally, each level of each attribute was statistically significant.

The results identified some logical inconsistencies in the preference weights. For example, under *Leisure activities* the weights for 'moderately' and 'slightly' are mis-ordered. Where logical inconsistencies occurred the inconsistent value (disutility) in the scoring algorithm was changed to be the same as the better level. In this case, the value for 'a moderate amount' would be the same as 'slightly'. This was considered a conservative approach. Logical inconsistencies also occurred whereby people preferred 'some' or 'slight problems' to the upper anchor (i.e. very little/ not at all). Where this has occurred those disutilities for 'some' or 'slight' were adjusted to 0, again as a conservative approach (74).

The coefficient weights for the worst level on each INQoL item were summed to calculate a scoring range. This range was then rescaled to sit within the equivalent range for full health (1.0) and worst health (-0.291). All response levels for each INQoL were rescaled to that range. (This was also repeated for the scoring range 1.0 to -0.594). Missing values for the response levels that were not included in the DCE were imputed as described above

Health state utility calculation

The DCE approach was used here to understand the importance that the general public place on eight items from the INQoL and resulted in coefficients that informed these preferences. These weights were then rescaled so that they had the same range as the EQ-5D by making the assumption that the selected INQoL items and EQ-5D overlapped in terms of their conceptual content and the range of severity that they covered.

As suggested by the expert in utilities, a conservative assumption was used in the generation of utility weights to explore the assumption of the value for the INQoL worst health state (74). The weights were determined from the UK tariff for EQ-5D-3L. In the base case, the worst health state in INQoL is equal to the worst health state in EQ-5D-3L (i.e. 33333) whilst an alternative assumption of 23233 was used in a scenario analysis. An illustration of these assumptions is set out in Table 55.

Table 55: Health state assumptions and roles within the analysis

Role of health state assumption	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
Base case	3	3	3	3	3
Scenario analysis	2	3	2	3	3

The rationale for the alternative levels for worst health assumption are:

- Mobility: Extreme muscle locking and muscle weakness could be considered to not equate to the worst health state in EQ-5D, confinement to bed.
- Usual activities: Unable to complete usual activities could be considered a more severe health state than the matching item in the INQoL, Extreme impact on your ability to complete leisure activities.

The above alternative worst health assumption rationale was validated by clinical experts ((74) and see Appendix M).

To enable the calculation of utility weights, the coefficients for each INQoL item were rescaled against a worse health state value for 23233 and 33333. These are presented in Table 56.

Table 56: Worst health state coefficient for health state assumptions (87)

Health state assumption	Worst health state coefficient
23233	-0.291
33333	-0.594

The DCE informs the importance of each included INQoL item with respect to the other items in the measure. In addition to the above assumptions regarding worst health state, preference data were assumed describable in terms of linear function with no interaction effects. The utility equation is:

Tot = 1 + Uweak + Ulock + Upain + Utired + Uwash + Uleis + Uanx + Udep

Where Utot is the individual's utility score, 1 is full health and Uweak through Udep are the utility weights (i.e. disutilities) for each item in the INQoL included in this exercise.

The DCE method informed disutility values for the four out of six or seven response levels of INQoL items. The scores without associated disutilities required imputation to enable patient level data to inform the utility calculation for all patients in the MYOMEX study at all time points when INQoL data were collected. Linear interpolation was used to estimate the utility values for the missing response categories on the INQoL questionnaire.

A summary of the assumptions are below:

- The valuation weights were based on the Dolan weights for the EQ-5D-3L in line with the NICE position statement on EQ-5D-5L (88).
- Given the conceptual match of the two sets of items we have assumed that the best state defined by INQoL is equivalent to the best state defined by EQ-5D and so can be given a value of 1.0.
- We assume that the preference data can be described in terms of linear function with no interaction effects.

- The INQoL items were conceptually matched to the EQ-5D items and the EQ-5D time trade off weights were used in order to be consistent with the NICE reference case.
- The weights from the DCE were rescaled onto the 1 to -0.594 in the 33333 health state and 1 to -0.291 in the 23233 health state using the simple function below:

$$U_{tot} = 1 + U_{weak} + U_{lock} + U_{pain} + U_{tired} + U_{wash} + U_{leis} + U_{anx} + U_{dep}$$

- Where U_{tot} is the individual's utility score, and U_{weak} through to U_{dep} are the disutilities for each item in the INQoL included in the exercise.

The calculated disutility values are presented in Table 57.

Table 57: Mapped utility weights by INQoL scores according to worst health state assumptions

Utot = 1 + Uweak + Ulock + Upain + Utired + Uwash + Uleis + Uanx + Udep										
Q1a	*How much weakness would you say you have in the muscles affected by your condition?*	INQoL score	*None*	*Very little*	*Some*	*A fair amount*	*A moderate amount*	*A considerable amount*	*A lot*	*An extreme amount*
			0	1	2	3	4	5	6	7
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q2a	*How much muscle 'locking' would you say you have at the moment?*	INQoL score	*None*	*Very little*	*Some*	*A fair amount*	*A moderate amount*	*A considerable amount*	*A lot*	*An extreme amount*
			0	1	2	3	4	5	6	7
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q3a	*How much pain would you say you have at the moment?*	INQoL score	*None*	*Very little*	*Some*	*A fair amount*	*A moderate amount*	*A considerable amount*	*A lot*	*An extreme amount*
			0	1	2	3	4	5	6	7
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q4a	*How much tiredness would you say you have at the moment?*	INQoL score	*None*	*Very little*	*Some*	*A fair amount*	*A moderate amount*	*A considerable amount*	*A lot*	*An extreme amount*
			0	1	2	3	4	5	6	7
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q5a	*At the moment, does your muscle condition affect your*	INQoL score	*Not at all*	*Slightly*	*A fair amount*	*Moderately*	*Considerably*	*Very much*	*Extremely*	

	ability to do the following activities? Daily activities e.g. washing, dressing & housework		0	1	2	3	4	5	6	
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Q5b	*At the moment, does your muscle condition affect your ability to do the following activities? Leisure activities*	INQoL score	*Not at all*	*Slightly*	*A fair amount*	*Moderately*	*Considerably*	*Very much*	*Extremely*	
			0	1	2	3	4	5	6	
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Q8a I	*At the moment, does your muscle condition make you feel Anxious?*	INQoL score	*Not at all*	*Slightly*	*A fair amount*	*Moderately*	*Considerably*	*Very much*	*Extremely*	
			0	1	2	3	4	5	6	
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Q8a II	*At the moment, does your muscle condition make you feel Depressed?*	INQoL score	*Not at all*	*Slightly*	*A fair amount*	*Moderately*	*Considerably*	*Very much*	*Extremely*	
			0	1	2	3	4	5	6	
		HS assumption – 33333	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		HS assumption – 23233	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

The disutility values in Table 57 were applied to the INQoL scores of the MYOMEX population, resulting in the health state utility values presented in Table 58.

Table 58: Health state utilities

Health state	MYOMEX study treatment arm	Health state utility
Alive on Treatment (AOT)	Mexiletine	[redacted]
Alive no Treatment (ANT)	Placebo	[redacted]

Validation of methodology

In addition to the clinical expert who informed the mapping process, Lupin interviewed patients and clinical experts to validate methodology utilised within the submission, see Appendix L and Appendix M.

Logical inconsistencies

The DCE resulted in some inconsistencies that have been observed in the assessment of other HRQoL measures including SF-6D. In the assessment of the impact of such inconsistencies, Brazier et al concluded these should be weighed against the rich descriptive ability of the HRQoL measure (89).

Selected INQoL items

Literature provides evidence that the conceptually mapped items are appropriate for the assessment of HRQoL in NDM disease. Sansone et al (33) and Trivedi et al (15) identified Muscle weakness, Muscle Locking, Pain, and Fatigue as important symptoms of this disease. Life domains such as Activities and Emotions were also identified as important domains within the literature in the assessment of quality of life in NDM patients (34). Clinical experts agreed that weakness and locking are important features of NDM that affect mobility and hence, could be incorporated into the mobility domain of EQ-5D (74). Patients and clinical experts have confirmed that these domains best reflect the nature of the disease ((74) and Appendix L, Appendix M).

The underlying uncertainty of this reduction is whether these excluded INQoL sections better describe quality of life impact of NDM disease. In addition to the three clinical experts who informed the conceptual mapping process, six clinical experts, including a clinician involved in the design of the INQoL measure, confirmed that the INQoL items chosen were appropriate in the assessment of HRQoL in NDM, see Appendix M.

Independence of INQoL items / implausible health states

As mentioned in the conceptual mapping section, clinical experts informing the mapping process identified a need for separate INQoL items for the assessment of muscle locking and muscle weakness due to the ability of these two symptoms to be present independently of each other in NDM patients. Additionally, Lupin has spoken with a number of patients with

who have informed us that their symptoms present in an entirely different way to members of their family who also have NDM (Appendix L) . The heterogeneous manifestation of myotonic symptoms makes it difficult to identify implausible health states according to these patients.

However, the CMS disability score collected during the MYOMEX study, which was used in the creation of a disease severity proxy for healthcare resource use in this assessment, proves such apparently implausible health states can exist in NDM. For example, some of the MYOMEX population had significant/severe problems ascending or descending stairs but had mild or no problems dressing or walking, see Figure 27 and Figure 28.

Additionally, as mentioned in the description of the DCE, methods to enable the assessment of health states for plausibility have not been developed. Additionally, patients confirm a lack of implausible health states as the way in which symptoms manifest in them and family members with NDM varies between and within individuals, see Section B.1.3.5 and Appendix L.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The economic SLR did not identify any studies reporting healthcare resource use for the NDM population, including the patient level data available from MYOMEX (Appendix I). International Statistical Classification of Diseases and Related Health Problems (ICD) codes were explored to understand the classification of NDM in national data sources. Non-dystrophic myotonia falls under the ICD10 Code: G71.1 – Myotonic Disorders. However, this also includes dystrophic myotonia which has systemic features and dystrophic weakness and other conditions. Disorders within this ICD10 code include:

- G71.1 Myotonic disorders
- G71.11 Myotonic muscular dystrophy
- G71.12 Myotonia congenita
- G71.13 Myotonic chondrodystrophy
- G71.14 Drug induced myotonia
- G71.19 Other specified myotonic disorders

Hospital Episode Statistics (HES) data was considered in order to obtain data for the NDM chloride channelopathy, myotonia congenita (G71.12). HES data diagnosis codes start with a letter and are followed by two or three digits which means HES data could only be obtained for G71.1 and not a level lower with a fourth digit. No meaningful cost data could therefore be used from the HES dataset.

Healthcare resource use was not collected during the MYOMEX study. Nevertheless, healthcare resource use needed to be approximated for the patient population in the economic model. The clinical myotonia scale (CMS), used during the MYOMEX was used as a proxy for

to predict healthcare resource requirement, along with clinical expert opinion. This is described in Section B.3.5.2.

B.3.5.1 Intervention and comparators' costs and resource use

Mexiletine is an oral therapy and therefore only the treatment acquisition and monitoring costs were applied to fully represent the costs of treatment for both mexiletine and placebo.

B.3.5.2 Mexiletine acquisition costs

Drug costs within this evaluation were associated with treatment of myotonic symptoms and adverse events of treatment. Drug costs of mexiletine, with and without PAS discount and broken down by per pack and per capsule, are presented in Table 59.

Table 59: Mexiletine treatment costs

Drug	Cost per pack	No. per pack	Cost per capsule/ tablet	Source
Mexiletine – list price	£5,000	100	£50	BNF (2019)(11)
Mexiletine – with PAS discount	[redacted]	[redacted]	[redacted]	Lupin Healthcare (UK) Limited

B.3.5.3 Comparator acquisition costs

As there is insufficient evidence to enable the indirect comparison of NaMuscla to other unlicensed medications in the patient population defined in the NICE scope, evidence from direct treatment comparison of mexiletine to placebo in the MYOMEX trial is used in this economic evaluation. There are no acquisition costs applied for the placebo arm.

B.3.5.4 Monitoring costs

The summary of product characteristics (SmPC) of NaMuscla outlines that a detailed cardiac evaluation is required prior to mexiletine initiation and again within 48 hours post initiation. According to the SmPC, such an evaluation involves an ECG, 24-48-hour Holter-monitoring and an echocardiography. It was assumed only one 24-48-hour monitoring and echocardiogram were required for each assessment (i.e. prior to treatment initiation in the first year).

According to the SmPC, monitoring of mexiletine occurs at least every two years depending on the presence of cardiac abnormalities (9). A conservative assumption of yearly cardiac monitoring was included within the base case and is presented in

Table 60 (9).

Table 60: Resource requirements for a detailed cardiac evaluation

Test	Number of activities			
	Year one			From year two
	Prior to initiation	Within 48 hours of initiation	Total	
Electrocardiogram (test only)	1	1	2	0.5
Electrocardiogram monitoring for 24-48 hours	1	0	1	0
Echocardiogram	1	0	1	0

B.3.5.5 Health-state unit costs and resource use

Within the model, health state related resource use for alive on treatment (AOT), alive no treatment (ANT) and death are informed by patient level data from the MYOMEX study. The heterogeneous nature of the presentation of myotonic symptoms in NDM means that there are no generally recognised and agreed upon definition of myotonia severity; symptoms may show a high inter- and intraindividual variability (69). Discussions with clinical experts to identify health states for NDM patients with symptoms of myotonia found that the impact of symptoms of myotonia on individual patients were very heterogeneous. Disease severity was considered patient-specific and dependent on the part of the patient's body affected by symptoms of myotonia, hence why no formal set of health states are described in the literature (Appendix M). Therefore, the Markov model assessed patients as being alive on treatment, alive without treatment or dead – either due to treatment or not.

Unfortunately healthcare resource use was not collected during the MYOMEX study (1) but an expert advisory board had provided information on the use of physiotherapy, mobility aids, day case attendance and hospital admissions for patients who the experts thought had mild, moderate or severe disease, caveating the fact that no formal descriptions exist for disease severity in the literature, in addition to the frequency of falls and fracture that were likely to occur with and without the use of mexiletine in in NDM patients (39). This led to the consideration of using the disability scale of the CMS to define resource use in the trial for mexiletine compared to placebo as it required patients to assess their disability in carrying out activities that are known to be affected by myotonia. This would provide more granular information that was needed to create a proxy for the mild, moderate, severe health states for the purpose of health resource allocation and clinical experts provided advice during this process ((39) and Appendix M). The INQoL was not considered suitable as a proxy for healthcare resource as it does not provide insight on this aspect compared to the CMS.

The CMS for NDM is based on the model developed in primary dystonia (also a disease with an episodic and segmental expression) and was developed in the pivotal phase III MYOMEX study of mexiletine in NDM patients (1).

The scoring algorithm of the CMS measure is divided into two sections (1):

- A myotonia severity scale based on examination of the patient which addresses severity and provoking factors of myotonia in eight regions using a scale of 0-4 that measures both intensity and frequency, and
- A disability scale based on the patient's view of disability in activities of daily living using gives ratings for seven activities of daily living, using a scale of 0-4 (for most scales except feeding).

For the resource use approximation, the disability scale was chosen. This self-reported disability scale gives ratings for seven activities of daily living (speech, handwriting, feeding, hygiene, getting dressed, walking and stair climbing up and down), see Table 61.

Table 61: CMS scoring scales: Disability scale (handicap score) based on the patient's view of disability in activities of daily living (1)

Parameter	Description	Score
Speech	Normal	0
	Slightly affected, no difficulty being understood	1
	Moderately affected, has to repeat oneself occasionally	2
	Seriously affected, has to repeat oneself frequently	3
	Incomprehensible most of the time	4
Writing	Normal	0
	Slightly slower	1
	Visibly slower, all words are legible	2
	Seriously affected, not all the words are legible	3
	Impossible to handle the pen OR most words are illegible	4
Eating and handling cutlery	Normal	0
	A bit slow and clumsy	1
	Able to feed oneself but needs help with preparation (cutting, opening yoghurt…)	2
	Has to be fed	3
Hygiene (Washing etc)	Normal	0
	A bit slow but does not require assistance	1
	Help required for a few gestures/movement	2
	Help required with most gestures/movement	3
	Help required with all gestures/movements	4
Dressing	Normal	0
	A bit slow but does not require assistance	1

	Help required for a few gestures/movement	2
	Help required with most gestures/movement	3
	Help required with all gestures/movements	4
Walking (tested on 3 to 5 metres)	Normal	0
	Discreet difficulties, hardly visible	1
	Moderate difficulties, asks for occasional help	2
	Serious difficulties, needs walking aid (walking stick, third-party help)	3
	Totally unable to walk, uses a wheelchair	4
Ascending and descending stairs (tested on 5 stairs if possible, otherwise based on questions)	Normal	0
	Discreet difficulties, a bit more difficult but achievable	1
	Moderate difficulty, uses a ramp	2
	Serious difficulty, ascends or descends step by step	3
	Impossible task	4

The total minimum-maximum range is 0–27 for the disability scale. A normal situation in each sub-domain corresponds to a score of 0.

Clinical experts ((74) and Appendix M) informed the development of the healthcare resource proxy by selecting minimum and maximum CMS disability scores for patients with severe and mild symptoms, respectively. This was carried out for each disability dimension within the CMS disability scale. Table 62 shows the scores within each disability dimension that clinical experts felt described NDM patients with mild, moderate and severe symptoms of myotonia.

Table 62: Clinical expert-informed 'disease severity' according to CMS disability scale

'Disease severity'	**CMS disability scale dimensions**						
	Speech	**Handwriting**	**Eating**	**Hygiene**	**Dressing**	**Walking**	**Stairs - ascending/ descending**
Mild	0-1	0-1	0-1	0-1	0-1	0-1	0-1
Moderate	2	2	2	2	2	2	2
Severe	3-4	3-4	3	3-4	3-4	3-4	3-4

Disease severity during the treatment and no treatment arms of the MYOMEX study are presented in Figure 27 and Figure 28, respectively. There are no severe patients in the mexiletine arm of the study suggesting mexiletine improves disability across CMS dimensions.

Figure 27: Percentage of MYOMEX patients in each level of 'disease severity' whilst on mexiletine.

Figure 28: Percentage of MYOMEX patients in each level of 'disease severity' whilst on placebo (no treatment)

Likely healthcare resource use was informed by expert elicitation according to the 'disease severity' proxy. Table 63 shows the base case healthcare usage according to disease severity proxy.

Table 63: Clinical expert-informed assumption of annual allied healthcare resource use according to 'disease severity' (39)

'Disease severity'	Clinical expert informed annual frequency of allied care events according to 'disease severity' assumption						
	Physio-therapy	Occupational therapist	Speech therapy	Day case attendance	Use of wheelchair	Use of walking stick	Use of walking frame
Mild	6	6	6	1	1	1	1
Moderate	6	6	6	1	1	1	1
Severe	6	6	6	2	1	1	1

The annual number of sessions for healthcare sessions in Table 63 were assumed to be 6 (i.e. bimonthly sessions) in the base case, as per clinical expert elicitation during the UK Advisory Board (39).

The probability of patients receiving a particular healthcare resource was dependent on the 'disease severity' level of the appropriate CMS disability scale dimension (Table 64 and Table 65).

Table 64: Clinical expert-informed assumption of allied healthcare resource use according to 'disease severity', as patient elicitation (Appendix L), expert elicitation (Appendix M) and the UK Advisory Board (39)

'Disease severity'	Physiotherapy annual care package	Occupational therapist annual care package	Speech therapy care package	Day case attendances per year
Mild	10%	10%	10%	100%
Moderate	60%	60%	60%	100%
Severe	80%	80%	80%	100%

Table 65: Clinical expert-informed assumption of mobility aid usage according to 'disease severity', as patient elicitation (Appendix L), expert elicitation (Appendix M) and the UK Advisory Board (39)

'Disease severity'	Use of wheelchair	Use of walking stick	Use of walking frame	No mobility aid
Mild	0%	0%	0%	100%
Moderate	0%	20%	10%	70%
Severe	5%	30%	40%	25%

Patients with disabilities associated with handwriting, walking and ascending or descending stairs, were assumed to require physiotherapy costs. Disabilities in feeding, hygiene and dressing received occupational therapy costs. Patients with disabilities associated with speech received speech therapy costs. Mobility aid costs were received only by patients with walking disabilities. These resource use allocations are presented in Table 66.

Table 66: Assumed healthcare resource use by CMS disability scale dimensions

Healthcare resource use	CMS disability scale dimension(s)
Physiotherapy sessions	Handwriting
	Walking
	Stairs - ascending/ descending
Occupational health sessions	Eating
	Hygiene
	Dressing
Speech therapy sessions	Speech
Mobility aids	Walking

Healthcare resource use multiplier

The patient surveys (2, 39) highlighted a disparity in possible events such as fractures experienced by patients compared to that perceived by clinical experts who typically may see patients once a year (Appendix M). Therefore, a multiplier of the resource use elicited from experts and reported above is applied in the model. The multiplier in the base case is a multiple of three for patients in the ANT health state. No multiplier was added to the AOT health state.

Unit costs

Unit costs of allied healthcare and other healthcare resource use are presented in Table 67 below.

Table 67: Healthcare resource use – unit costs

Healthcare resource use	Unit costs (£)			
	National average	Lower quartile	Upper quartile	Source
Cost of genetic test				
Muscle Channelopathy Disorders 4 Gene Panel	£800.00	-	-	*UK Genetic Testing Network (90)*
Muscle channel clinics	£167.00	-	-	*NHS Reference Costs - Neurology outpatient appointment (72)*
Genetic test	£967.00	-	-	*NHS Reference Costs - Neurology outpatient appointment (72)*
Detailed cardiac evaluation				
Electrocardiogram	£38.00	-	-	*NHS Reference costs, 2017-2018* (72)
Electrocardiogram monitoring for 24-48 hours	£96.00	-	-	*NHS Reference costs, 2017-2018 (72)*

Echocardiogram	£97.00	-	-	*NHS Reference costs, 2017-2018 (72)*
Community services unit costs				
1:1 Physiotherapy session	£54.00	£44.00	£63.00	*PSSRU Unit Costs 2018 (73)*
1:1 Occupational therapy session	£78.00	£54.00	£99.00	*PSSRU Unit Costs 2018 (73)*
1:1 Speech therapy session	£97.00	£69.00	£113.00	*PSSRU Unit Costs 2018 (73)*
Annual unit cost of mobility aids				
*Wheelchair - Self- or attendant-propelled	£101.00	-	-	*PSSRU Unit Costs 2018 (73)*
Wheelchair - Active user	£202.00	-	-	*PSSRU Unit Costs 2018 (73)*
Wheelchair - Powered	£468.00	-	-	*PSSRU Unit Costs 2018 v(73)*
Wheelchair	£257.00			*Calculated – mean cost of all wheelchair types*
Walking stick	£17.50	£5.00	£30.00	*NHS.uk website (91)*
Walking frame	£150.00	£120.00	£200.00	*NHS.uk website (91)*
Primary care				
GP appointment	£34.00	-	-	*PSSRU Unit Costs 2018* (73)
Secondary care				
Day case attendance	£207.00	-	-	*NHS Reference costs, 2017-2018 (72)*
A&E attendance	£130.00	-	-	*NHS Reference costs, 2017-2018 (72)*
Treatment of a fracture	£733.00	-	-	*NHS Reference costs, 2017-2018 (72)*

Table 68: Summary of costs that inform the cost utility model

Resource	Probability or rate of use		Annual total units	Unit costs	Expected (model) costs	
	Mexiletine arm	Placebo arm			Mexiletine	Placebo
Mexiletine administration						
Mexiletine capsules (list price) – Year 1	[redacted]	0%	1071	£50	£53,550	£0.00
Mexiletine capsules (list price) – Year 2+	[redacted]	0%	1092	£50	£54,600	£0.00
ECG	100%	0%	0.5	£38	£76.00	£0.00

ECG 24-48 hour monitoring (year 1 only)	100%	0%	1	£96	£96.00	£0.00
Echocardiogram (year 1 only)	100%	0%	1	£97	£97.00	£0.00
Adverse event due to mexiletine intake						
GP consultation	0.168	0	1	£34	£5.71	£0.00
Prescription cost per consultation	0.168	0	1	£31	£5.21	£0.00
Omeprazole	0.168	0	358	£0.03	£1.80	£0.00
Falls resulting in fracture - mild symptoms						
A&E attendance	0.1	0.2	1	£130	£13.00	£26.00
Secondary care treatment for fractures	0.1	0.2	1	£733	£73.30	£146.60
Allied healthcare						
Physiotherapy - mild symptoms	10%	10%	6	£54	£32.40	£32.40
Physiotherapy - moderate symptoms	60%	60%	6	£54	£194.40	£194.40
Physiotherapy - severe symptoms	80%	80%	6	£54	£259.20	£259.20
Occupational health - mild symptoms	10%	10%	6	£78	£46.80	£46.80
Occupational health - moderate symptoms	60%	60%	6	£78	£280.80	£280.80
Occupational health - severe symptoms	80%	80%	6	£78	£374.40	£374.40
Speech therapy - mild symptoms	10%	10%	6	£97	£58.20	£58.20
Speech therapy - moderate symptoms	60%	60%	6	£97	£349.20	£349.20
Speech therapy - severe symptoms	80%	80%	6	£97	£465.60	£465.60
Wheelchair - mild symptoms	0%	0%	1	£257	£0.00	£0.00
Wheelchair - moderate symptoms	0%	0%	1	£257	£0.00	£0.00
Wheelchair - severe symptoms	5%	5%	1	£257	£12.85	£12.85

Walking stick - mild patients	0%	0%	1	£17.50	£0.00	£0.00
Walking stick - moderate patients	20%	20%	1	£17.50	£3.50	£3.50
Walking stick - severe patients	30%	30%	1	£17.50	£5.25	£5.25
Walking frame - mild symptoms	0%	0%	1	£20	£0.00	£0.00
Walking frame - moderate symptoms	10%	10%	1	£20	£2.00	£2.00
Walking frame - severe symptoms	40%	40%	1	£20	£8.00	£8.00
Day case attendance - mild symptoms	100%	100%	1	£207	£207.00	£207.00
Day case attendance - mild symptoms	100%	100%	1	£207	£207.00	£207.00
Day case attendance - mild symptoms	100%	100%	2	£207	£414.00	£414.00

B.3.5.6 Adverse reaction unit costs and resource use

The cost of adverse reactions and healthcare resource are reported in Table 69.

It was assumed that treatment for adverse events would require an average of one visit to the GP per year and the cost of treatment for dyspepsia. Dyspepsia treatment costs was based on treatment with omeprazole 20 mg once daily.

Table 69: Adverse event drug costs

Drug	Cost per pack	No. per pack	Cost per capsule/ tablet	Source
Omeprazole 20 mg	£0.84	28	£0.03	BNF (2019) (11)

B.3.5.7 Miscellaneous unit costs and resource use

No additional costs and healthcare resource use were applied in the model.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 70 shows the base-case *de novo* analysis inputs. Further detail on these inputs can be found in other sections noted in the reference column.

Table 70: Summary of variables applied in the economic model

Variable	Value	Lower bound	Upper bound	Measurement of uncertainty	Reference to Section in submission
Model settings					
Time horizon	56 years	39.2 years	72.8 years	Upper and lower bounds ±30%; Gamma distribution	B.3.2.5
Discount rate for costs	3.50%	Not included in PSA	Not included in PSA	Not included in PSA; scenario analysis for 1.5% discount rate for outcomes	B.3.2.5
Discount rate for outcomes	3.50%	Not included in PSA	Not included in PSA		B.3.2.5
Population characteristics					
Age	44	30.8	57.2	Upper and lower bounds ±30%; Gamma distribution	B.3.3.1
Compliance rate	0.95	0.66	1	Upper and lower bounds ±30%; Beta distribution	B.3.3.4
Discontinuation rate	0.06	0.04	0.2		B.3.3.5
Health state utility - mexiletine	[redacted]	[redacted]	[redacted]		B.3.4.5
Health state utility – no treatment	[redacted]	[redacted]	[redacted]		B.3.4.5
Disease progression differential mexiletine	0	0	1		B.3.3.3
Disease progression differential no treatment	0	0.11	0.06		B.3.3.3
Likelihood of falls resulting in fracture whilst taking mexiletine	0.1	0.07	0.13		B.3.3.6 Table 50

Likelihood of falls resulting in fracture whilst taking no treatment	0.2	0.14	0.26		B.3.3.6 Table 50
Mexiletine first titration dose (7 capsules), year 1	7	7	21	Upper and lower bounds ±30%; Gamma distribution	B.3.3.2
Mexiletine second titration dose (14 capsules), year 1	14	7	21		B.3.3.2
Mexiletine maintenance dose	15	7	21		B.3.3.2
Quantity of weeks on mexiletine first titration dose, year 1	1	0	2		B.3.3.2
Quantity of weeks on mexiletine second titration dose, year 1	1	0	2		B.3.3.2
Quantity of weeks on maintenance dose of mexiletine, year 1	50	48	52		B.3.3.2
Disease severity proxy					
CMS Disability score maximum for speech for mild patients	1	0	2	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
CMS Disability score maximum for speech for severe patients	3	2	4		B.3.5.2
CMS Disability score maximum for handwriting for mild patients	1	0	2		B.3.5.2
CMS Disability score maximum for handwriting for severe patients	3	2	4		B.3.5.2
CMS Disability score maximum for feeding for mild patients	1	0	2		B.3.5.2
CMS Disability score maximum for feeding for severe patients	3	2	4		B.3.5.2
CMS Disability score maximum for hygiene for mild patients	1	0	2		B.3.5.2
CMS Disability score maximum for hygiene for severe patients	3	2	4	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
CMS Disability score maximum for dressing for mild patients	1	0	2		B.3.5.2
CMS Disability score maximum for dressing for severe patients	3	2	4		B.3.5.2

CMS Disability score maximum for walking for mild patients	1	0	2		B.3.5.2
CMS Disability score maximum for walking for severe patients	3	2	4		B.3.5.2
CMS Disability score maximum for stairs for mild patients	1	0	2		B.3.5.2
CMS Disability score maximum for stairs for severe patients	3	2	4		B.3.5.2
Mexiletine initiation and maintenance					
Number of Electrocardiogram (biannual)	2	1	3	Upper and lower bounds ±30%; Gamma distribution	B.3.5.3
Number of Electrocardiogram monitoring for 24-48 hours (only in the first year)	1	0	2		B.3.5.3
Number of Echo-cardiogram (only in the first year)	1	0	2		B.3.5.3
Healthcare resource utilisation (annual)					
Percentage of mild patients who utilise physiotherapy annual care package	0.1	0.07	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.2
Percentage of moderate patients who utilise physiotherapy annual care package	0.6	0.42	1		B.3.5.2
Percentage of severe patients who utilise physiotherapy annual care package	0.8	0.56	1		B.3.5.2
Percentage of mild patients who utilise occupational therapist annual care package	0.1	0.07	1		B.3.5.2
Percentage of moderate patients who utilise occupational therapist annual care package	0.6	0.42	1		B.3.5.2
Percentage of severe patients who utilise occupational therapist annual care package	0.8	0.56	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.2
Percentage of mild patients who utilise speech therapy care package	0.1	0.07	1		B.3.5.2

Percentage of moderate patients who utilise speech therapy care package	0.6	0.42	1		B.3.5.2
Percentage of severe patients who utilise speech therapy care package	0.8	0.56	1		B.3.5.2
Percentage of mild patients who utilise day case attendances per year	1	0.7	1		B.3.5.2
Percentage of moderate patients who utilise day case attendances per year	1	0.7	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.2
Percentage of severe patients who utilise day case attendances per year	1	0.7	1		B.3.5.2
Percentage of mild patients who utilise wheelchair	0	0	1		B.3.5.2
Percentage of moderate patients who utilise wheelchair	0	0	1		B.3.5.2
Percentage of severe patients who utilise wheelchair	0.05	0.04	1		B.3.5.2
Percentage of mild patients who utilise walking sticks	0	0	1		B.3.5.2
Percentage of moderate patients who utilise walking sticks	0.2	0.14	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.2
Percentage of severe patients who utilise walking sticks	0.3	0.21	1		B.3.5.2
Percentage of mild patients who utilise walking frame	0	0	1		B.3.5.2
Percentage of moderate patients who utilise walking frame	0.1	0.07	1		B.3.5.2
Percentage of severe patients who utilise walking frame	0.4	0.28	1		B.3.5.2
Healthcare resource units (annual)					
Number of annual physiotherapy visits for mild patients	6	4	8	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
Number of annual physiotherapy visits for moderate patients	6	4	8		B.3.5.2

Number of annual physiotherapy visits for severe patients	6	4	8		B.3.5.2
Number of annual occupational therapy visits for mild patients	6	4	8		B.3.5.2
Number of annual occupational therapy visits for moderate patients	6	4	8		B.3.5.2
Number of annual occupational therapy visits for severe patients	6	4	8	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
Number of annual speech therapy visits for mild patients	6	4	8		B.3.5.2
Number of annual speech therapy visits for moderate patients	6	4	8		B.3.5.2
Number of annual speech therapy visits for severe patients	6	4	8		B.3.5.2
Number of annual day case attendances for mild patients	1	0	2		B.3.5.2
Number of annual day case attendances for moderate patients	1	0	2	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
Number of annual day case attendances for severe patients	2	1	3		B.3.5.2
Number of wheelchairs for mild patients (provision and maintenance)	1	0	2		B.3.5.2
Number of wheelchairs for moderate patients (provision and maintenance)	1	0	2		B.3.5.2
Number of wheelchairs for severe patients (provision and maintenance)	1	0	2		B.3.5.2
Number of walking sticks for mild patients (provision and maintenance)	1	0	2		B.3.5.2
Number of annual units of walking sticks for moderate patients (provision and maintenance)	1	0	2	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
Number of walking sticks for severe patients (provision and maintenance)	1	0	2		B.3.5.2

Number of walking frames for mild patients (provision and maintenance)	1	0	2		B.3.5.2
Number of walking frames for moderate patients (provision and maintenance)	1	0	2		B.3.5.2
Number of walking frames for severe patients (provision and maintenance)	1	0	2		B.3.5.2
Number of omeprazole 20mg capsules per day for treatment for dyspepsia	1	0	2		B.3.5.2
Adverse events probability					
Probability of requiring treatment for dyspepsia	0.7	0.49	1	Upper and lower bounds ±30%; Beta distribution	B.3.3.6
Probability of adverse events	0.33	0.23	1		B.3.3.6
Costs					
Cost per capsule of omeprazole	£0.03	£0.02	£0.04	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
Cost per capsule of imported mexiletine	£9.29	£6.50	£12.08		B.3.5.2
Genetic test cost	£800.00	£560.00	£1,040.00		B.3.5.2
Cost of Genetic consultation visit	£167.00	£116.90	£217.10		B.3.5.2
Cost per capsule of NaMuscla	£27.50	£35.00	£65.00		B.3.5.2
Cost of Electrocardiogram	£38.00	£26.60	£49.40		B.3.5.2
Cost of Electrocardiogram monitoring for 24-48 hours	£96.00	£67.20	£124.80		B.3.5.2
Cost of Echocardiogram	£97.00	£67.90	£126.10		B.3.5.2
Cost of Physiotherapy 1:1 session	£54.00	£37.80	£70.20		B.3.5.2
Cost of Occupational therapy 1:1 session	£78.00	£54.60	£101.40		B.3.5.2
Cost of Speech therapy 1:1 session	£97.00	£67.90	£126.10	Upper and lower bounds ±30%; Gamma distribution	B.3.5.2
Cost of General Practitioner consultation	£65.00	£45.50	£84.50		B.3.5.2
Cost of Day case attendance	£207.00	£144.90	£269.10		B.3.5.2
Cost of A&E attendance	£130.00	£91.00	£169.00		B.3.5.2
Cost of treatment of fracture	£733.00	£513.10	£952.90		B.3.5.2
Cost of Wheelchair - Self- or attendant-propelled (annual)	£101.00	£70.70	£131.30		B.3.5.2

Cost of Wheelchair - Active user (annual)	£202.00	£141.40	£262.60		B.3.5.2
Cost of Wheelchair - Powered (annual)	£468.00	£327.60	£608.40		B.3.5.2
Cost of Walking sticks (annual)	£17.50	£12.25	£22.75		B.3.5.2
Cost of Walking frame (annual)	£150.00	£105.00	£195.00		B.3.5.2

B.3.6.2 Assumptions

Table 71 presents the assumptions of the de novo cost utility model created for this analysis.

Table 71: Assumptions underpinning cost effectiveness model

Variable	Assumed value	Justification
Time horizon	56 years	Patients entering the model have a mean age of 44 years based on MYOMEX study population, see Section B.2.3.1. Patients in the cohort are not expected to live beyond 100 years and therefore a 56 year time horizon was deemed appropriate (100-44 = 56). In the modelled population, 99% of the population are in the death health state at 100 years of age. This is considered appropriate as the MYOMEX population inform the utility and health care resource calculations. Additionally, individuals with NDM have specified worsening symptoms (assumed to progressively require BSC and finally pharmacological treatment) with increasing age Appendix L. Hence, a mean age of 44 years is appropriate. The time horizon is included in the sensitivity analysis.
Half-cycle correction applied	Yes	A half-cycle correction was applied to both costs and health outcomes in the Markov model due to the long time horizon of the model.
Baseline characteristics of patients	Whole cohort: Age (years) = 44 % male = [redacted]%	The indicated population were enrolled in the MYOMEX study, so it is suitable to use the baseline characteristics of the MYOMEX cohort for model.
Clinically effective dose	400 mg daily (14 capsules per week)	MYOMEX long term efficacy and feedback from Advisory Board (39, 50). Corroborated by clinical experts (Appendix M).
Disease progression differential	15%	Literature (17) and patient experience (2, 27), Appendix L) report increasing severity of disease over time. Feedback from two German clinical experts support that in the absence of an effective treatment a decline in QoL over time occurs, as imported mexiletine has not been an option (Appendix M). Long-term data from MYOMEX (50) shows clinical benefit is at least maintained and is supported by clinical experts (Appendix M).

		A disease progression differential is therefore applied to 'no treatment' arm utilities under the assumption that quality of life worsens in the absence of treatment. See Section 3.3.3
Discontinuation rate	5.51%	Based on real world (long term) data by Suetterlin et al (49). This was included in place of the discontinuation rate observed in the MYOMEX study which had a short-term follow-up, see section B.2.3.1.
Disease severity proxy (for healthcare resource use allocation)	Mild Moderate Severe	As healthcare resource use data was not available from the MYOMEX study nor results of the SLR, it was approximated for each patient in the MYOMEX study using a proxy for disease severity. The disability scale of the Clinical Myotonia Scale (CMS) was chosen because it is a subjective measure that enables patients to assess their ability to carry out tasks. Clinical experts informed the allocation of mild, moderate or severe to scores within each dimension of the scale. See section B.3.5.5.
Multiplier of healthcare resource use for patients on no treatment	Multiple of 3	Healthcare resource use, as informed through expert elicitation using a proxy of the CMS disability scale, was a lot less than is usually observed in chronic disease. This suggested an underestimate, particularly for symptomatic patients in the absence of treatment. A multiple of healthcare resource use in the absence of treatment was assumed in the base case to address this likely underestimation.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case result, at list price, was associated with an incremental cost of [redacted] and incremental QALY of [redacted] which resulted in an ICER of [redacted] The ICER, when incorporating the PAS discount (see Table 59 of Section B.3.5.1), was [redacted] which was associated with a lower incremental cost of [redacted] with no change in incremental QALYs.

The disaggregated results presented in Appendix J show that the largest QALY gains are obtained in the Alive on Treatment health state ([redacted]%) due to no patients being in this health state when receiving no treatment. The majority of costs also occur in the Alive on Treatment with the [redacted]% being due treatment costs.

Table 72: Base-case results

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
List price							
No treatment	[redacted]	38.92	[redacted]				
Mexiletine	[redacted]	38.92	[redacted]	[redacted]	0	[redacted]	[redacted]
PAS price							
No treatment	[redacted]	38.92	[redacted]				
Mexiletine	[redacted]	38.92	[redacted]	[redacted]	0	[redacted]	[redacted]

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To assess parameter precision in the model, all model parameters were varied simultaneously in a probabilistic sensitivity analysis (PSA). The convergence method presented by Hatswell et al (92) was used to inform the number of iterations to include in the simulation. Confidence intervals did not cross zero at 5,000 iterations, however, due to the potential uncertainty in the model, 10,000 PSA iterations were run to obtain a stable estimate and convergence of the mean model output.

Mean values, standard deviation, and distributions of each parameter included within the PSA are presented in Table 70. Beta distributions were used for the event probabilities and utilities, with Gamma distributions used for quantities of resource use and costs.

The mean results presented in Table 73, at list and PAS price, show a slight reduction in the ICER compared to the base case. This is due to an increase in total costs for both mexiletine and no treatment, combined with a greater decrease in total QALYs for no treatment than mexiletine. The list price ICER is [redacted] with the inclusion of PAS price reducing the ICER to [redacted] The results are in line with the deterministic base case, providing additional confidence in the results.

Table 73: Mean results of probabilistic sensitivity analysis

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
List price					
No treatment	[redacted]	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAS price					
No treatment	[redacted]	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean incremental results at list and PAS price are presented in the cost-effectiveness planes (CEP) below, see Figure 29 and Figure 30 respectively.

The PSA results and the deterministic base case result at both list and PAS price sit in the North East quadrant of the CEP, suggesting that mexiletine is both more effective and more costly than no treatment. Of the individual results of the 10,000 iterations, [redacted] are cost-effective, sitting under the £30,000 threshold at PAS price, with [redacted] at list price. In addition, a small proportion [redacted] of scenarios sit in the North West quadrant, indicating a small degree of uncertainty about the incremental benefits of mexiletine versus no treatment.

The cost-effectiveness acceptability curve (CEAC), at list and PAS price, are presented in

Figure 31 and

Figure 32 respectively. The CEAC show that, at a maximum willingness to pay of £30,000, mexiletine has a [redacted] probability of cost-effectiveness than no treatment. At a WTP threshold of £100,000, the probability of cost effectiveness is approximately [redacted] at PAS price but falls to approximately [redacted] when considering list price. A [redacted] probability of cost-effectiveness is obtained at a WTP threshold of approximately £300,000 for the PAS price.

Figure 29: [redacted]

Figure 30: [redacted]

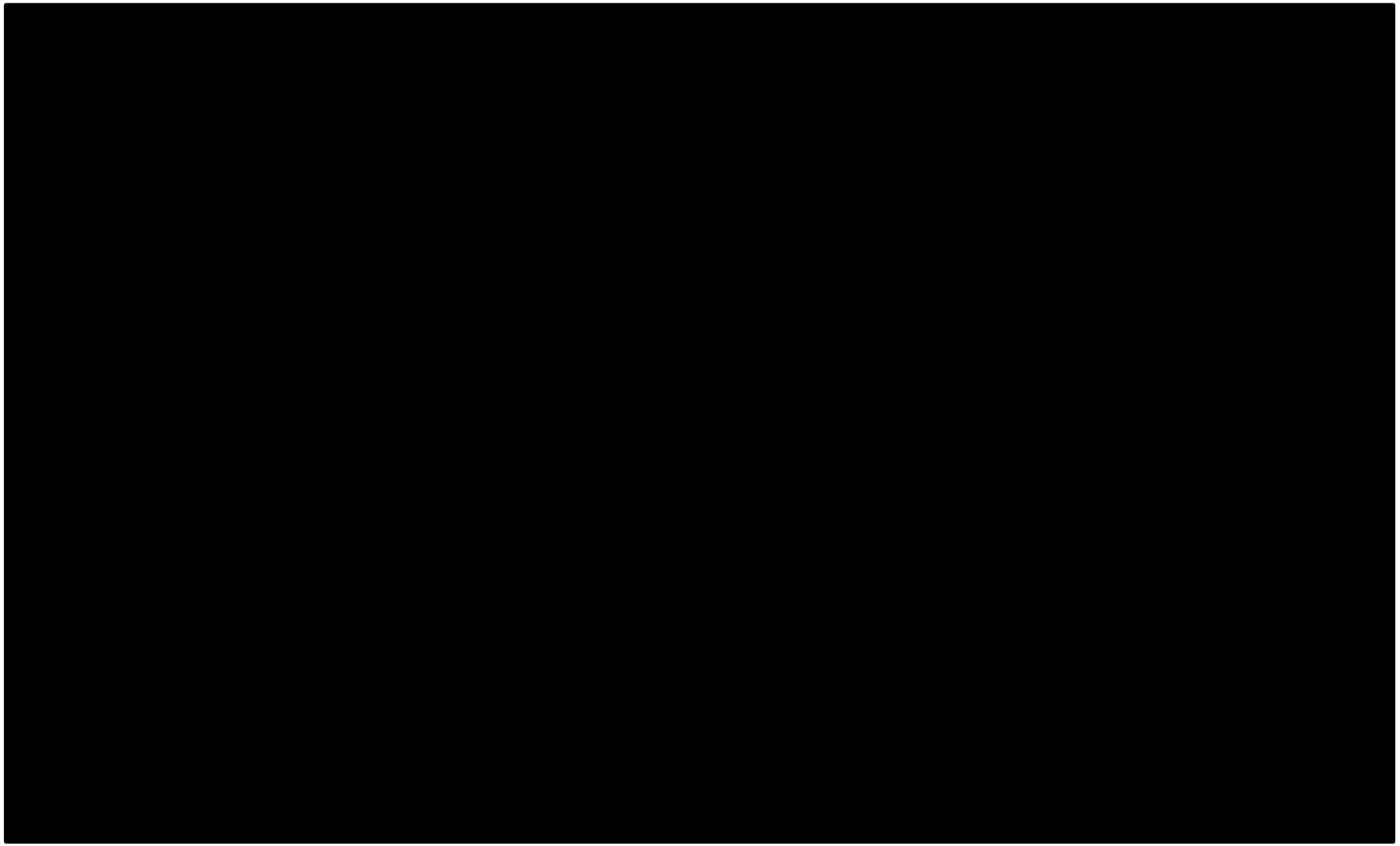
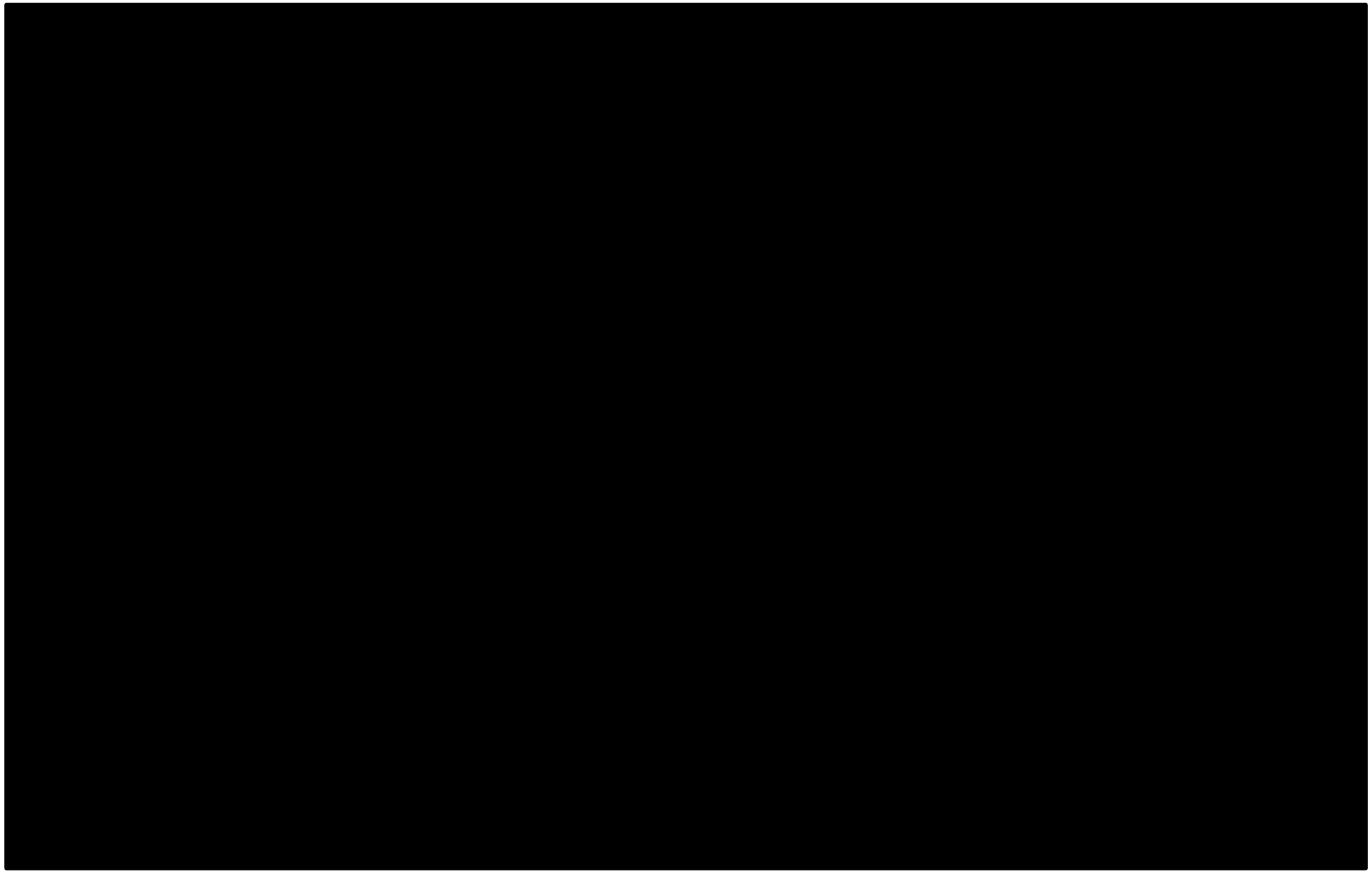


Figure 31: [redacted]

Figure 32: [redacted]



B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. As the majority of model parameters were informed by a small study population and assumptions informed by clinical experts, upper and lower CIs could not be sourced from literature for the OWSA. Instead, upper and lower CIs were assumed to be 30% of the mean value where it was not possible to derive data from literature, see Table 70.

A tornado diagram (Figure 33 for the list price and Figure 34 for PAS price) illustrate that the model is most sensitive to the utility value whilst on mexiletine, the mexiletine maintenance dose, mexiletine's disease progression differential, cost per mexiletine capsule, utility value for no treatment and compliance rate. These parameters affect how much cost and health effect is accrued in the AOT health state.

Figure 33: [redacted]

Table 74 and Table 75 show that the mexiletine health state utility value causes the largest change in base case ICER, varying it by [redacted] at list price and [redacted] with PAS price. Whilst varying the utility value for no treatment causes only a third of the variation at [redacted] at list price and [redacted] at PAS price. As an increase in the mexiletine disease progression differential leads to a decrease in QALY gain, this causes a large variation from the base case.

Table 74: OWSA results of mexiletine versus No treatment for the whole cohort (list price)

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Base case ICER (without PAS discount)		[redacted]	
Utility value - Mexiletine	[redacted]	[redacted]	[redacted]
Mexiletine maintenance dose	[redacted]	[redacted]	[redacted]
Disease progression differential mexiletine	[redacted]	[redacted]	[redacted]
Cost per capsule for mexiletine	[redacted]	[redacted]	[redacted]
Utility value – no treatment	[redacted]	[redacted]	[redacted]
Compliance rate	[redacted]	[redacted]	[redacted]
Quantity of weeks on maintenance dose of mexiletine, year 1	[redacted]	[redacted]	[redacted]
Disease progression differential - No Treatment	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine second titration dose, year 1	[redacted]	[redacted]	[redacted]
Percentage of mild patients who utilise speech therapy care package	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine first titration dose, year 1	[redacted]	[redacted]	[redacted]
Mexiletine second titration dose (14 capsules), year 1	[redacted]	[redacted]	[redacted]
Mexiletine first titration dose (7 capsules), year 1	[redacted]	[redacted]	[redacted]
Percentage of mild patients who utilise occupational therapist annual care package	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for moderate patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for feeding for mild patients	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for severe patients	[redacted]	[redacted]	[redacted]

CMS Disability score maximum for speech for mild patients	[redacted]	[redacted]	[redacted]
Cost of Physiotherapy 1:1 session	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for stairs for severe patients	[redacted]	[redacted]	[redacted]

Figure 34: [redacted]

Table 75: OWSA results of mexiletine versus No treatment for the whole cohort (PAS price)

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Base case ICER (without PAS discount)		[redacted]	
Utility value - Mexiletine	[redacted]	[redacted]	[redacted]
Mexiletine maintenance dose	[redacted]	[redacted]	[redacted]
Disease progression differential mexiletine	[redacted]	[redacted]	[redacted]

Cost per capsule for mexiletine	[redacted]	[redacted]	[redacted]
Utility value – no treatment	[redacted]	[redacted]	[redacted]
Compliance rate	[redacted]	[redacted]	[redacted]
Quantity of weeks on maintenance dose of mexiletine, year 1	[redacted]	[redacted]	[redacted]
Disease progression differential - No Treatment	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine second titration dose, year 1	[redacted]	[redacted]	[redacted]
Percentage of mild patients who utilise speech therapy care package	[redacted]	[redacted]	[redacted]
Percentage of mild patients who utilise occupational therapist annual care package	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine first titration dose, year 1	[redacted]	[redacted]	[redacted]
Mexiletine second titration dose (14 capsules), year 1	[redacted]	[redacted]	[redacted]
Mexiletine first titration dose (7 capsules), year 1	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for moderate patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for feeding for mild patients	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for severe patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for speech for mild patients	[redacted]	[redacted]	[redacted]
Cost of Physiotherapy 1:1 session	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for stairs for severe patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for dressing for mild patients	[redacted]	[redacted]	[redacted]

B.3.8.3 Scenario analysis

Scenario analyses were performed to analyse the effect of using alternative data sources for the following model parameters and assumptions, quantifying the uncertainty surrounding the true values:

- *Disease progression differential* in the base case is 15% between mexiletine treatment and no treatment over the lifetime of an NDM patient. In the scenario analysis, it is varied between 0-25%. A differential effect is assumed to exist in NDM such that quality of life decreases over time in the absence of treatment for myotonic symptoms as described in Section B.3.3.3.
- The *time horizon* in the base case is 56 years. Scenario analysis to assess the impact of a reduced time horizon of 10, 20, 30 and 40 years were carried out to assess the impact on the base case results.
- The source of the modelled population, MYOMEX, informed the base case *compliance rate* of [redacted]%. Scenario analysis where the reported compliance rates in Statland et al (90.2%) and Stunnenberg (94%) were carried out to assess the impact on cost-effectiveness.
- The discontinuation rate in the base case was informed by the long term follow-up study by Suetterlin et al and equated to 5.15%. As this informed annual movement from the alive on treatment health state to the alive no treatment health state, the impact of reported discontinuation rates in other studies - MYOMEX study ([redacted]%), Statland et al (7%) and Stunnenberg (3%) – were assessed for their impact on cost effectiveness of mexiletine.
- The base case value of the adoption of the *healthcare resource multiplier* considering a multiple of three for comparator arm. A reduction in this multiplier (multiple of two and no multiplier) was assessed to understand the impact of reducing the base case assumption of higher healthcare resource use in the absence of treatment.
- The *adverse event rate* of 33.33% for gastrointestinal side effects of mexiletine was informed by Suetterlin et al in the base case. Scenario analysis where the reported rates in the MYOMEX study ([redacted]%), Statland et al (32%) and Stunnenberg (70%) were carried out to assess the impact of adverse events on the cost-effectiveness.
- A dose (*mexiletine maintenance dose*) of 400 mg daily or 14 capsules per week was used in the base case. In Suetterlin, an effective dose of mexiletine is reported as 416.7 mg daily. This scenario analysis explored a slightly higher dose of 429 mg daily (15 capsules per week) to assess the impact of an increased dose on the base case ICER.
- A scenario analysis was carried out to assess the impact of a conservative *worst health state assumption*, 23233, in comparison to the worst health state 33333 assumed in the base case. Worst health state in NDM disease, as measured by the INQoL

questionnaire, is assumed to not be as severe as the worst health state in EQ-5D-3L (i.e. 33333), see Section B.3.4.2. Clinical experts informed the following assumptions:

  - Mobility: Extreme muscle locking and muscle weakness does not equate to confinement to bed in NDM so worst health state is 2 in EQ-5D-3L i.e. 23333
  - Usual activities: The worst health state in Usual activities observed in NDM is less severe than the worst state in EQ-5D, hence, 33233.

- The structural assumption of a *discount rate* of 3.5% was adopted in the base case. The adoption of a discount rate of 0% and 1.5% for health outcomes was assessed, keeping a discount rate of 3.5% for costs (as indicated on HM treasury green book in 2018) (70).
- *Genetic test costs* were assumed for all patients, regardless of health state, in year one in the base case. The exclusion of genetic testing costs was assessed in scenario analysis due to the assumption that patients would not be diagnosed to initiate mexiletine treatment as they would already be diagnosed to receive best supportive care. So the cost of this healthcare resource use should not be associated with treatment.

The same percentage change from base case ICER was found at both list and PAS price for the majority of scenarios tested, see Table 76 and Table 77.

Table 76: Results of scenario analyses (PAS price)

Scenario	Mexiletine cost (£)	Mexiletine QALY	No Treatment costs	No Treatment QALY	Incr. cost	Incr. QALY	ICER	% change from base-case ICER
Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No multiplier for HC resource use in No Treatment health state (i.e. x1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two multipliers for HC resource use in No Treatment health state (i.e. x2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Four multipliers for HC resource use in No Treatment health state (i.e. x4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events – MYOMEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events - Statland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events – Stunnenberg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily dose 429 mg (15 capsules)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23233 EQ-5D worst health state for INQoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No discount rate for health outcomes and costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcome discount rate 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate Statland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate Stunnenberg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 77: Results of scenario analyses (List price)

Scenario	Mexiletine cost (£)	Mexiletine QALY	No Treatment costs	No Treatment QALY	Incr. cost	Incr. QALY	ICER	% change from base-case ICER
Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 0 %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No multiplier for HC resource use in No Treatment health state (i.e. x1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No multiplier for HC resource use in No Treatment health state (i.e. x2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No multiplier for HC resource use in No Treatment health state (i.e. x4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events - MYOMEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events - Statland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events - Stunnenberg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily dose 429 mg (15 capsules)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23233 EQ-5D worst health state for INQoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No discount rate for health outcomes and costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcome discount rate 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate Statland	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate Stunnenberg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Disease progression differential (No Treatment)

An increasing disease progression differential from 0-25% for the no treatment (AOT) health state causes a gradual increase in QALY gain resulting in a reduction in the ICER in comparison to the base case. An increasing differential causes a progressive decrease in the utility value for no treatment leading to increasing incremental QALY. Hence, if NDM in untreated patients worsened at a faster rate than NDM in mexiletine treated patients, the cost effectiveness of mexiletine increases at lower WTP thresholds.

Time Horizon

There was no change in ICER value with increasing model time horizons as incremental costs and QALYs increased at a similar rate, resulting in ICERs that were within £14 of the base case. The reason for this result is that the model is informed by short term data from the MYOMEX population and point estimates from other studies. Hence, the same healthcare usage and health outcomes are observed throughout the NDM patient's lifetime with differences across years solely due to parameters that inform the same changes across the cohort i.e. discount rates.

Healthcare resource use multiplier (No Treatment)

No multiplier results in a [redacted] increase in the base case ICER. There is no change in the QALY gain in comparison to the base case and increasing multiplier reduces the base case ICER.

Adverse events

Different sources for the probability of gastrointestinal adverse events whilst on mexiletine led to small changes in the cost of the Alive on Treatment health state which resulted in equally small changes in the ICER. Hence, the changes in the probability of the most frequent adverse event whilst on mexiletine does not lead to significant changes in the base case ICER.

Mexiletine maintenance dose

Increasing the maintenance dose of mexiletine by one capsule leads to a [redacted] rise in the base case ICER. This enables the assessment of an alternative long term maintenance (or effective) dose as reported by Suetterlin et al (49).

Worst health state assumption

Updating the worst health state assumption from 33333 in the base case to 23233 results in a [redacted] increase in the ICER value. This is as expected as more severe INQoL scores can be associated with more severe disutility values.

Discount rate

Reduction in the discount rate to 1.5% lead to a reduction of [redacted] from the base case ICER.

Genetic testing

Removal of genetic testing had no impact on the base case ICER, as it is included for both mexiletine and no treatment in the first year of the Markov model. A patient needs to be diagnosed with NDM prior to a decision to initiate treatment or not is made.

Compliance rate

A reduction of [redacted] and [redacted] from the base case ICER was observed for compliance rates informed by Statland et al and Stunnenberg et al respectively. This is due to a slightly lower incremental cost with each of these rates in comparison to the base case.

B.3.8.4 Summary of sensitivity analyses results

Compared to the base case, the ICER value generated by the probabilistic sensitivity analysis is slightly lower due to a greater relative increase in the total QALYs gained than the total costs of mexiletine treatment in comparison to no treatment.

The deterministic sensitivity analysis illustrated that the largest reductions in the base case ICER were due to improvements in QALY gain whilst patients are in the AOT health state. The parameters that drove this were utility value whilst on mexiletine, the mexiletine maintenance dose, mexiletine's disease progression differential, cost per mexiletine capsule, utility value for no treatment and compliance rate. This suggests the need for further gathering of evidence to the costs and consequences of mexiletine treatment.

The results of the scenario analyses show that significant differences to the base case are observed following changes from base case values for key model parameters and assumptions: worst health state assumption, disease progression differential (no treatment) and reduction in the discount rate of outcomes and compliance. Hence, the model is most sensitive to scenarios that make assumptions of the natural history of the disease and the dose of mexiletine treatment.

B.3.9 Subgroup analysis

No subgroups of interest were identified for this submission. This is in line with the NICE Final Scope.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The economic model was subject to extensive internal and external validation by programmers who were not involved in the model build. Internally, the finalised model was quality checked for the following components:

- Basic validity checks; logical checks of the Markov trace and output in relation to inputs and intended functions
- Costs; checks of cost inputs for most recent sources and application
- Utilities and clinical; most applicable sources and application
- Model settings; standard model functionality and usability
- Sensitivity analysis; PSA, DSA and scenario analyses incorporation
- Macros/User Forms; VBA code functionality and efficiency

External validation of the model structure and function was provided by two third party health economics consultancies, who were consulted during the development of the health economic model and checked the model inputs were working correctly.

B.3.11 Interpretation and conclusions of economic evidence

Over a 56-year time horizon, the QALY gain for the modelled population of NDM patients was [redacted] at a total cost of [redacted] resulting in a base case ICER of [redacted] at PAS price. The probabilistic ICER is [redacted] per QALY at PAS price supporting the base case ICER in its proximity. The small reduction in probabilistic ICER is due to a slight increase in incremental QALYs as well as a reduction in incremental costs when parameter and model uncertainty is taken into account with the probabilistic analysis.

Disaggregated results of the model show that the majority of costs and outcomes in the model are accrued whilst patients are in the Alive on Treatment health state. The main drivers of the model identified in the one way sensitivity analysis affect how much cost and health outcomes are accrued in the AOT health state. Some conservative assumptions in this analysis reduced such accrual. For example, Suetterlin et al observed patients reinitiating mexiletine treatment after stopping because of ineffectiveness or adverse events. An assumption was made that such re-initiation would occur within a year of stopping mexiletine and so the model only required annual discontinuation rates.

As this is the first economic evaluation of treatment for myotonic symptoms in NDM, there are no economic evaluations for this clinical area to validate the results against. However, the base case ICER obtained in this analysis is well below the £100,000 ICER threshold for the QALY gain in the NICE Highly Specialised Technology appraisals – the usual route for very rare disease appraisals.

The use of patient level data to inform model parameters has been a major advantage for this analysis. As NDM is a very rare disease, a paucity of data exists which would usually lead to the requirement of many assumptions to inform the relative effectiveness of comparators. With access to the MYOMEX dataset, a direct comparison of mexiletine and no treatment was possible. Additionally, as HRQoL was collected in this dataset, effectiveness could be informed by the same dataset i.e. the generation of utilities from INQoL scores collected during the MYOMEX study. It will be noted that the utility gain derived from the health economic model is high where treatment with mexiletine can restore the health of patients with NDM to the same level of that of the general population. This is expected when taking into account the impact the condition can have on patients – see Section B.1.3.5 for qualitative insights on the impact that the symptoms of myotonia can have on patient lives.

A limitation of this analysis was that healthcare resource use was not collected in the same dataset. However, the assessment of subjective myotonia-related disability using the CMS disability score enabled allocation of healthcare resources according to an individual's scoring of their own health – a good measure of the healthcare need they are likely to seek. Clinicians identified few healthcare resources, as most impact caused by myotonia disrupts an individual's ability to carry out everyday activities (see Section B1.3.5.) but direct healthcare resource use is possibly underestimated. Coping strategies are then developed that often mean the individual has to forgo many aspects of their lives including the ability to be independent or even take care of their own children. Hence a healthcare resource use multiplier has been incorporated into the model to account for costs that are not completely captured within the model focusing on an NHS perspective.

Health state preferences which enabled the valuation of utilities from the disease-specific HRQoL instrument, INQoL, to the preference-based instrument EQ-5D were informed by a generalisable sample of the UK population. Hence, utility weights that informed this economic evaluation were generated according to the preferences of the UK population. The efficacy of mexiletine used in this analysis was obtained from the MYOMEX study and the improved outcomes observed whilst patients are taking mexiletine are in keeping with findings of a UK retrospective analysis of the treatment of channelopathies by Suetterlin et al.

Additionally, the healthcare resource use utilised in NDM was informed by expert clinicians in this evaluation due to the rarity of NDM and the fact that such data was not collected during the MYOMEX study. The unit costs of resources were obtained from the most recent NHS Reference Costs and Personal Social Services Research Unit datasets which provide reasonable estimates of the cost of healthcare provision in NHS England.

In conclusion, when compared to no treatment, mexiletine is both more costly and more effective. Uncertainties around the natural history of the disease such as disease progression differentials were shown to have greatest impact on the ICER when assessed in the scenario analyses. This is to be expected for very rare diseases such as NDM where much uncertainty is present due to difficulty collecting evidence of effectiveness. Lupin have addressed this by ensuring large variation of the model inputs during sensitivity analysis. The base case ICER with PAS is [redacted] is above the NICE threshold for cost-effectiveness for a Single Technology

Appraisal but in the context of a very rare disease and under a Highly Specialised Technology appraisal NaMuscla would be cost-effective with undiscounted gain of [redacted] QALYs, well below the £100,000 cost per QALY threshold.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Clarification questions

February 2020

File name	Version	Contains confidential information	Date
ID1499 Mexiletine ERG Clarifications Response Document v2 20Mar2020 FINAL REDACTED [CIC] [AIC]	**V2.0**	**Yes**	**20/03/2020**

Notes for company

Highlighting in the template

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To delete grey highlighted text, click anywhere within the text and press DELETE.

List of Abbreviations

A&E	Accidents and Emergency
AE	Adverse Event
ANT	Alive No Treatment
AOT	Alive On Treatment
ATC	Anatomical Therapeutic Chemical Classification System
BNF	British National Formulary
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curve
CEP	Cost-Effectiveness Planes
CI	Confidence Interval
CMS	Clinical Myotonia rating Scale
CS	Company Submission
CSR	Clinical Study Report
DCE	Discrete Choice Experiment
DSA	Deterministic Sensitivity Analysis
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
ICER	Incremental Cost-Effectiveness Ratio
HRQoL	Health Related Quality of Life
HST	Highly Specialised Technology
INQoL	Individualised Neuromuscular Quality of Life
KOL	Key Opinion Leader
LR	Logistic Regression
MC	Myotonia Congenita
MP	Mexiletine then Placebo
mITT	modified Intention-To-Treat
NDM	Non-Dystrophic Myotonia
NHNN	National Hospital for Neurology and Neurosurgery
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
OWSA	One-Way Sensitivity Analysis
PAS	Patient Access Scheme
PC	Paramyotonia Congenita
PCA	Prescription Cost Analysis
PM	Placebo then Mexiletine

PP	Per Protocol
PPI	Proton-Pump Inhibitor
PSA	Probabilistic Sensitivity Analysis
PSUR	Periodic Safety Update Reports
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Control Trial
SD	Standard Deviation
SE	Standard Error
SMPC	Summary of Product Characteristics
TRT	Number of Treatments Taken
TTO	Time-trade-off
VAS	Visual Analogue Scale
WTP	Willingness-To-Pay

Additional information

Delphi panel

Lupin are currently conducting a Delphi Panel research project, focusing on non-dystrophic myotonia (NDM) in the UK setting to support refinement of the economic model if required. The project follows the methodology originally developed by the RAND Corporation in the 1950s as a practical and structured method of obtaining opinions on a given question from a range of experts (1). The participants take part anonymously in sequential rounds of surveys, with each round being refined based on the feedback from the previous version. The goal is to reach a consensus on the questions posed. This project will comprise two rounds of surveys, with each round taking no more than 1 hour. A synthesis of responses will be conducted between each survey round to formulate the subsequent surveys.

The Delphi Panel project is currently under way and it is expected that the project will be completed by June. Questions where we expect to be informed by the Delphi Panel have been identified in individual responses.

Updated economic model

Whilst addressing the ERG clarifications, erroneous inputs were found in the patient level data within the model. The errors include the use of the incorrect values for the 'Activities AII' INQoL inputs at baseline (column CW of 'Patient level analysis' sheet), after treatment with placebo (column DO of 'Patient level analysis' sheet) and after treatment with mexiletine (column EG of 'Patient level analysis' sheet). These inputs were previously taken from the 'Activities BI' in the original CS economic model, rather than the correct 'Activities AII'. The inputs have been corrected in the updated economic model. Additional validation and external review have been commissioned, as outlined in response to B28.

Updated base case results are presented below in Table 1, with updated deterministic and probabilistic sensitivity analyses presented in response to B27a. All other presented scenarios in response to clarification questions have been conducted using the updated economic model.

Table 1. Updated economic model base case results at list and PAS price

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
List price					
No treatment	50,645	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAS price					
No treatment	50,645	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The economic model was also amended in line with responses to ERG feedback. Full details of each update are outlined in individual responses and summarised below.

- The model includes the functionality to choose between additional data sources for utilities, where in addition to 'MYOMEX DCE', there is the choice of 'MYOMEX Vignettes', including the utility weights derived from the vignettes study (see Cell C81 in Inputs sheet). The new utility weights are reported in the Utilities sheet where row 106 reports the weights associated to each question and level derived from the vignettes study.

- An additional dropdown list was included in the Input sheet within section E "Adverse events". The dropdown list allows the choice between inclusion of all adverse events and those included in the original model, incorporating all additional costs (cell C76).

- Additional bottom anchors for DCE of 33233 and 23333, to explore any uncertainty between the bae case and scenarios.

- The clinical inputs sheet contains two updates related to:

    - Discontinuation rate: includes the additional functionality to choose between the rates derived from the studies reported in the CS and a pooled value based on the average.

    - Adverse events: updated to incorporate the costs of all of the adverse events reported in the CS from MYOMEX, as requested. Adverse events were grouped into ten main categories (Gastrointestinal disorders, General disorders and administration site, Nervous system

disorders, Respiratory, Thoracic and Mediastinal disorders, Cardiac disorders, Ear and Labyrinth disorders, Muscoloskeletal and connective tissue disorders, Injury, Poisoning and Procedural complications, Skin and subcutaneous tissue disorders, Vascular disorders). The detail of each adverse event is reported in the CS.

- The costs of adverse events were reported in the cost inputs sheet. Row 81 to row 123 reports the adverse event category, the unit cost of the drug and the pack size.

- The parameters for the DSA and PSA were updated with the addition of the above cited data. The total costs per treatment, total QALYs and incremental life years as aggregated and disaggregated results were reported in the Results sheet.

Section A: Clarification on effectiveness data

The decision problem

A1. Please provide an outline of the clinical pathway into which mexiletine might fit. Is it expected that mexiletine would be offered solely as a first line treatment or could it also be used at later points in the pathway?

Mexiletine is recognised as a well-established first line choice treatment for Non-Dystrophic Myotonia (NDM) in the UK (Appendix M of CS and (2-4)) and NaMuscla (mexiletine) is the first and only licensed medicine. In accordance with MHRA guidance note 14 (5), NaMuscla should be used ahead of any other off licence therapies.

Other treatments are a high-risk strategy as none are approved or licensed by EMA for clinical use to support patients.

We understand on discontinuation of NaMuscla patients may revert to being treated by Best Supportive Care (6), be treated on retrial with NaMuscla (7), or with other medicines without NaMuscla's (mexiletine) known and proven efficacy and safety.

We understand in general other medicines without NaMuscla/mexiletine's known and proven efficacy and safety may have been considered as in first line position only if:

1. NaMuscla/ mexiletine is contraindicated, there are special warnings and precautions for use, or if the use is cautionary or not recommended (8), including Female NDM patients who are pregnant (8) (including higher chance of pregnancy (2))

2. Imported Mexiletine historically was not made available due to the uncertain special medicines supply (Appendix L of CS and (9) or the lack of local commissioning for a special medicine (6).

3. NaMuscla is not available due to commissioning restrictions or delays (10-12), or delays in diagnosis (13). NHSE interim national commissioning restricts use of NaMuscla to specialist centres, patient diagnosis, blueteq completion and Multi-disciplinary Team approval.

4. The patient has milder myotonia symptoms and NaMuscla used when the patient's symptoms of myotonia are severe enough to treat (14, 15)

There are no NICE guidelines for the management of NDM and neither are there any over-arching, international treatment guidelines for NDM.

Systematic review

A2: Please confirm that more than one reviewer was involved in extracting data from and assessing quality of trials in the systematic review.

Two reviewers were involved in the data extraction and assessment of the trials for the systematic review. Titles and abstracts were reviewed and extracted by one reviewer and checked by a second reviewer with any discrepancies resolved through discussion involving a third reviewer, if required.

A3: The systematic review included only RCTs (appendix D, page 17). However, the company stated that 'supportive longer-term data are provided by a retrospective chart review by Suetterlin et al (2015)'. Are any relevant observational studies available in addition to this study?

The Suetterlin et al (2015) (7) is the most relevant clinical effectiveness evidence source and provided as a significant supportive study in the assessment by the EMA for NaMuscla for the treatment of NDM patients (15).

The study is a retrospective review of a cohort of patients with genetically confirmed NDM and provides data on long-term mexiletine use with observational data of up to 17.8 years of follow-up, which in the context of a rare disease is unusual and significant.

Further evidence that supports the longer term efficacy of NaMuscla is provided in the submission from the MYOMEX follow-up data (16), with a mean follow up period of [redacted] months (range [redacted] – [redacted] months), which demonstrate that the reduction in stiffness scores achieved with mexiletine at the end of the MYOMEX trial were least

maintained as there was a [redacted] in the average in the VAS stiffness score at the last data point for each patient at follow-up, compared to that recorded at the end of the original MYOMEX study period versus baseline.

One other supportive study in the assessment by the EMA which focused on NDM patients, but with lower relevance to the clinical effectiveness evidence in the submission is an uncontrolled prospective, open-label, uncontrolled study by Lo Monaco et al. (2015)(17).

Included trials

A4: Priority Question: The inclusion criteria for the MYOMEX trial were stated to include: "…myotonic symptoms severe enough to justify treatment with mexiletine. For the purposes of the MYOMEX study, criteria for patients who experience myotonic symptoms severe enough to justify treatment were considered as those with myotonia that involved at least two body segments (upper limb, lower limb or face) and that had an impact on at least 3 daily activities)." (company submission [CS], page 39).

a) Please explain how this definition of patients with NDM requiring treatment of symptomatic myotonia was derived; and

The MYOMEX study was sponsored and conducted by the Assistance Publique Hôpitaux de Paris, the largest hospital system in Europe and one of the largest in the world. To meet requirements from patients and physicians in France, a marketing authorisation for mexiletine was granted in 2010 for the treatment of myotonic symptoms. 1,346,500 units of MEXILETINE AP-HP 200mg mexiletine hydrochloride capsule have been distributed during the period of 01.11.2012 to 29.01.2018 (15)

Patients were recruited from 6 centres in France. Inclusion criteria in the MYOMEX study included a clinician-based decision about the need to treat, based on the vast experience of the sponsor and its hospital network, as a leading voice in Europe and the world, of treating NDM patients with mexiletine.

It isn't unusual for clinical trials to homogenise the patient cohort, and NaMuscla in practise is used on NDM patients with myotonia symptoms interfering with their daily life.

b) Please confirm that this is the population that the company expect will be eligible for mexiletine in UK clinical practice.

In taking this inclusion criteria into account, the EMA in its assessment of NaMuscla stated "only patients with severe enough myotonia were included in the MYOMEX

study” (15) and reflects NaMuscla’s Marketing Authorisation for use in clinical practice.

This does not necessarily mean these patients suffered from “severe myotonia”; rather, they have clinical symptoms of myotonia that are severe enough to justify treatment with NaMuscla. There is no generally recognised and agreed upon definition of myotonia severity (Appendices L & M of CS); symptoms may show a high inter- and intraindividual variability. Clinical findings span a continuum from mild to severe, not only between individuals but also, within the same patient, from day to day and even within the same day, depending on factors such as the outside temperature, the level of physical activities, stress, and the diet. Only patients with myotonia symptoms interfering with their daily life will receive treatment which was accepted by the EMA.

Since launch in January 2019 licensed NaMuscla has been well received for clinical use in accordance with its Marketing Authorisation which is underpinned by the MYOMEX trial (15), and has been under national commissioning arrangements since April 2019 (11).

A5. Patients in MYOMEX had to be aged between 18 and 65 and there are no patients older than 68 across the three main trials.

a) What evidence is there for the efficacy and safety of mexiletine in older patients?

It isn’t unusual for clinical trials to homogenise the patient cohort, including a restriction of the age criteria.

As noted, patients up to 68 have been in clinical trials. There is some additional evidence within the controlled clinical trials, and from the literature:

1. The MYOMEX trial included [redacted] subjects of which [redacted] patient was over the age of 65 (14)

2. The uncontrolled trial conducted by Lo Monaco et al (17) included 21 subjects of which 2 patients were over the age of 65

Mexiletine has been used for many years as a treatment for NDM patients, and we have not identified anything in the literature that has reported a concern for use in older patients.

It is noted that the EMA did not impose any age restriction on granting the NaMuscla marketing authorisation, and in the NaMuscla SmPC (8) no dosage adjustment is required in patients aged 65 years and over.

The post-authorisation safety study has commenced and will capture data over time, whist no safety concerns were raised in the NaMuscla post-launch PSUR (18)

b) What percentage of non-dystrophic myotonia (NDM) disorder patients in the UK are 65 years or older?

There is no published natural history set of patients in the UK to refer to which might indicate the number of patients over the age of 65.

A6: Please comment on whether patients in the trials (particularly MYOMEX) are representative of those who would receive mexiletine in UK clinical practice.

All three of the clinical trials support the Marketing Authorisation of NaMuscla to treat NDM patients in the UK, with a positive outcome for multiple significant treatment effects.

The three mexiletine studies were conducted in France (MYOMEX) (14), the Netherlands (Stunnenberg) (19) and in the USA and Europe (Statland) (20).

The clinical trial inclusion criteria for patient recruitment was different, and below we outline the key issues which differentiate the patient populations.

In taking the inclusion criteria into account, the EMA in its assessment of NaMuscla stated “only patients with severe enough myotonia were included in the MYOMEX study” (15) and reflects NaMuscla’s Marketing Authorisation for use in clinical practise. Neither the Stunnenberg trial nor the Statland trial include such criteria and therefore the patients in those trials may not fully reflect the NaMuscla Marketing Authorisation for clinical use.

The Stunnenberg N-of-1 trial and MYOMEX study both included inclusion criteria of genetically confirmed patients (14, 19). For the Statland trial the inclusion criteria stated eligible patients could have clinical features of NDMs (20). By not having all patients genetically confirmed as NDM patients, this could introduce some uncertainty that all the patients recruited into the trial had NDM. In addition, patients enrolled in the Statland trial were from the age of 16, which is not reflective of adults in the UK for which NaMuscla is indicated.

The Stunnenberg N-of-1 trial and the Statland trial both used the same VAS scales (0-9) to measure stiffness as their primary outcome. Based on this baseline characteristic from the two trials the patient cohorts look quite different, which might be explained by the different inclusion criteria, including genetic testing.

However, it is difficult to fully determine in the absence of patient level data, which is compounded by up to 25% of the primary outcome data missing from the Statland trial, and it was not reported how these missing data were interpreted. Efforts were made to contact the Statland et al and Stunnenberg et al trial authors to obtain patient level data but without success.

As stated in the answer to question 5, Since launch in the UK in January 2019 licensed NaMuscla has been well received for clinical use in accordance with its Marketing Authorisation which is underpinned by the MYOMEX trial (15), and has been under national commissioning arrangements since April 2019 (11).

A7: Please comment on whether the patients in the Statland trial are representative for the index population used in the model, given that they do not necessarily have genetically confirmed NDM.

As highlighted in our answer to Question 6, the trials are different, based on inclusion criteria and setting, including the uncertainty of genetically confirmed NDM from the Statland trial (20). This may account for the baseline characteristics looking different to those of other mexiletine trials.

Ultimately the Statland trial lacks the inclusion criteria of the MYOMEX trial as outlined in our answers to 4b and 6, which underpins the NaMuscla Marketing Authorisation for clinical use.

Unfortunately, up to 25% of outcome data for the IVR, nearly 50% for some domains of the INQoL, were missing, and it was not reported how these missing data were interpreted (20).

We do strongly believe the Statland trial adds significant supportive evidence to mexiletine as an effective medicine but has very different inclusion criteria to MYOMEX trial which underpins the NaMuscla Marketing Authorisation for clinical use.

The results from the Statland trial are only used in our model in scenario analysis, and as instructed by the ERG we will leave in our model, but we are happy if disregarded.

A8. Priority Question: in the CS section B.2.3.1 it is mentioned that "additional inclusion criteria were participants who were drug-naïve or those receiving mexiletine at an effective dosage agreeing to stop treatment at least four days before inclusion". Please clarify whether those patients receiving mexiletine were responders to the drug. Also, please report the proportion of patients included in MYOMEX study that had received mexiletine at an effective dosage before they were included in the study.

[redacted] patients were currently treated with mexiletine at screening: [redacted] patients with MC ([redacted] in the placebo-mexiletine sequence and [redacted] in the mexiletine-placebo sequence) and [redacted] patients with PC ([redacted] in each treatment sequence). Of the [redacted] patients with MC already treated with mexiletine hydrochloride, [redacted] was taking 200 mg/day, [redacted] were taking 400 mg/day and [redacted] were taking 600 mg/day. Of the [redacted] patients with PC already treated with mexiletine hydrochloride, [redacted] was taking 200 mg/day, and [redacted] was taking 600 mg/day. (14).

In order to address the question, whether those patients previously receiving mexiletine were responders to the drug during the study, we present below the data using the stiffness VAS score (14, 21).

A9: Please provide a breakdown of prior treatments received by patients in the MYOMEX trial.

The tables below provide a breakdown of prior treatments received by patients in the MYOMEX trial (data pooled from the CSR) (14).

Table 2. Previous treatment (except mexiletine) – mITT Population (CSR 14.1.2.14).

Pathology			Placebo – Mexiletine (N=[redacted])	Mexiletine – Placebo (N=[redacted])	Total (N=[redacted])
Concomitant treatments received	MC	N	[redacted]	[redacted]	[redacted]
		Missing data	[redacted]	[redacted]	[redacted]
		No	[redacted]	[redacted]	[redacted]
		Yes	[redacted]	[redacted]	[redacted]
	PC	N	[redacted]	[redacted]	[redacted]
		Missing data	[redacted]	[redacted]	[redacted]
		No	[redacted]	[redacted]	[redacted]
		Yes	[redacted]	[redacted]	[redacted]
	Total	**N**	[redacted]	[redacted]	[redacted]
		Missing data	[redacted]	[redacted]	[redacted]
		No	[redacted]	[redacted]	[redacted]
		Yes	[redacted]	[redacted]	[redacted]
Treatments stopped for the study	MC	N	[redacted]	[redacted]	[redacted]
		Missing data	[redacted]	[redacted]	[redacted]
		No	[redacted]	[redacted]	[redacted]
		Yes	[redacted]	[redacted]	[redacted]
	PC	N	[redacted]	[redacted]	[redacted]
		Missing data	[redacted]	[redacted]	[redacted]
		No	[redacted]	[redacted]	[redacted]
		Yes	[redacted]	[redacted]	[redacted]
	Total	**N**	[redacted]	[redacted]	[redacted]
		Missing data	[redacted]	[redacted]	[redacted]
		No	[redacted]	[redacted]	[redacted]
		Yes	[redacted]	[redacted]	[redacted]
Type of treatment stopped	MC	Diuretics	[redacted]	[redacted]	[redacted]
		Antiarrhythmics	[redacted]	[redacted]	[redacted]
		Corticosteroids	[redacted]	[redacted]	[redacted]
		Betablockers	[redacted]	[redacted]	[redacted]
		Antiepileptics	[redacted]	[redacted]	[redacted]
	Total	Diuretics	[redacted]	[redacted]	[redacted]
		Antiarrhythmics	[redacted]	[redacted]	[redacted]
		Corticosteroids	[redacted]	[redacted]	[redacted]
		Betablockers	[redacted]	[redacted]	[redacted]
		Antiepileptics	[redacted]	[redacted]	[redacted]

Table 3. Previous treatments by ATC code and active substance (except mexiletine) – mITT Population (CSR 14.1.2.15).

	Placebo – Mexiletine (N=[redacted])		Mexiletine – Placebo (N=[redacted])		Total (N=[redacted])	
	TRT	***Patient (%)***	***TRT***	***Patient (%)***	***TRT***	***Patient (%)***

MYOTONIA CONGENITA						
ANILIDES						
PARACETAMOL						
CARBOXAMIDE DERIVATIVES						
CARBAMAZEPINE						
OTHER COLD COMBINATION PREPARATIONS						
PRIORONIC ACID DERIVATIVES						
FLURBIPROFER						
ANTIDEPRESSANTS						
ANTIDEPRESSANTS						
ANTIEPILEPTICS						
PREGABALIN						

Table 4. Concomitant treatment by ATC code and active substance (except mexiletine) – mITT Population (CSR 14.1.2.16).

	Placebo – Mexiletine (N=[redacted])		**Mexiletine – Placebo (N=[redacted])**		**Total (N=[redacted])**	
	TRT	***Patient (%)***	***TRT***	***Patient (%)***	***TRT***	***Patient (%)***
MYOTONIA CONGENITA						
ANILIDES						
PARACETAMOL						
OTHER OPIOIDS						
PARACETAMOL W/TRAMADOL						
PROPIONIC ACID DERIVATIVES						
FLURBIPROFEN						
IBUPROFEN						
HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE						
DEAOGESTREL W/ESTRADIOL						
MUCOLYTICS						
AMBROXOL						
OTHER EMOLLIENTS AND PROTECTIVES						
DEXERYL “PIERRE FABRE”						
SALICYLIC ACID AND DERIVATIVES						
ACETYLSALICYLIC ACID						

BENZODIAZEPINE RELATED DRUGS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ZOLPIDIEM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CORTICOSTEROIDS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BUEDENSONIDE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PIPERAZINE DERIVATIVES	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LEVOCETIRIZINE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PROTON PUMP INHIBITORS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESOMEPRAZOLE MAGNESIUM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SYMPATHOMMETICS, PLAIN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NAPHAZOLINE NITRATE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A10. Priority Question: please provide the treatment effects for all outcomes reported in the MYOMEX study. At present some are missing and results from the mixed models are only presented as tables of p-values (e.g. Tables 18 and 20). Please provide the following for the modified intention to treat (mITT) population:

a) Stiffness measured using visual analogue scale (VAS) – This was analysed using a mixed effect linear model on ranks, presumably as the data were skewed.

i. **Please provide median (with range) or mean (with 95% CI) treatment effect estimates (mexiletine – placebo) for the change from baseline in VAS for period 1 and period 2**

Descriptive results of the primary efficacy analysis (MYOMEX CSR Section 11.4.1.1) by treatment period are displayed in Table 1 for the overall mITT (modified intent-to-treat) population.

Table 5 Visual Analogue Scale – Descriptive Analysis – mITT Population

ii. Please also provide the median (range) or mean (95% CI) of the within patient change (mexiletine – placebo) during the whole study period as there was no evidence of a significant period effect.

As presented in the MYOMEX CSR, the mixed effect linear model performed to evaluate a potential carry-over effect did not show any significant effect of the treatment sequence (p = [redacted]). Therefore, the hypothesis of a carry-over effect was rejected and consequently the data from the two periods were combined in subsequent analyses. The model showed a significant effect of treatment (p < [redacted]) in the mITT population, demonstrating the efficacy of mexiletine.

The table below shows descriptive results of the primary efficacy analysis for the overall mITT. (modified intent-to-treat) population

Table 6 Visual Analogue Scale (VAS) – Primary efficacy analysis for overall population – mITT Population (from Table 14.2.1.3.A. in (14))

	Placebo	Mexiletine
N	[redacted]	[redacted]
Baseline (before treatment) median VAS	[redacted]	[redacted]

Range	[redacted]	[redacted]
End of treatment median VAS	[redacted]	[redacted]
Range	[redacted]	[redacted]
Median change in VAS (range)	[redacted]	[redacted]

In the analysis of both periods combined, the mixed effect linear model for Period 1 showed a significant effect of treatment (p = [redacted]) in the mITT population, demonstrating the efficacy of mexiletine.

b) Chair test – This also appeared to be skewed and was analysed using a Wilcoxon signed-rank test. Please provide the median (range) of the within person-changes (mexiletine – placebo) during the whole study period. Please provide results of any analysis used to evaluate whether there was a period effect, if this analysis was performed.

The chair test was performed at baseline (V2) and at the end of each treatment period (V3 or V5). Results for the first period are provided in the table below (22):

Table 7 Descriptive efficacy: Chair test in period 1

The median (and range) of the within person-changes (mexiletine – placebo) for the chair test during the whole study period is shown in table (14) below.

Table 8 Chair Test (seconds) for Whole Study Effect – mIIT population.

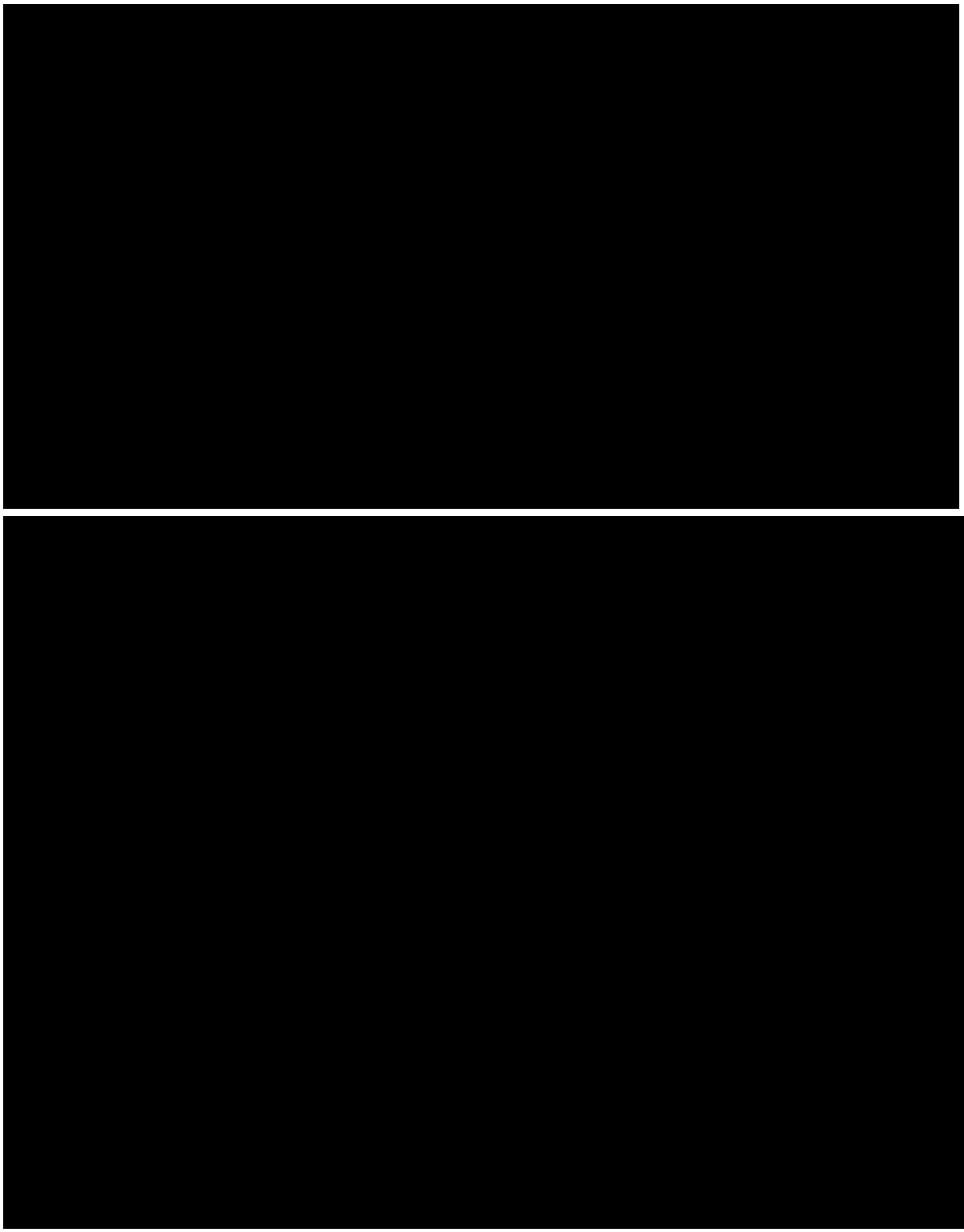
	Before treatment (V2)	Placebo	Mexiletine	**Chair test (secs) change from V2 placebo**	**Chair test (secs) change from V2 Mexiletine**
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median seconds (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

c) Individualized Neuromuscular Quality of Life (INQoL) – This was analysed using a mixed effect linear model and some domains showed a significant period effect. For each domain and overall, please provide the mean (95% CI) treatment effect (mexiletine – placebo) for periods 1 and 2. For those outcomes where there was no significant period effect please also provide the mean (95% CI) of the treatment effect estimates (mexiletine – placebo) from the mixed model.

i. For each domain and overall, please provide the mean (95% CI) treatment effect (mexiletine – placebo) for periods 1 and 2.

The health-related quality of life scores (measured using the INQoL scale) before and after treatment at the end of the first period are presented for the mITT population in the table below (23).

Table 9 Individualised Neuromuscular Quality of Life Before and After Treatment – mITT Population, Period 1



The mixed effect linear model showed no significant effect of the treatment sequence for the mITT population (p > [redacted]; Tables 14.2.2.24 to 14.2.2.35 from the CSR, data on file).

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

Table 10 Mixed Effect Linear Model for Each Domain of the INQoL Questionnaire– mITT Population (CSR 11-16).

Domain	Parameter	p-value
Weakness	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Locking	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Pain	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Fatigue	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Activities	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Independence	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Social relationship	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Emotions	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Body image	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Overal quality of life	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Perceived treatment effect	Treatment	[redacted]
	Period	[redacted]
	Baseline value	[redacted]
Expected treatment effect	Treatment	[redacted]
	Period	[redacted]

	Baseline value	[redacted]

Systematic statistical analyses of all domains have proven that there is no carry-over effect between period 1 and period 2. This is supported by the pharmacokinetics of mexiletine.

An indication of possible carry over within a single sub-domain like “expected treatment effect” in INQoL is most likely a chance finding.
The only “true” confirmation of the absence of a carry-over effect is by analysing results for the first period, and we have conducted an analysis of all efficacy endpoints for Period 1. All results obtained through this analysis in the first period only confirmed those initially presented for both periods combined, demonstrating the efficacy of mexiletine. Therefore, no mixed effect linear model has been applied for period 2.

II. For those outcomes where there was no significant period effect please also provide the mean (95% CI) of the treatment effect estimates (mexiletine – placebo) from the mixed model.

The table below outlines the treatment effect estimates including mean (SD) from all domains in INQoL for the whole mITT population (CSR 11-15)..

Domain	Diagnosis		Absolute values			Absolute changes from V2	
			Before treatment (V2)	Placebo	Mexiletine	Placebo	Mexiletine
Weakness							
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Locking			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Activities			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Independenc			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

relationships	**Total (N=[redacted])**	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emotions			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body image			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall QOL			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total (N=[redacted])	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perceived			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment	**Total (N=[redacted])**	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
effects		**Med [range]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Expected	**Total (N=[redacted])**	**Mean (SD)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
treatment		**Med [range]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
effects			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*N=[redacted]: Baseline value was missing for one MC patient ([redacted])

**N=[redacted]: Baseline value was missing for one MC patient ([redacted])

d) **Clinical Myotonia rating scale (CMS) scores – This was also analysed using a mixed effect linear model. Please provide the results in the same format as requested for INQoL.**

i. **For which scores/scales was a significant period effect seen?**

The period effect for global severity score in the mITT population (p=[redacted]) as shown in the table below.

Table 11 Mixed effect linear model for severity global score- mITT population (14)

[redacted]

The period effect for disability global score (p=[redacted]) as shown in the table below.

Table 12 Mixed effect linear model for disability global score- mITT population (14)

[redacted]

ii. **Please provide the mean (95% CI) treatment effect (mexiletine – placebo) for periods 1 and 2**

The severity and disability global scores before and after treatment at the end of the first period are presented in the table below (24, 25). 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.

Table 13 Severity global score and disability global score for period 1 mITT population

End of treatment period values were collected at V3.
* 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 Source: Annex 5 and Annex 6

A mixed effect linear model analysis was performed to evaluate the difference between the two treatments regarding the absolute change from baseline in both the severity and the disability global scores at the end of Period 1.

Table 14 Mixed effect linear model for severity and disability global scores for period 1- mITT population (26, 27).

II. For those outcomes where there was no significant period effect please also provide the mean (95% CI) of the treatment effect estimates (mexiletine – placebo) from the mixed model.

Severity global score and disability global scores for the whole population- mITT, is provided in the table below (14)

Table 15 Severity global score and disability score for whole mITT population

Item		Absolute value before Treatment (V2) N=	Absolute value Placebo N=	Absolute value Mexiletine N=	Absolute change from V2 placebo N=	Absolute change from V2 Mexiletine N=
Severity global score	Mean (SD) Median (range)					
Disability global score	Mean (SD) Median (range)					

A11. The observational study by Suetterlin provides longer-term data than in the randomised trials. Please provide any further information available on this study other than the Jama publication cited (ref 49).

Lupin does not have any additional data outside of the cited publication. No additional follow on studies by the same author were identified through a targeted search.

The study is a retrospective review of a cohort of patients with genetically confirmed NDM and provides data on long-term mexiletine use with observational data of up to 17.8 years of follow-up, which in the context of a rare disease is unusual and significant.

A12. On page 117 of the CS it was stated that "The doses used in the mexiletine studies were in line with the Summary of Product Characteristics of NaMuscla. However, in all the trials patients were force titrated to achieve the maximum dose of 600 mg mexiletine hydrochloride daily at which point efficacy was assessed." Please comment on the implications of this strategy in terms of real-world efficacy where the 400mg may be used.

For all of the mexiletine trials, patients were titrated to achieve the maximum dose of 600 mg mexiletine hydrochloride (the equivalent to 500mg mexiletine) daily.

For patients receiving mexiletine in the MYOMEX trial, the stiffness VAS scores decreased as a function of time, while the stiffness VAS scores remained generally stable for patients receiving placebo with patients achieving clinical benefit by [redacted] on the [redacted] mg mexiletine hydrochloride dose (14). It can be concluded that the majority of patients may not have needed the [redacted] mg mexiletine hydrochloride dose.

In clinical practice NDM patients would be dose titrated to an effective dose until relief of symptoms and improvement in quality of life were achieved. This would typically be on a mean dose of 400 mg mexiletine hydrochloride daily (Appendix M of CS (7, 16)), [redacted] and where efficacy does not drop at the lower dose, and the average dosing in the Suetterlin long term observational study, with data of up to 17.8 years of follow-up, which in the context of a rare disease is unusual and significant.

A13: In the trials mexiletine hydrochloride treatment was up titrated in 200 mg increments every 3 days whereas in practice the CS stated that patients would

take at least two weeks to reach a dose equivalent to 600 mg mexiletine hydrochloride based on clinical response (CS, page 15). Please comment on the implications of the different titration periods.

In assessing NaMuscla, the EMA noted that the SmPC posology *"reflects that different dose levels could be effective and allows a treating physician to make a choice"* (15).

Based on this, EMA has considered that the optimal dose regimen of NaMuscla in NDM has been established.

The titration of the MYOMEX study occurred during the titration phase by increasing the starting 200 mg/day dose of mexiletine hydrochloride by 200 mg/day every 3 days until the target dose was reached as outlined in question A12.

However, the titration period, as outlined on Table 2 (page 15, CS) of the original submission, is reflective of the posology in section 4.2 of the NaMuscla SmPC (8) Patients are dose titrated up, according to clinical response, after at least 1 week of treatment, to a daily dose of 333 mg mexiletine daily (i.e. two capsules per day or equivalent to 400 mg mexiletine hydrochloride). After at least 1 further week of treatment, the dose can be further increased to 500 mg daily (three capsules per day or equivalent to 600 mg mexiletine hydrochloride) based on clinical response.

Patients are, therefore, titrated in increments of 200mg mexiletine hydrochloride every 7 days and although titration maybe a little slower according to the SmPC, the maximum dose the patient could get would be 600mg mexiletine hydrochloride in both cases. Therefore, it is expected that there will be no difference in efficacy.

A14: Priority Question: The commissioning expert statement states that current clinical practice is find an optimal dose from titrating up to the maximum of 600mg unlicensed dose in 50mg increments (mean unlicensed dose of 400mg). Clinicians described this as critical to avoid the gastric adverse events. Currently the 50mg and 100mg tablets are bought from Canada at the cost of approximately £1 per capsule to support this titrating approach.

a) **Please verify that this is the approach to dosing that currently applies, and will continue in clinical practice.**

In the MYOMEX clinical trial, patients were titrated in 200mg mexiletine hydrochloride increments every 3 days to the maximum dose of 600mg mexiletine hydrochloride. The MYOMEX study shows a relatively low incidence of

gastrointestinal disorders at [redacted] % ([redacted] patients, n=[redacted]), and none were reported as severe or serious.

In accordance with the NaMuscla SmPC (8), a more gradual dosing regimen to the MYOMEX trial for NaMuscla is provided. NaMuscla is always started at a low dose regimen (167mg mexiletine/200mg mexiletine hydrochloride).

Based on clinical response (anti-myotonic efficacy and good tolerability), and after at least 1 week of treatment, the daily dose may be increased to 2 capsules per day. After at least a further 1 week, and again based on clinical response (anti-myotonic efficacy and good tolerability), the daily dose may be increased to a maximum dosage of 3 capsules per day.

Based on this, EMA has considered that the optimal dose regimen of NaMuscla in NDM has been established (15).

There is no data to suggest that a different titration is a more effective way of avoiding the gastric adverse events that the commissioning report describes. Indeed, the new data provided by the MYOMEX trial, suggests that dose titration reflected in the NaMuscla's SmPC is effective.

Additionally, the supply of imported medicines, such as special imported mexiletine is uncertain (28-31). We strongly recommend all clinicians follow the good practice to titrate to the licensed product SmPC. We therefore cannot verify that the approach in the commissioning statement will continue and expect clinical practice to reflect the titration in line with the licensed NaMuscla product.

Lastly, we cannot verify the cost of the imported medicines, as the only publicly available costs to the NHS are provided by the Prescription Cost Analysis data (PCA data) (32). This data suggests different costs to those provided by the commissioning statement.

b) Please explain precisely how, given how dosing will occur in clinical practice and the source of tablets, the cost per patient is and will be calculated.

As presented in table 5 on page 17 of the budget impact model, the cost per patient per year on 400 mg daily dose of mexiletine hydrochloride (avg of 730 capsules required per patient per year) will be £34,597.45 (list price)/£[redacted] (PAS price); cost per mexiletine hydrochloride capsule at £50 (list price)/£[redacted] (PAS price).

c) Please ensure that costs and adverse events relating to this issue are accurately incorporated in the cost-effectiveness analysis.

All costs of adverse events have now been incorporated in the model over a lifetime horizon, reflective of longer-term real-world evidence from Suetterlin (7), as the time horizon, and mean dosing are more appropriate.

As answered in 14a) we expect clinical practice to reflect the titration in line with the licensed NaMuscla's SmPC.

A15: Priority Question: Regarding the INQoL questionnaire:

a) Please provide a full list of questions from the INQoL questionnaire (in English).

The full list of the INQoL questionnaire is reported the following table.

Table 16. Full list of items in the INQoL questionnaire (33)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]

[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]

		[redacted]
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[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]

[redacted]		[redacted]
[redacted]		[redacted]

b) Please explain how the questionnaire was translated in French for the MYOMEX study and how this version was validated.

The French translation of the INQoL is available and validated (34).

c) Please explain which questions contributed to which domains as reported in Table 19 of the CS, and how the scores from Table 19 were calculated.

Table 19 in the company submission is informed from the patient reported outcomes (14), and all of the patient level data is provided within the companies submitted economic model (Sheet “Patient level data”). The calculations are informed by the INQoL calculation methodology by Vincent et al (34).

The handling of missing data is outlined in Table 11-27 within the CSR (14).

The scores are calculated as a mean from the absolute values at baseline for the total mITT population.

d) Please explain how the INQoL items reported in Table 52 of the CS relate to the individual questions from the INQoL questionnaire (For example, the first INQoL item in Table 52 is “How much weakness would you say you have in the muscles affected by your condition?”. Does this relate to Question 1 as a whole (a, b and c combined), or to Question 1a alone)

Table 17 summarises the mapping of INQoL items that, from the process described above, have been conceptually mapped to the appropriate EQ-5D domains (35).

Table 17. Mapping of INQoL items to the appropriate EQ-5D domains.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Pages 131-135 of the original submission provides the methodology of how each question of the INQoL was 'included' or 'excluded' for the mapping process to EQ-5D.

e) Please explain how the INQoL items reported in Table 52 of the CS relate to the domains reported in Table 19 of the CS. If the domains from Table 19 do not correspond exactly with the INQoL items reported in Table 52, please provide the same results as in Table 19 for each of the eight INQoL items reported in Table 52.

How the INQoL items reported in Table 52 of the CS relate to the domains in Table 19 is described in the answer to 15 d) above. Table 19 from the CS is provided below, updated with only the corresponding domains as informed by the eight INQoL items.

Table 18. INQoL Before and After Treatment - mITT Population.

			Absolute values			Absolute changes from baseline	
Domain	Diagnosis		Before treatment	Placebo	Mexiletine	Placebo	Mexiletine
Weakness	Total (N= [redacted])	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Locking	Total (N= [redacted])	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	Total (N= [redacted])	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	Total (N= [redacted])	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Activities	Total (N= [redacted])	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emotions	Total (N= [redacted])	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Med [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority Question: The model in the CS might not reflect the treatment pathway for the NDM patients, since in the model, the patients can receive maximum one line of pharmacological treatment in their lifetime and not all relevant comparators as defined in the scope, such as lamotrigine, were included.

a) **Given the claim, based on a comparison of standardized effect sizes, by Anderson et al, 2017 of "..a similar treatment effect of mexiletine and lamotrigine.', every effort should be made to incorporate a comparison between lamotrigine and mexiletine in the economic model. The clinical inputs used in the economic model should be based on comparative effectiveness of lamotrigine versus mexiletine. Ideally this should employ an indirect comparison with RCTs. However, if infeasible, then other methods should be considered, including the use of non-RCTs and clinical expert opinion.**

Lupin has reached out to gain clinical opinion to answer the question regarding Lamotrigine as a potential comparator (Appendix M of CS and (6)). Lamotrigine cannot be considered as a relevant or appropriate comparator because it is not established practice in the NHS. Below we explore in more depth the reasons why Lamotrigine should be excluded as a comparator.

- There is no evidence that lamotrigine is used in established practice in the NHS and is very rarely used to treat NDM patients (Appendix M of CS and (2, 6)). Market research, conducted in November 2019, involving eight neurology centres in the England and Wales (including the largest centre, the NHNN, Queens Square Centre for Neuromuscular Diseases, London) shows that lamotrigine is not established in practice with less than 3% of patients currently on or having ever received lamotrigine.

This data was further supported by an NDM patient survey conducted by Janet Stone where of the 37 responses provided by patients to the questions “Please indicate any medications you have taken for myotonia”, only one patient indicated they had ever taken Lamotrigine. Hence lamotrigine is not a relevant comparator as it is not established practice.

Finally, NICE has confirmed that they expect the number of NDM patients on Lamotrigine to be low.

- The RCT by Andersen et al was conducted between 2013 and 2015 and published in 2017 (36). Despite this the market research does not indicate an increase in use in the UK that could at all suggest Lamotrigine is gaining established use in the NHS.
- Lamotrigine is not licensed for the indication to treat NDM patients in the UK or any other country and no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients.
- There are no randomised/non-randomised clinical trials, that assess the impact of lamotrigine in comparison with established first-line treatment for symptoms of myotonia in NDM patients.
- The recent RCT by Andersen et al lacks common outcome measures and results to enable any indirect treatment comparison with mexiletine NDM RCTs (36) – see Document B, Section B.2.9.1 for further details.
- There are no existing NICE guidelines for the treatment of NDM patients and no known published natural history of NDM patients.

b) Please incorporate health state(s) for “2nd and further line treatments” into the model structure, so that the patients after discontinuing from mexiletine or “best supportive care without pharmacological treatment” would be able to receive further lines of pharmacological treatment in their lifetime.

NaMuscla, as highlighted in our answer to Question 1 is a well-established first choice treatment for Non-Dystrophic Myotonia (NDM) in the UK.

As evidenced by the Suetterlin et al observational study (7) 8 of the 11 patients (72.7%) who stopped mexiletine previously because of inefficacy or intolerable adverse events found it effective and tolerable on retrial. Subsequent treatment following discontinuation of NaMuscla is therefore most likely to be NaMuscla.

Additionally, Lupin has conducted research in to NDM clinical management (6). Of the 265 patients within the report that have ever been treated for NDM, of the centres that reported 132 remain on their first line treatment and only 78 are currently on a second line therapy, suggesting many patients (up to 55 or 41%) who have been treated but failed 1st line therapy currently are not treated.

Based on the data available above, the use of unlicensed second line therapies when NaMuscla is first line is likely to be low, with 16% of patients who discontinue NaMuscla (calculated by (1-72.7%) x (1-41%)) a good representation of likely estimated numbers (6, 7).

From the research the most common alternative medicines currently used to treat in a second line position are Phenytoin, Flecainide and Acetazolamide, which are not consider standard of care (37). As these are unlicensed medicines, their efficacy is unproven or substantiated through clinical trials with no data supporting their use as a second line therapy, and their long-term safety profile uncertain/unfavourable (6, 15). These products have been found to have substantial adverse events and special warnings for use, as outlined in their individual SmPC's.

The placebo effect is increasingly well understood, especially for conditions which include pain and fatigue (38), and therefore in the absence of any substantial efficacy evidence, a sensible conclusion is that these medicines should have no additional benefit to placebo, reflected in the economic model.

Any changes to the current base case to include pharmacological treatments would increase the costs in the BSC arm with no evidence around the efficacy and safety within the targeted population. Therefore, as a conservative assumption, they are not included.

B2. Please provide the details of how the estimate 15% for the "disease progression differential" for no pharmacological treatment was derived.

Data suggests that NDM disease severity worsens over time. In one study, 58% of patients reported that the severity of their myotonia had increased since the onset of symptoms (39). A UK patient survey found that 87.3% of patients reported their stiffness and 70.8% reported their weakness had worsened since diagnosis (2). Feedback from two German clinical experts support that in the absence of an effective treatment a decline in QoL over time occurs, as imported mexiletine had not been an option for them (Appendix M of CS). Long-term data from MYOMEX shows the clinical benefit of NaMuscla is at least maintained, as there was a [redacted] in the average in the VAS stiffness score at the last data point for each patient at follow-up, compared to that recorded at the end of the original

MYOMEX study period versus baseline (16). The maintenance of the clinical benefit of NaMuscla is supported by clinical experts (Appendix M of CS).

Therefore, in the base case it was assumed there was a differential effect between NaMuscla treatment and no treatment over the lifetime of an NDM patient of 15%. Differential effects were explored between NaMuscla and no treatment in scenario analyses.

The ongoing Delphi panel, with results expected to be available in June, should be able to provide further information and justifications on this question.

B3. Please incorporate the possibility of using discontinuation rates from other sources in Table 48 in the CS, as well as the possibility of using a pooled discontinuation rate (where the pooling should be based on a meta-analysis) in the economic model.

This functionality has now been included in the updated economic model (Clinical input sheet, cells B5-E10), including the option of choosing the discontinuation rates as a pooled value based on the average, based on the sources, as per Table 48 in the CS.

B4. Regarding adverse events:

a) **Please explain why gastrointestinal disturbance was included as the only adverse event in the economic analysis, why dyspepsia was considered to be reflective of all ranges of gastrointestinal disturbances and why continuous PPI treatment was considered to be reflective of the treatments for all types of gastrointestinal disturbances.**

The base case of the economic model uses Suetterlin et al (2015) (7) as a retrospective long horizon real-world data source to consider adverse events. No serious adverse events were seen (no life-threatening AE, deaths, hospitalisations or severely disabling conditions).

In this retrospective review of 63 patients treated with mexiletine, the most common adverse event reported was dyspepsia, and this was the only gastrointestinal disturbance recorded. Sixteen of the 23 patients (69.6%) who reported dyspepsia required dyspeptic therapy. As none were reported as serious it could be expected they were treated with a PPI.

Other AE’s include headache, palpitations and nausea. As none were reported as serious, we would expect patients with a headache to self-manage with simple painkillers, palpitations generally self-resolve, and for those with nausea to take

medicines with food or if applicable reduce the dose. Therefore, it is expected that dyspepsia is the only AE with economic impact

Further, the authors concluded that the absence of any significant change in ECG parameters or serious adverse events within a total of 302.4 years of patient follow-up demonstrates the long-term safety of mexiletine and suggests that frequent routine ECG monitoring of patients on maintenance dose may not be necessary.

b) Please include all relevant adverse events as listed in section B.3.3.6 of the company submission, taking into account the adverse management costs and also taking into account the utility decrements associated with these adverse events, using literature-based estimates.

Adverse events have been included in the model for MC in the MYOMEX trial.

The list of the adverse events is reported in the following table. No disutilities are assumed, as the utilities and adverse events in the model are both derived from the same source, the MYOMEX trial (14), and therefore it would not be appropriate to be any other than zero.

Table 19. Adverse events included in updated economic model

Adverse event category	Events	Patients	%	Source	Cost	Source
Gastrointestinal disorders (Abdominal pain, Nausea, Abdominal pain upper)	[redacted]	[redacted]	[redacted]	MYOMEX	£0.84	BNF Online 2020(40)
General disorders and administration site conditions (Fatigue, Chest pain, Asthenia, Chest discomfort, Malaise)	[redacted]	[redacted]	[redacted]		£0.59	
Nervous system disorders (Headache, Somnolence, Paraesthesia)	[redacted]	[redacted]	[redacted]		£0.59	
Respiratory, Thoracic and Mediastinal disorders (Dyspnoea)	[redacted]	[redacted]	[redacted]		£10.50	
Cardiac disorders (Tachycardia)	[redacted]	[redacted]	[redacted]		£0.78	
Ear and Labyrinth disorders (vertigo)	[redacted]	[redacted]	[redacted]		£0.59	

Muscoloskeletal and connective tissue disorders (Pain in extremity)	[redacted]	[redacted]	[redacted]		£3.13	
Injury, Poisoning and Procedural complications	[redacted]	[redacted]	[redacted]		£3.13	
Skin and subcutaneous tissue disorders (Acne)	[redacted]	[redacted]	[redacted]		£1.15	
Vascular disorders (Flushing, Hypotension)	[redacted]	[redacted]	[redacted]		£0.80	
Total	[redacted]	[redacted]	[redacted]	**100.00%**	**£1.44**	

The results for both list price and PAS when all adverse events are included are presented in Table 20. This results in only minor changes to the ICER for both list and PAS prices.

Table 20. Scenario result for including all adverse events

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
List price					
No treatment	50,645	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAS price					
No treatment	50,645	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

c) Please explain in detail how the probability of falls with fractures (0.1 for mexiletine and 0.2 for no pharmacological treatment) were derived from the clinical experts consulted during the advisory board, since in the slides, the KoLs estimated the risk of falls with fractures to be between 0 and 20% for patients on best supportive care and between 0 and 10% for patients on mexiletine.

Additional scenarios have been provided below exploring the impact on the results for both list price and PAS when exploring different likelihood of falls resulting in fracture for placebo and mexiletine arms. A more conservative scenario of 5% for mexiletine and 10% for no treatment and an extreme scenario of 0% for both mexiletine and no treatment were explored to quantify the uncertainty of the

parameters. Both scenarios show only minor changes to the base case ICER, suggesting that the model is not sensitive to these inputs.

Table 21. Probability of falls with fractures 5% for mexiletine and 10% for no treatment

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
List price					
No treatment	45,381	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAS price					
No treatment	45,381	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22. Probability of falls with fractures 0% for both mexiletine and no treatment

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
List price					
No treatment	40,116	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAS price					
No treatment	40,116	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B5. Priority Question: Please provide all details of the communication between the company and the clinical experts. These details should include not only the slides summarising "discussion topics" but also all the "Pre-work inputs", detailed excerpts, as well as how the inputs used in the economic model were elicited.

Below we outline the communications with the clinical experts:

Clinical elicitation Individual face to face meetings (Appendix M of CS) November 2019

As outlined in Appendix M of CS, key topic areas were developed into a PowerPoint presentation for a facilitated discussion with individual experts (41) for the clinical elicitation with 4 clinicians.

The Lupin medical director emailed any of the 18 neurology specialist centres that he had contact with to ask that they take part in clinical elicitation within the next 2 weeks. Due to short timelines, 4 responded to be available in this time period. There was no intended selection bias.
The clinical experts were provided with the slides (41), which have been submitted to NICE in the reference pack.
Discussions with the experts were led by a senior member of staff from the consultancy who assisted Lupin with the preparation of the NICE submission, with other Lupin participants (no more than two) able to contribute and ask clarification questions to the experts.

The interviews were not recorded, and the notes were captured in the format adapted from the recommended guideline by Iglesias et al, 2016 (42), an appropriate tool for the collation of expert elicitation, and can be found in full in Appendix M of CS.

Clinical elicitation Telephone interviews (Appendix M of CS) November 2019
The same process as outlined above and in Appendix M of CS was carried out with 2 clinical experts from Germany, however for pragmatic reasons, the interviews were conducted by telephone.

Market research – telephone interviews (6) November 2019
Market research involving eight neurology centres in the England and Wales
All communications and the interviews were carried out by a market research company. All interview responses were anonymised, so Lupin did not know who the participants were.
Please find attached the screener and questionnaire used in the non-dystrophic myotonia current clinical management research conducted on behalf of Lupin (43, 44).

INQol Mapping– telephone interviews - (Appendix M of CS) February to June 2019
For the INQoL mapping allocation work a series of telephone interviews were conducted. 3 experts were approached.

A PowerPoint presentation was created to facilitate the discussion for the INQoL mapping exercise (45). This was led by a senior member of the consultancy conducting the DCE (and subsequent vignette) work.
Two Lupin European colleagues (now left the company) participated in the interviews. The advice and how the discussions with the experts informed the process are detailed in the B.3.4.2 of the company submission, and the vignettes report provided.

CMS disability scale resource allocation – telephone interviews – (Appendix M of CS) May to June 2019

A PowerPoint presentation to facilitate discussions for the CMS disability scale resource use allocation was created by a senior member of staff from the consultancy who assisted Lupin with the preparation of the NICE submission, who lead a series of discussions with the experts in order to gain consensus.
We note an incorrect reference was applied in Appendix M of CS and the company submission, for which we apologise, and slides presented to the clinicians are now submitted (46) .

The elicitation resulted in informing the CMS disability scale resource use as detailed in section B.3.5.5 of the company response.

Advisory board (47)– November 2018

The purpose of the Advisory Board was primarily payer led - “Pressure-test on value proposition, pricing and access of Mexiletine in non-dystrophic myotonia (NDM)”.
All arrangements with the attendees were managed by a third-party agency.
Of the 10 participants, evenly split between Scottish and English participants, two clinical experts in attendance.
The inputs that informed the economic model were anonymised, so Lupin did not know who the responses were from, and have been already provided (47).
Further inputs from the clinicians that to a lesser degree informed the economic model is now provided (48).

The Delphi panel should be able to provide further information and justifications for clinical elicitation and is expected to be available in June.

HRQoL

B6. Priority Question: Please answer the following SF-36 related queries below.

a) **Please provide further analyses to demonstrate that SF-36 is not appropriate for the NDM patients in terms of psychometric criteria such as validity and responsiveness.**

The INQoL questionnaire is the only validated QoL questionnaire (34, 49, 50) that referred specifically to the presence and impact of myotonic symptoms. It is a valid measure of quality of life or health status in patients with myotonia because it covers the different aspects of HRQoL that are affected in myotonia (content validity) and additionally the tool measures these concepts accurately (construct validity) (34).

The EQ-5D is the preferred HRQoL measure for the assessment of QoL in the NICE Reference case, and the INQoL data collated at a patient level in the MYOMEX study has been mapped to EQ-5D dimensions using two methodologies. SF-36 data was not collated in the MYOMEX (14) study which informs our economic model. INQoL data was collated as the only validated QoL questionnaire for the relevant trial population, and therefore it is the only preferred measure for capturing patient level changes in HRQoL for the mITT and PP populations from the MYOMEX study.

The INQoL has the advantage of recording specific NDM disease symptom impacts omitted by the SF-36 questionnaire such as locking, independence and body image (34, 50). INQoL also has the advantage that the effects of symptoms are separated from questions about life domains. This separation allows “shifts” in patients’ internal standards to be identified if satisfaction with life domains has altered independently from a change in perceived symptoms. Sansone and colleagues concluded that INQoL was an appropriate measure because *“…it can quantify the impact of muscle symptoms that are specific to this group of patients (e.g. myotonia, muscle pain)” (51)*. Trivedi and colleagues described INQoL as *“a more relevant instrument for determining symptom impact on quality of life in non-dystrophic myotonia compared with the generic SF-36”* (52).

This is further confirmed in Figure 6 of the company submission which shows SF-36 to be less capable of capturing disease nuances when compared with INQoL.

The inability of SF-36 to assess myotonia is particularly important as Sansone and colleagues state that *“…myotonia should be the treatment target for patients…and improvement of myotonia should be the primary outcome measure …”* (51).

With regards to sensitivity of a QoL measure, some SF-36 items are considered not relevant to muscle disease and could easily be influenced by other factors (34).

Sansone and colleagues concluded that INQoL was more capable of capturing the *"physical limitations owing to the muscle condition"* than SF-36. INQoL also assesses *"the extent by which [myotonia] has a detrimental effect on QoL perception. This [enabled the authors] to pick out differences amongst the channelopathies that are not captured by SF-36 alone" (51).* Clinical experts consulted by Lupin unanimously agreed that INQoL more relevant and appropriate to capture the impact on the quality of life of NDM patients compared to SF-36 (Appendix M of CS).

For these reasons, it was concluded that the SF-36 is not an appropriate outcome measure and therefore not included within the analyses.

b) Please incorporate health state utilities using SF-36 based estimates derived from the literature into the economic model.

As described above the SF-36 is not an appropriate outcome measure for NDM patient's and has therefore not been included within the model.

The EQ-5D is the preferred HRQoL measure for the assessment of QoL in the NICE Reference case, and the INQoL data collated at a patient level in the MYOMEX study has been mapped to EQ-5D dimensions using two methodologies. SF-36 data was not collated in the MYOMEX (14) study which informs our economic model. INQoL data was collated as the only validated QoL questionnaire for the relevant trial population, and therefore it is the only preferred measure for capturing patient level changes in HRQoL for the mITT and PP populations from the MYOMEX study.

B7. Priority Question: Please provide the answers for the following district choice experiment (DCE) related questions:

a) How was the DCE task explained to respondents?

The respondents were provided a summary at the start of the online survey which explained very simply the task required and the meaning of the attributes of the DCE. The consent form and draft survey have been provided in Appendix A, Appendix B and Appendix C, respectively.

b) How exactly was the DCE conducted? For example, how was the sample chosen and how was the exercise administered?

As outlined above, the respondents were provided documentation which explained the task and the meaning of the attributes of the DCE. The survey was hosted online and a sample of 508 members of the UK general public were recruited to complete the questionnaire. Respondents were provided with contact details of those carrying out the online survey, allowing them to ask questions about the survey and exercise at hand. Quota sampling was used to balance geographic distribution, gender, and

ethnicity, see Table 23. All participants were aged 18 or over and provided consent to take part. Non-UK residents were excluded from the sample.

Table 23. DCE Exercise – Respondent Characteristics.

Characteristic	**N=**
Age (years)	
Mean (SD)	
Min, Max	
Gender, n (%)	
Male	
Female	
Ethnicity, n (%)	
White Caucasian	
Black British	
Black Caribbean	
Black African	
Black Other	
Asian Indian	
Asian Pakistani	
Asian Bangladeshi	
Asian Other	
Chinese	
Mixed - White and Black	
Mixed - White and Asian	
Mixed – Other	
Prefer not to answer	
Other	
Education, n (%)	
No formal qualifications	
Left school at 16	
Left school at 18	
University degree	
Other	
Prefer not to answer	
Main activity, n (%)	
Paid employment	
Looking after family/home	
Retired	
Seeking work, unemployed	
Not working, health problems	
In education or training	
Other	

Prefer not to answer	[redacted]
Geographic region, n (%)	
England	[redacted]
Scotland	[redacted]
Wales	[redacted]
Northern Ireland	[redacted]

A published fractional factorial method informed the design of the DCE, minimising participant burden whilst representing INQoL items with different response levels in a balanced and statistically efficient manner. The eight conceptually mapped INQoL items were combined with the conceptually mapped response choices using an orthogonal design to produce DCE scenarios. The orthogonal design combined questions and response choices with zero correlation. One implication of this is that conceptually related items were not related in the choice sets (e.g. no muscle locking was as likely to be paired with no muscle weakness as extreme muscle weakness). This assumption was later corroborated by patients who described heterogenous symptoms that reduced the chance of implausible states (see Appendix L of CS).

c) Did the DCE task begin with a practice question (or series of practice questions). If so, please provide details.

No practice questions were provided to the respondents, please see Appendices 1 and 2 for further details. These are not often provided for DCE's as there is more of an emphasis on providing clear instructions on the DCE task than discussion around practice questions. Respondents are recruited from a select panel where the likes of DCE is a common tool for market research and therefore it can be assumed that respondents had some experience and prior knowledge of what would be expected. Additionally, previous research investigating the impact of a ranking exercise on TTO values found that a warm up did not have an impact on the quality of data (53). The reviewers of the vignettes also concluded that the study was appropriate and well conducted.

d) Were any checks of respondent understanding built into the DCE? Please provide details.

Respondents were able to contact the facilitators to ask questions around their understanding. The number of participants over time was tracked and fell in line with expectations. Only completed surveys were included within the final results and therefore any participants that dropped out prior to completing the full survey due to their understanding of the task were excluded from the final analysis.

e) **Please provide details of any quality control checks or tests of internal or external validity performed on the data obtained from the DCE, including but not limited to:**

- **Identification or removal of respondents who stated a preference for a state within a pair which is clearly inferior to the other state shown.**
- **Identification or removal of respondents who always (or too often) answered A or B (or left or right) (we need to ask to AL)**
- **Identification or removal of respondents who completed the task too quickly to have properly considered the choices (we need to ask to AL)**
- **Identification or removal of participants who made choices which defied transitivity (we need to ask to AL)**

Identification or removal of respondents who stated a preference for a state within a pair which is clearly inferior to the other state shown.

The survey was purposefully designed so that no such pairs existed and therefore this would not have been needed.

Identification or removal of respondents who always (or too often) answered A or B (or left or right)

A review of the study suggested that no respondent always answered A or B.

Identification or removal of respondents who completed the task too quickly to have properly considered the choices

Guidance was given on the expected length of time to complete the study. However, no analysis was conducted to investigate respondents who may have been perceived to have completed the survey too quickly. It is not expected that this would make a significant difference to the results, as the number of respondents would have reduced any such results to white noise.

Identification or removal of participants who made choices which defied transitivity

Transitivity tests were not built into the DCE design or examined in the analysis. However, the results were analysed for logical inconsistencies which only required minor adjustments and is explained in the response to B8.

B8. Page 141 of the company submission states that "the results identified some logical inconsistencies in the preference weights". Please provide a full list of the logical inconsistencies in the results of the DCE.

The results identified minor logical inconsistencies in the preference weights. For example, under Leisure activities the weights for 'moderately' and 'slightly' are mis-ordered. Where logical inconsistencies occurred the inconsistent value (disutility) in the scoring algorithm was changed to be the same as the better level. In this case, the value for 'a moderate amount' would be the same as 'slightly'. This was considered a conservative approach. Logical inconsistencies also occurred whereby people preferred 'some' or 'slight problems' to the upper anchor (i.e. very little/ not at all). Where this has occurred those disutilities for 'some' or 'slight' were adjusted to 0, again as a conservative approach.

The logical inconsistencies in the DCE results are highlighted in the table below. This table shows the coefficient weights with respect to the reference category, whether that is significantly different to the reference category and the 95% confidence intervals around each coefficient. The confidence intervals around the inconsistent value suggest that they are not statistically significantly inconsistent.

Table 24. Logical Inconsistencies in the Coefficiencies derived from the DCE.

Attributes and levels	Coefficients	SE	z	P>|z|	95% CI	
Muscle weakness						
An extreme amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A moderate amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very little	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Locking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
An extreme amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A moderate amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very little	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Washing, dressing, housework	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extremely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderately	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slightly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not at all	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leisure activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extremely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderately	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slightly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Not at all	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
An extreme amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A moderate amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very little	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tiredness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
An extreme amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A moderate amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Some	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very little	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxious/worried	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extremely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderately	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slightly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not at all	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extremely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderately	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Slightly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not at all	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B9. Please provide a table showing all inter-item correlations for those INQOL items included in the DCE (based on original INQOL MYOMEX data).

The inter-item correlation for INQoL items included in the DCE for mexiletine and placebo arms are reported in Table 25 and Table 26.

Table 25. Correlation Inter-INQoL item for Mexiletine.

Mexiletine										
	Weakness	**Locking**	**Pain**	**Fatigue**	**Activities**	**Independence**	**Social relationships**	**Emotions**	**Body image**	**Overall score**
Weakness	[redacted]									
Locking	[redacted]	[redacted]								
Pain	[redacted]	[redacted]	[redacted]							
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]						
Activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					
Independence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
Social relationships	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
Emotions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Body image	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Overall score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26. Correlation Inter-INQoL item for Placebo.

Mexiletine										
	Weakness	**Locking**	**Pain**	**Fatigue**	**Activities**	**Independence**	**Social relationships**	**Emotions**	**Body image**	**Overall score**

Weakness										
Locking										
Pain										
Fatigue										
Activities										
Independence										
Social relationships										
Emotions										
Body image										
Overall score										

B10. Priority Question: Please provide any relevant goodness of fit or other statistical quality indicators to accompany the DCE and Vignette model results presented in Table 2 of the Lupin Vignettes Utilities Final Submission document.

For the DCE project the conditional logit produced the following results:

- Conditional (fixed-effects) logistic regression
- Log likelihood = [redacted]
- Number of obs= [redacted]
- LR chi^2 (25) = [redacted]
- Prob > chi^2 = [redacted]
- Pseudo R^2= [redacted]

For the Vignettes project, a mixed effects model with random parameters and random coefficients which was tested against the more standard OLS 'linear regression' model was used. This showed a better model fit and so the mixed effects model was selected.

- LR test vs. linear model: chi^2 = [redacted]
- Prob > chi^2 = [redacted]

B11. Please provide all detail regarding the comments made by experts in relation to HRQoL issues. Appendix M provides only a minimal summary of discussions.

Key points and all available notes were structured and formatted in Appendix M of the CS.

The clinical expert elicitation process was adapted from the recommended guideline by Iglesias et al, 2016 (42), an appropriate tool for the collation of expert elicitation.

The clinical expert interviews were conducted, following discussion with NICE and the ERG on the checkpoint teleconference, on the 29th October.

There is no published natural history set of patients in the UK. All relevant information elicited in the meetings were appropriately noted using the tool to collate the information, and is presented in Appendix M of CS.

Further expert elicitation will become available for the Delphi panel being conducted, which is estimated to be available in June.

B12. Priority Question: Please provide responses to the following questions regarding the cross-over study design in relation to HRQoL data.

a) Please comment on the bias that could be introduced into the HRQoL data by the cross-over study design.

The cross-over design offers advantages over a parallel study in the evaluation of treatments for NDM. Most notably, the use of a crossover design means that possible confounders between treatment groups do not need to be considered as patients are in fact their own control.

Within the MYOMEX(14) study at first mexiletine intake, plasma concentration was null or below the detection threshold for all patients in both periods (baseline or at Visit 4 (Day 22) depending on the treatment sequence), regardless of treatment sequence, meaning that the wash-out period was sufficient. Finally, the Mixed Effect Linear Model did not show a difference in treatment effect for treatment periods with no evidence of a carry-over effect (treatment sequence effect).

b) Please provide separate utility values per treatment arm for those patients who first received Mexiletine then Placebo and those who first received Placebo and then Mexiletine (for both the DCE study and vignette study)

The utility outputs per treatment arm (Mexiletine then Placebo (MP), and Placebo then Mexiletine (PM)) for DCE study (using as worst health state 33333, 23233) and Vignettes study are reported in the Table 27 below.

Table 27. Utility outputs for mexiletine, split by treatment sequence

Discounted	QALY Total	QALY MP	QALY PM
33333 Worst HS	[redacted]	[redacted]	[redacted]
23233 Worst HS	[redacted]	[redacted]	[redacted]
Vignettes	[redacted]	[redacted]	[redacted]

B13. Priority Question: Please provide the option in the model for the ERG to select any top or bottom anchor of their choice for DCE utilities (as opposed to only including options for bottom anchors of -0.594 and -0.291).

In line with discussion during ERG clarifications call on Friday the 6th of March, the functionality to use two additional bottom anchors (33233 and 23333) for the DCE utility has been included in the updated economic model. These were selected as additional options for the ERG due to the uncertainty surrounding NDM patients potentially not meeting the worst health state criteria for 'Mobility' and 'Usual Activities'. Patient research shows that symptoms for NDM patients can be very severe (2, 9). During the development of the CMS disability scale, clinicians allowed for disabilities where help was required in a number of criteria. This includes all

gestures/movement related parameters, including “Eating and handling cutlery”, “Hygiene”, and “Dressing”. Conversely, “Walking” and “Ascending and descending stairs” were not possible at all; reflecting the severity of symptoms.

B14. Priority Question: Please provide a full list of logical inconsistencies in the results of the vignette study.

As previously provided in Tables 1 to 4 of the Vignettes report (Appendix 3), there was a need to impute values for the following reasons:

- Not all levels of the Likert scale of each INQoL item had disutility value generated from the statistical assessment of the vignettes response
- When more severe levels within an item generated lower utility values
- When there was a lack of statistical significance of the coefficients in the regression results

B15. Priority Question: Please answer the following time trade off (TTO) interview related questions below:

a) **Please clarify whether any practice TTO exercises were undertaken by participants within each TTO interview.**

No practice TTO exercises were undertaken by participants during the TTO interviews. The study included a large number of Vignettes (16 in total) and therefore inclusion of a warmup would have added even greater time constraints to the exercise. Additionally, previous research investigating the impact of a ranking exercise on TTO values found that warm up did not have an impact on the quality of data (53). The reviewers of the vignettes also concluded that the study was appropriate and well conducted.

b) **Please provide details of any quality control checks performed either during or after TTO interviews (e.g. checks of respondent understanding or checks for logical inconsistencies within participants) and clarify how these were dealt with.**

No control checks were performed during and after the TTO, and no provision of a description of the symptoms given to the participants. There is no scope for logical inconsistencies with what was being asked of respondents; no inclusion of minor/moderate/severe states within the orthogonal design. Whilst this may allow for clinically implausible combinations, the exercise included participants from the general public and would therefore not impact the results. However, the reviewers of the vignettes reported that the study was appropriate and well conducted.

B16. Priority Question: Please provide the full critical appraisal report/communication details from each of the three experts consulted on the methodology of the DCE and the Acaster Lloyd report on the Vignette study.

The three reports are provided in Appendices D, E and F. Details of the reviews have been previously provided in the Vignette study report.

In order to generate vignettes/dimensions for valuation, three clinical experts and a health economist conceptually mapped the INQoL to the EQ-5D. The rationale was to identify those dimensions that most closely relate to EQ-5D and to use those dimensions in the valuation studies. As a part of this, patients were included in both the development and validation of the mapping exercise (Appendix L of CS and(34)). The inclusion of patients provides validation of the measure from the patients perspective, reflected in INQoL being a recognised standard measure and therefore being less prone to bias. Additionally, clinical elicitation was undertaken to support the mapping of INQoL onto EQ-5D (Appendix M of CS).

We believe that there are strengths on the methodologies that were used which should be considered when reviewing them. The DCE and the vignette study both relied on the use of an orthogonal design to combine the dimensions of the INQoL into choice sets or vignettes. For the DCE this means that for every choice that participants made we were able to capture information on every INQoL item because they all varied. The orthogonal design underlying the vignette development also supported efficient data collection because the design described the minimum number of health states that could describe the different combinations of INQoL items (the fractional factorial design). This design supports the estimation of the utility algorithm but avoiding issues such as multicollinearity in the data.

For the DCE approach we believe it is worth emphasising that the INQoL utilities were estimated from preference weights from the DCE by refitting the values to the EQ-5D range. This helps to standardise the results against the EQ-5D. The DCE analysis estimated a simple linear logistic model which is easily interpretable and is similar to the scoring function for the EQ-5D-3L. The vignette modelling required a more complex statistical approach. Both studies produced sets of coefficient weights that had a logical ordering (albeit with some inconsistencies). The independent review also commented how the relative size of the coefficient weights was consistent with previous valuation research (i.e. pain was a very important issue for participants, depression was also important and more important than anxiety etc).

The study necessitated the use of linear interpolation for several reasons. Firstly, no datasets were available which would allow us to undertake psychometric work on the

INQoL to reduce the number of items and responses (mainly because this is a rare disease). Therefore, it was necessary to create a scoring algorithm that worked with the original instrument. Items were selected based on conceptual fit with EQ-5D, but in order to score all of the possible response choices we relied on interpolation because it was not possible to include all response choices in the DCE or vignette work. In addition, though interpolation was also used as the logically fairest approach to dealing with logical inconsistencies in the regression results. The use of interpolation did not favour treatment in any way and the analysis team that undertook this work did not have access to the trial datasets so could not have known how it would affect the ICER.

One possible limitation with the vignette work is the sample size for the TTO interviews. Normally valuation projects would have a larger sample than the 200 we recruited. We tried to compensate by asking each participant to rate 16 states. Also, after we had finished the TTO work we realised that participants did not receive the same background to the disease and how issues such as locking affect people compared with the DCE participants. Therefore, it is possible that people undervalued the impact of muscle weakness and muscle locking in the vignette work

B17. Priority Question: The Table captions in Appendix Tables 3 and 4 in the Lupin Vignettes Utilities Final Submission document refer to post hoc amendments to results – please provide detail of all post hoc amendments.

Full details of amendments can be found in the vignettes report (appendix 3 of CS).

For table 3, coefficient results for the situations below were set to zero and all missing values were imputed using linear interpolation:

- Not all levels of the Likert scale of each INQoL item had disutility value generated form the statistical assessment of the vignettes response
- When more severe levels within an item generated lower utility values
- When there was a lack of statistical significance of the coefficients in the regression results

For table 4, all the coefficient results for the situations below were set to zero and all missing values were imputed using linear interpolation:

- Not all levels of the Likert scale of each INQoL item had disutility value generated form the statistical assessment of the vignettes response

- When more severe levels within an item generated lower utility values

B18. Priority Question: Please provide the version of the electronic model, where the option to use vignette data was incorporated.

The functionality to choose between DCE and vignette output has been included in the updated economic model.

B19. Priority Question: Please clarify the specific utility values assigned to Mexiletine and Placebo from the Vignette study results (as in Table 58 of the CS for the DCE study)

The utility values reported in the table below are derived from patient level data for mexiletine and placebo.

Table 28. Health State Utilities from the Vignette Study Results.

Health state	MYOMEX study treatment arm	Health state utility
Alive on Treatment (AOT)	Mexiletine	[redacted]
Alive no Treatment (ANT)	Placebo	[redacted]

Resource use and costs

B20. Priority Question: Please explain in full detail how the clinical expert-informed 'disease severity' categories according to CMS disability scale were obtained. The consensus among the clinical experts consulted in the expert elicitation exercise in Appendix M, that categorisation of the disease severity to "mild, moderate and severe" would not be plausible.

Healthcare resource use was not collected during the MYOMEX study (14) but an expert advisory board had provided information on the use of physiotherapy, mobility aids, day case attendance and hospital admissions for patients who the experts thought had mild, moderate or severe disease, caveating the fact that no formal descriptions exist for disease severity in the literature,. This led to the consideration of using the disability scale of the CMS to define resource use in the trial for mexiletine compared to placebo as it required patients to assess their disability in carrying out activities that are known to be affected by myotonia. This would provide more granular information that was needed to create a proxy for the mild, moderate, severe health states for the purpose of health resource allocation and clinical experts provided advice during this process (Appendix M of CS). The INQoL was not considered

suitable as a proxy for healthcare resource as it does not provide insight on this aspect compared to the CMS disability scale.

Clinical experts ((46) Appendix M of CS) informed the development of the healthcare resource proxy by selecting minimum and maximum CMS disability scores for patients with severe and mild symptoms, respectively. This was carried out for each disability dimension within the CMS disability scale. Table 62 in the CS shows the scores within each disability dimension that clinical experts felt described NDM patients with mild, moderate and severe symptoms of myotonia.

Within the CS, likely healthcare resource use was informed by expert elicitation according to the 'disease severity' proxy. Table 63 (CS, page 153) shows the base case healthcare usage according to disease severity proxy.

The CMS is a new scale for non-dystrophic myotonias, which was developed in the pivotal phase III study of mexiletine in NDM patients. The validation of this new scale for rating myotonia in NDM is ongoing.

The Delphi panel should be able to provide further information and justifications and is currently expected to be available in June.

B21. Please answer the following resource use related questions:

a) **Two detailed cardiac evaluations are required for mexiletine initiation. Please confirm that the second cardiac evaluation, that is performed within 48 hours of treatment initiation, is assumed only to consist of an ECG, and indicate whether this assumption has been validated by clinical expert opinion.**

According to the NaMuscla SmPC (8), before starting mexiletine treatment, detailed and careful cardiac evaluation (ECG, 24-48-hour Holter-monitoring and echocardiography) should be carried out in all patients in order to determine the cardiac tolerability of mexiletine. A cardiac evaluation is recommended shortly after treatment start (e.g. within 48 hours).

Throughout treatment with mexiletine, and in relation with dose changes, cardiac monitoring of patients' needs to be adapted as a function of the heart condition of the patient:

- In patients without cardiac abnormalities, periodic ECG monitoring is recommended (every 2 years or more frequently if considered necessary).
- In patients with cardiac abnormalities, and in patients prone to such abnormalities, detailed cardiac evaluation, including ECG, should be carried out before and after any dose increase. During maintenance treatment, detailed cardiac evaluation, including ECG, 24-48 hour Holter-monitoring and

echocardiography, is recommended at least annually, or more frequently if considered necessary as part of routine cardiac assessment.

Further, the authors of the Suetterlin et al 2015 study (7) concluded that the absence of any significant change in ECG parameters or serious adverse events within a combined total of 302.4 years of patient follow-up demonstrates the long-term safety of mexiletine and suggests that frequent routine ECG monitoring of patients on maintenance dose may not be necessary.

b) The company states that it has included yearly cardiac monitoring as a conservative assumption in their base case. However, Table 60 of the CS shows that the annual frequency of monitoring from the second year onwards is assumed to be 0.5 (i.e. once every two years), and that monitoring consists of an ECG. Please explain this inconsistency.

The annual frequency of monitoring from the second year onwards is 0.5 for the majority of patients (i.e. once every two years), and that monitoring consists of an ECG. This is included in the economic model as once every two years by costing out the annual cost a dividing by two, providing a calculated frequency of 0.5 (see named cell 'Annual_cost_ECG' in the economic model.

B22. Priority Question: Table 70 of the CS (starting at p. 158) provides a summary of the variables that are used in the model. For the variables listed over (approximately) the last five pages of this table, section B.3.5.2 is stated as a reference. However, section B.3.5.2 is a section consisting of two short sentences and a small table with two entries regarding the costs of mexiletine with and without PAS. Please provide the correct references to sections in the CS for the corresponding variables, and please make sure that each section is present and complete (i.e. including proper referencing to sources used, justification of any assumptions that were made, and the validation efforts that were performed for each variable) in the CS.

Table 29. Summary of variables applied in the economic model.

Variable	Value	Lower bound	Upper bound	Measurement of uncertainty	Reference to Section in submission
Model settings					
Time horizon	56 years	39.2 years	72.8 years	Upper and lower bounds ±30%; Gamma distribution	B.3.2.5

Discount rate for costs	3.50%	Not included in PSA	Not included in PSA	Not included in PSA; scenario analysis for 1.5% discount rate for outcomes	B.3.2.5
Discount rate for outcomes	3.50%	Not included in PSA	Not included in PSA		B.3.2.5
Population characteristics					
Age	44	30.8	57.2	Upper and lower bounds ±30%; Gamma distribution	B.3.3.1
Compliance rate	0.95	0.66	1	Upper and lower bounds ±30%; Beta distribution	B.3.3.4
Discontinuation rate	0.06	0.04	0.2		B.3.3.5
Health state utility - mexiletine	[redacted]	[redacted]	[redacted]		B.3.4.5
Health state utility – no treatment	[redacted]	[redacted]	[redacted]		B.3.4.5
Disease progression differential mexiletine	0	0	1		B.3.3.3
Disease progression differential no treatment	0.15	0.11	0.06		B.3.3.3
Likelihood of falls resulting in fracture whilst taking mexiletine	0.1	0.07	0.13		B.3.3.6
Likelihood of falls resulting in fracture whilst taking no treatment	0.2	0.14	0.26		B.3.3.6
Mexiletine first titration dose (7 capsules), year 1	7	7	21	Upper and lower bounds ±30%; Gamma distribution	B.3.3.2
Mexiletine second titration dose (14 capsules), year 1	14	7	21		B.3.3.2
Mexiletine maintenance dose	14	7	21		B.3.3.2
Quantity of weeks on mexiletine first titration dose, year 1	1	0	2		B.3.3.2
Quantity of weeks on mexiletine second titration dose, year 1	1	0	2		B.3.3.2

Quantity of weeks on maintenance dose of mexiletine, year 1	50	48	52		B.3.3.2
Disease severity proxy					
CMS Disability score maximum for speech for mild patients	1	0	2	Upper and lower bounds ±30%; Gamma distribution	B.3.5.5 (Table 61)
CMS Disability score maximum for speech for severe patients	3	2	4		B.3.5.5 (Table 61)
CMS Disability score maximum for handwriting for mild patients	1	0	2		B.3.5.5 (Table 61)
CMS Disability score maximum for handwriting for severe patients	3	2	4		B.3.5.5 (Table 61)
CMS Disability score maximum for feeding for mild patients	1	0	2		B.3.5.5 (Table 61)
CMS Disability score maximum for feeding for severe patients	3	2	4		B.3.5.5 (Table 61)
CMS Disability score maximum for hygiene for mild patients	1	0	2		B.3.5.5 (Table 61)
CMS Disability score maximum for hygiene for severe patients	3	2	4	Upper and lower bounds ±30%; Gamma distribution	B.3.5.5 (Table 61)
CMS Disability score maximum for dressing for mild patients	1	0	2		B.3.5.5 (Table 61)
CMS Disability score maximum for dressing for severe patients	3	2	4		B.3.5.5 (Table 61)
CMS Disability score maximum for walking for mild patients	1	0	2		B.3.5.5 (Table 61)
CMS Disability score maximum for walking for severe patients	3	2	4		B.3.5.5 (Table 61)

CMS Disability score maximum for stairs for mild patients	1	0	2		B.3.5.5 (Table 61)
CMS Disability score maximum for stairs for severe patients	3	2	4		B.3.5.5 (Table 61)
Mexiletine initiation and maintenance					
Number of Electrocardiogram (biannual)	2	1	3	Upper and lower bounds ±30%; Gamma distribution	B.3.5.4 (Table 60)
Number of Electrocardiogram monitoring for 24-48 hours (only in the first year)	1	0	2		B.3.5.4 (Table 60)
Number of Echo-cardiogram (only in the first year)	1	0	2		B.3.5.4 (Table 60)
Healthcare resource utilisation (annual)					
Percentage of mild patients who utilise physiotherapy annual care package	0.1	0.07	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.5 (Table 64)
Percentage of moderate patients who utilise physiotherapy annual care package	0.6	0.42	1		B.3.5.5 (Table 64)
Percentage of severe patients who utilise physiotherapy annual care package	0.8	0.56	1		B.3.5.5 (Table 64)
Percentage of mild patients who utilise occupational therapist annual care package	0.1	0.07	1		B.3.5.5 (Table 64)
Percentage of moderate patients who utilise occupational therapist annual care package	0.6	0.42	1		B.3.5.5 (Table 64)
Percentage of severe patients who utilise occupational therapist annual care package	0.8	0.56	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.5 (Table 64)
Percentage of mild patients who utilise speech therapy care package	0.1	0.07	1		B.3.5.5 (Table 64)
Percentage of moderate patients who utilise speech therapy care package	0.6	0.42	1		B.3.5.5 (Table 64)

Percentage of severe patients who utilise speech therapy care package	0.8	0.56	1		B.3.5.5 (Table 64)
Percentage of mild patients who utilise day case attendances per year	1	0.7	1		B.3.5.5 (Table 64)
Percentage of moderate patients who utilise day case attendances per year	1	0.7	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.5 (Table 64)
Percentage of severe patients who utilise day case attendances per year	1	0.7	1		B.3.5.5 (Table 64)
Percentage of mild patients who utilise wheelchair	0	0	1		B.3.5.5 (Table 65)
Percentage of moderate patients who utilise wheelchair	0	0	1		B.3.5.5 (Table 65)
Percentage of severe patients who utilise wheelchair	0.05	0.04	1		B.3.5.5 (Table 65)
Percentage of mild patients who utilise walking sticks	0	0	1		B.3.5.5 (Table 65)
Percentage of moderate patients who utilise walking sticks	0.2	0.14	1	Upper and lower bounds ±30%; Beta distribution	B.3.5.5 (Table 65)
Percentage of severe patients who utilise walking sticks	0.3	0.21	1		B.3.5.5 (Table 65)
Percentage of mild patients who utilise walking frame	0	0	1		B.3.5.5 (Table 65)
Percentage of moderate patients who utilise walking frame	0.1	0.07	1		B.3.5.5 (Table 65)
Percentage of severe patients who utilise walking frame	0.4	0.28	1		B.3.5.5 (Table 65)
Healthcare resource units (annual)					
Number of annual physiotherapy visits for mild patients	6	4	8	Upper and lower bounds ±30%; Gamma distribution	B.3.5.5 (Table 63)
Number of annual physiotherapy visits for moderate patients	6	4	8		B.3.5.5 (Table 63)

Number of annual physiotherapy visits for severe patients	6	4	8		B.3.5.5 (Table 63)
Number of annual occupational therapy visits for mild patients	6	4	8		B.3.5.5 (Table 63)
Number of annual occupational therapy visits for moderate patients	6	4	8		B.3.5.5 (Table 63)
Number of annual occupational therapy visits for severe patients	6	4	8	Upper and lower bounds ±30%; Gamma distribution	B.3.5.5 (Table 63)
Number of annual speech therapy visits for mild patients	6	4	8		B.3.5.5 (Table 63)
Number of annual speech therapy visits for moderate patients	6	4	8		B.3.5.5 (Table 63)
Number of annual speech therapy visits for severe patients	6	4	8		B.3.5.5 (Table 63)
Number of annual day case attendances for mild patients	1	0	2		B.3.5.5 (Table 63)
Number of annual day case attendances for moderate patients	1	0	2	Upper and lower bounds ±30%; Gamma distribution	B.3.5.5 (Table 63)
Number of annual day case attendances for severe patients	2	1	3		B.3.5.5 (Table 63)
Number of wheelchairs for mild patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)
Number of wheelchairs for moderate patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)
Number of wheelchairs for severe patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)
Number of walking sticks for mild patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)

Number of annual units of walking sticks for moderate patients (provision and maintenance)	1	0	2	Upper and lower bounds ±30%; Gamma distribution	B.3.5.5 (Table 63)
Number of walking sticks for severe patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)
Number of walking frames for mild patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)
Number of walking frames for moderate patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)
Number of walking frames for severe patients (provision and maintenance)	1	0	2		B.3.5.5 (Table 63)
Number of omeprazole 20mg capsules per day for treatment for dyspepsia	1	0	2		B.3.5.6 (Table 69)
Adverse events probability					
Probability of requiring treatment for dyspepsia	0.7	0.49	1	Upper and lower bounds ±30%; Beta distribution	B.3.3.6
Probability of adverse events	0.33	0.23	1		B.3.3.6
Costs					
Cost per capsule of omeprazole	£0.03	£0.02	£0.04	Upper and lower bounds ±30%; Gamma distribution	B.3.5.6 (Table 69)
Genetic test cost	£800.00	£560.00	£1,040.00		B.3.5.5 (Table 67)
Cost of Genetic consultation visit	£167.00	£116.90	£217.10		B.3.5.5 (Table 67)
Cost per capsule of NaMuscla	£27.50	£35.00	£65.00		B.3.5.2 (Table 59)
Cost of Electrocardiogram	£38.00	£26.60	£49.40		B.3.5.5 (Table 67)
Cost of Electrocardiogram monitoring for 24-48 hours	£96.00	£67.20	£124.80		B.3.5.5 (Table 67)
Cost of Echocardiogram	£97.00	£67.90	£126.10		B.3.5.5 (Table 67)

Cost of Physiotherapy 1:1 session	£54.00	£37.80	£70.20		B.3.5.5 (Table 67)
Cost of Occupational therapy 1:1 session	£78.00	£54.60	£101.40		B.3.5.5 (Table 67)
Cost of Speech therapy 1:1 session	£97.00	£67.90	£126.10	Upper and lower bounds ±30%; Gamma distribution	B.3.5.5 (Table 67)
Cost of General Practitioner consultation (including prescription cost)	£65.00	£45.50	£84.50		B.3.5.5 (Table 67)
Cost of Day case attendance	£207.00	£144.90	£269.10		B.3.5.5 (Table 67)
Cost of A&E attendance	£130.00	£91.00	£169.00		B.3.5.5 (Table 67)
Cost of treatment of fracture	£733.00	£513.10	£952.90		B.3.5.5 (Table 67)
Cost of Wheelchair - Self- or attendant-propelled (annual)	£101.00	£70.70	£131.30		B.3.5.5 (Table 67)
Cost of Wheelchair - Active user (annual)	£202.00	£141.40	£262.60		B.3.5.5 (Table 67)
Cost of Wheelchair - Powered (annual)	£468.00	£327.60	£608.40		B.3.5.5 (Table 67)
Cost of Walking sticks (annual)	£17.50	£12.25	£22.75		B.3.5.5 (Table 67)
Cost of Walking frame (annual)	£150.00	£105.00	£195.00		B.3.5.5 (Table 67)

B23. Priority Question: To differentiate between resource use on and off mexiletine treatment, the company assumed that resource use off treatment is a threefold of resource use on treatment. The company states that this multiplication by a value of three was elicited from experts, but no reference is given for this. Please provide the reference (as well as the corresponding details) to the information elicited from clinical experts, that was the basis for assuming a 'health care resource use multiplier' value of three.

The patient surveys (2, 9) highlighted a disparity in possible events such as falls & fractures experienced by patients compared to that perceived by clinical experts who typically may see patients once a year (Appendix M of CS). Therefore, a multiplier of the resource use elicited from experts and reported above is applied in the model. The

multiplier in the base case is a multiple of three for patients in the ANT health state. No multiplier was added to the AOT health state.

The Delphi panel should be able to provide further information and justifications, and is expected to be available in June

B24. As noted in appendix M, there is a general consensus among clinical experts that a substantial proportion of patients have mental health issues due to their myotonic symptoms. Therefore, the ERG considers it as plausible that this will lead to additional use of (mental) health care resources. Please justify why these aspects are not considered as relevant for the analysis.

There is a paucity of data around the health care resource use for mental health related to NDM. Expert elicitation has been sought through the Delphi panel which is expected to be available in June.

B25. Priority Question: Please justify and explain the extent to which the choices for including health care resource use in the model (e.g. physiotherapy, occupational therapy, speech therapy, and A&E attendances) are validated by clinical expert opinion, or informed by sources from the literature.

Please see response to question B20.

The Delphi panel should be able to provide further information and justifications which is expected to be available in June.

B26. Please make sure all of the following is provided in the model: total costs per treatment, total QALYs gained per treatment, total life years gained per treatment, incremental costs, incremental QALYs, incremental life years, both as aggregate and disaggregate results (i.e. reported separately for each health state in the model), and for all the deterministic and probabilistic analyses.

The updated economic model now includes disaggregated incremental results, as requested.

Uncertainty analysis & inputs used in the model

B27. Priority Question: Please answer the following questions about the uncertainty analyses.

a) **Please provide a new probabilistic and one-way sensitivity analysis where all relevant parameters (i.e. parameters that are subject to parametric uncertainty unlike time horizon, patient age and capsule cost**

per NaMuscla) are included alongside a description of the selection criteria for relevant parameters.

The revised section B.3.8 of the original submission using the updated economic model is as follows:

Probabilistic sensitivity analysis

To assess parameter precision in the model, all model parameters were varied simultaneously in a probabilistic sensitivity analysis (PSA). The convergence method presented by Hatswell et al (54) was used to inform the number of iterations to include in the simulation. Confidence intervals did not cross zero at 5,000 iterations, however, due to the potential uncertainty in the model, 10,000 PSA iterations were run to obtain a stable estimate and convergence of the mean model output. In this analysis where included all the parameters subjected to variation, without any selection as our aim was exploring the impact of the parameters under uncertainty.

Mean values, standard deviation, and distributions of each parameter were included within the PSA. Beta distributions were used for the event probabilities and utilities, with Gamma distributions used for quantities of resource use and costs.

The mean results presented in Table 30, at list and PAS price, show a slight reduction in the ICER compared to the base case. This is due to an increase in total costs for both NaMuscla (mexiletine) and no treatment, combined with a greater decrease in total QALYs for no treatment than NaMuscla (mexiletine). The list price ICER is £[redacted], with the inclusion of PAS price reducing the ICER to £[redacted]. The results are in line with the deterministic base case, providing additional confidence in the results.

Table 30: Mean results of probabilistic sensitivity analysis

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
List price					
No treatment	62,842	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAS price					
No treatment	62,671	[redacted]			
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean incremental results at list and PAS price are presented in the cost-effectiveness planes (CEP) below, see

and Figure 2 respectively.

The PSA results and the deterministic base case result at both list and PAS price sit in the North East quadrant of the CEP, suggesting that NaMuscla (mexiletine) is both more effective and more costly than no treatment. Of the individual results of the 10,000 iterations, [redacted] are cost-effective, sitting under the £30,000 threshold at PAS price, with [redacted] at list price. In addition, a small proportion ([redacted]) of scenarios sit in the North West quadrant, indicating a small degree of uncertainty about the incremental benefits of NaMuscla (mexiletine) versus no treatment.

The cost-effectiveness acceptability curve (CEAC), at list and PAS price, are presented in Figure 2 and Figure 4, respectively. The CEAC show that, at a maximum willingness to pay of £30,000, mexiletine has a [redacted] and [redacted] probability of being cost-effectiveness vs no treatment at list and PAS price, respectively. At a WTP threshold of £100,000, the probability of being cost-effectiveness is approximately [redacted] at PAS price but falls to approximately [redacted] at list price. A [redacted] probability of cost-effectiveness is obtained at a WTP threshold of approximately £300,000 for both PAS price and list price.

List price

Figure 1. Cost-effectiveness Plane (List Price).

Figure 2. Cost-effectiveness Acceptability Curve (List Price).

PAS

Figure 3. Cost-effectiveness Plane (PAS Price).

Figure 4. Cost-effectiveness Acceptability Curve (PAS Price).

Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. As the majority of model parameters were informed by a small study population and assumptions informed by clinical experts, upper and lower CIs could not be sourced from literature for the OWSA. Instead, upper and lower CIs were assumed to be 30% of the mean value where it was not possible to derive data from literature.

A tornado diagram (Figure 5 for the list price and 6 for PAS price) illustrate that the model is most sensitive to the utility value whilst on mexiletine, the mexiletine maintenance dose, mexiletine's disease progression differential, cost per mexiletine capsule, utility value for no treatment and compliance rate. These parameters affect how much cost and health effect is accrued in the AOT health state.

Figure 5. Tornado Diagram (List Price).

Figure 6. Tornado Diagram (PAS price).

Table 31 and Table 32 show that the NaMuscla (mexiletine) health state utility value causes the largest change in base case ICER, varying it by £[redacted] at list price and £[redacted] with PAS price.. As an increase in the NaMuscla (mexiletine) disease

progression differential leads to a decrease in QALY gain, this causes a large variation from the base case.

Table 31. Results of the DSA (List Price).

Parameter	Lower Bound (£)	Upper Bound (£)	Difference (£)
Utility value - mexiletine	[redacted]	[redacted]	[redacted]
Mexiletine maintenance dose	[redacted]	[redacted]	[redacted]
Cost per capsule for mexiletine	[redacted]	[redacted]	[redacted]
Utility value - no treatment	[redacted]	[redacted]	[redacted]
Compliance rate	[redacted]	[redacted]	[redacted]
Disease progression differential mexiletine	[redacted]	[redacted]	[redacted]
DCE Utility Upper Bound	[redacted]	[redacted]	[redacted]
Disease progression differential no treatment	[redacted]	[redacted]	[redacted]
Quantity of weeks on maintenance dose of mexiletine, year 1	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine second titration dose, year 1	[redacted]	[redacted]	[redacted]
Percentage of mild patients who utilise speech therapy care package	[redacted]	[redacted]	[redacted]
Mexiletine second titration dose (14 capsules), year 1	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine first titration dose, year 1	[redacted]	[redacted]	[redacted]
Mexiletine first titration dose (7 capsules), year 1	[redacted]	[redacted]	[redacted]
Percentage of mild patients who utilise occupational therapist annual care package	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for moderate patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for feeding for mild patients	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for severe patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for speech for mild patients	[redacted]	[redacted]	[redacted]

Table 32. Results of the DSA (PAS price).

Parameter	Lower Bound (£)	Upper Bound (£)	Difference (£)
Utility value - mexiletine	[redacted]	[redacted]	[redacted]
Mexiletine maintenance dose	[redacted]	[redacted]	[redacted]
Cost per capsule for mexiletine	[redacted]	[redacted]	[redacted]
Utility value - no treatment	[redacted]	[redacted]	[redacted]
Compliance rate	[redacted]	[redacted]	[redacted]
Disease progression differential mexiletine	[redacted]	[redacted]	[redacted]
DCE Utility Upper Bound	[redacted]	[redacted]	[redacted]
Disease progression differential no treatment	[redacted]	[redacted]	[redacted]
Quantity of weeks on maintenance dose of mexiletine, year 1	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine second titration dose, year 1	[redacted]	[redacted]	[redacted]
Percentage of mild patients who utilise speech therapy care package	[redacted]	[redacted]	[redacted]

Percentage of mild patients who utilise occupational therapist annual care package	[redacted]	[redacted]	[redacted]
Mexiletine second titration dose (14 capsules), year 1	[redacted]	[redacted]	[redacted]
Quantity of weeks on mexiletine first titration dose, year 1	[redacted]	[redacted]	[redacted]
Mexiletine first titration dose (7 capsules), year 1	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for moderate patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for feeding for mild patients	[redacted]	[redacted]	[redacted]
Number of annual units of day case attendances for severe patients	[redacted]	[redacted]	[redacted]
CMS Disability score maximum for speech for mild patients	[redacted]	[redacted]	[redacted]
Cost of Day case attendance	[redacted]	[redacted]	[redacted]

These results can be seen as robust and relevant to the population in the decision problem and all patient groups for which NaMuscla is licensed and on the context of a very rare disease would be deemed cost-effective under NICE HST thresholds.

b) Please provide a detailed guidance on how to conduct each of the reported scenario analysis in the economic model.

Provided below is a list on how to conduct each of the reported scenario analysis in the submitted economic model:

- **No Treatment disease progression differential 0%:** Inputs sheet > Change cell (C93) value to 0.00%.
- **No Treatment disease progression differential 5%:** Inputs sheet > Change cell (C93) value to 5.00%.
- **No Treatment disease progression differential 10%:** Inputs sheet > Change cell (C93) value to 10.00%.
- **No Treatment disease progression differential 20%:** Inputs sheet > Change cell (C93) value to 20.00%.
- **No Treatment disease progression differential 25%:** Inputs sheet > Change cell (C93) value to 25.00%.
- **Time horizon 10 years:** Settings sheet > Change cell (C18) value to 10.
- **Time horizon 20 years:** Settings sheet > Change cell (C18) value to 20.

- **Time horizon 30 years:** Settings sheet > Change cell (C18) value to 30.
- **Time horizon 40 years:** Settings sheet > Change cell (C18) value to 40.
- **No multiplier for HC resource use in No Treatment health state (i.e. x1):** Inputs sheet > Change Cell (C66) value to 1.
- **Two multipliers for HC resource use in No Treatment health state (i.e. x2):** Inputs sheet > Change Cell (C66) value to 2.
- **Four multipliers for HC resource use in No Treatment health state (i.e. x4):** Inputs sheet > Change Cell (C66) value to 4.
- **Adverse events – MYOMEX: :** Inputs sheet > From the dropdown in Cell (C13) choose the option *MYOMEX*.
- **Adverse events - Statland** : **:** Inputs sheet > From the dropdown in Cell (C13) choose the option *Statland et al (2015)*.
- **Adverse events – Stunnenberg: :** Inputs sheet > From the dropdown in Cell (C13) choose the option *Stunnenberg et al (2018)*.
- **Daily dose 429 mg mexiletine hydrochloride (15 capsules):** Inputs sheet > From the dropdown in Cell (C25) choose the option *15*.
- **23233 EQ-5D worst health state for INQoL:** Inputs sheet > From the dropdown in Cell (C31) choose the option *23233 EQ5D = Worst HS INQoL*.
- **No discount rate for health outcomes and costs:** Settings sheet > Change cells (C31) and (C32) values to 0.0%.
- **Health outcome discount rate 1.5%:** Settings sheet > Change cell (C32) value to 1.5%.
- **Compliance rate Statland:** Inputs sheet > From the dropdown in Cell (C7) choose the option *Statland et al (2015)*.
- **Compliance rate Stunnenberg:** Inputs sheet > From the dropdown in Cell (C7) choose the option *Stunnenberg et al (2018)*.

c) **Please clarify what "Cost per capsule of imported mexiletine" in Table 70 of the CS is referring to, and where it is used in the economic analysis.**

This is not included within the economic analysis and was included within Table 70 in error.

Validation

B28. Priority Question: Please provide details about what validation efforts were performed in Section B.3.10 of the company submission and the results of these validation efforts. This could be presented for example (but not necessarily) with the help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/). Please confirm whether black-box/ white-box/ replication-based tests to detect modelling errors were conducted. If yes, please present the results transparently (e.g. the format in TECH-VER can be utilised: https://www.imta.nl/techver/). If not, please include these steps as well.

As outlined in the original submission, internal and an external quality control of the model were conducted according to the NICE guideline checklist. The external review was conducted by two leading health economic consultancies. However, these did not include review of confidential patient level data. In light of the errors discovered as part of updating the analysis for response questions, additional external reviews of the model to include the patient level data have been commissioned and will be shared with the ERG and NICE on conclusion.

Section C: Textual clarification and additional points

C1. The references supplied by the company do not include the CS reference number in their file name. We have endeavoured to match up the references supplied with their corresponding CS reference but there appear to be missing reference files. Furthermore, several references are listed as 'data on file' but it is unclear how these relate to the data on file documents supplied with the submission.

a) Please provide all data on file documents cited in the submission (references 1, 2, 3, 27, 39, 50, 58-61, 64, 69 and 75) with a filename indicating which reference they relate to in the CS.

b) The following reference papers appear to be missing: 31, 37 (same as reference 2?), 62, 63, 89 and 92. Please provide these references.

c) The references from Appendix D do not appear to have been supplied in full. Please check all appendices and ensure that all full documents of all references have been provided.

An updated reference pack has been provided including all references requested.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Muscular Dystrophy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Muscular Dystrophy UK (previously known as the Muscular Dystrophy Campaign) is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 70,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them. We are also a member of NHS England's Paediatric Neurosciences and Adults Clinical Reference Groups. Our funding comes from donations, gifts, grants and trusts. We have received funds from 13 pharmaceutical companies, including Lupin. These were educational grants and one grant for mitochondrial disease research. The funds equate to 0.1% of our overall income. We don't receive any government funding.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Yes, £7,000.00 was contributed by Lupin towards the UK Neuromuscular Translational Research Conference 2019

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered by: 1. Published evidence on disease burden 2. Participation at the Channel Patient Day held on Saturday 16 November 2019 organised by the team at the Specialist Muscle Channel Clinical Service at the Centre for Neuromuscular Diseases, Queen's Square, London. Over 40 patients and carers attended the day and MDUK participated in group sessions where 16 patients and carers shared their experience of living with the condition and of Mexiletine. A hard copy of these questions was shared with the group. 1 participant shared his experiences in writing after the meeting. 3. Data taken from a survey of patients with nondystrophic myotonia. The survey was carried out in November 2019 by an online Facebook international support group - Myotonia Congenita Project. 85 patients completed the survey. Of these, 27 patients reported that they lived in the UK and of these, 15 patients indicated that they have taken Mexiletine. For the purposes of this submission, only the responses of 27 patients living in the UK (including those who have taken Mexiletine) have been included. The age of the 27 respondents was 8 years to 59 years old. Three patients were under the age of 18 years old.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Nondystrophic myotonias are an extremely rare group of muscle disorders in which voluntary muscles are slow to relax after movement. This problem occurs intermittently, although often on a daily basis, and can sometimes be painful. Muscle wasting with fixed weakness can occur, usually after the age of 40 years. The main clinical symptom of the non-dystrophic myotonias is muscle stiffness as a result of the myotonia (Matthews et al., 2010). Additional common features of the condition include pain, weakness and fatigue (Walsh et al., 2007; Trivedi et al., 2008; Wang et al., 2008c). The clinical severity of these conditions can range from a neonatal life threatening presentation through to mild late-onset symptoms (Matthews et al., 2010). This group of muscle disorders includes myotonia congenita, paramyotonia congenita, sodium channel myotonia, potassium-aggravated myotonia, and hyperkalemic periodic paralysis with myotonia. **Patients used a number of words to describe what it is like to live with the condition:** “It’s horrible, terrible”, and also the words “awkward”; “tiring” “dangerous” and “invisible”. The word invisible was used more than once to describe the condition. **One patient said:** “you wouldn’t know there was anything wrong as it doesn’t always show on the outside.” **Another patient described what it was like when you have an attack. He said**: “You can’t get up from the chair…you just can’t move.” **Another added:** “If I sneeze my eyes close and I can’t open them.” For patients, one of the biggest worries is falling. **A patient said:** “It’s dangerous because of the risk of falling.” **One patient wrote to us with his thoughts of living with the condition. He said: "**I have been living with muscle problems all of my life. In the first place I just thought this was how everyone was. It was only in my thirties when the constant aches and pains became a hindrance to daily life. I found with a combination of chocolate, paracetamol and ibuprofen I could bear the symptoms. But with time these symptoms became worse. One day when I found myself curled up in a heap on the kitchen floor rocking backwards and forwards due to the aches and pains, I knew it was time to get some help.”

	In the online survey, when asked how nondystrophic myotonia affected their daily life, the 27 respondents most commonly selected the following: - Cold exposure makes the symptoms worse - 84.6% - Cannot participate in most sports - 65.4% - Anxiety related to negative experiences (falling, shaming, bullying) - 65.4% - Injuries from falls 69.2% - Social activities are restricted because of stiffness - 61.5% - Public transport is a challenge, 57.7% - School settings cause stress (stairs, hand fatigue when writing, awkward gait, falls, etc) - 53.8% - Difficulty lifting (babies and toddlers, groceries, boxes at work, etc), 50% Respondents mentioned other ways in which their daily life is affected including difficulty bathing (34.6%), bullied or teased by classmates or co-workers (23.1%), hard to find employment that accommodates issues caused (23.1%), and difficulty dressing (23.1%). One respondent said "Public transport (trains, bus, cab/Uber) is very difficult because sitting down for more than a min cause muscles to be come weak and stiff. It can take me up to 30 secs to stand and safely exit public transport. The faster I try to go the more likely I am to fall and hurt myself. It is a very embarrassing social situation to go through." **During the channel patient day, we also heard from carers, their experience of caring for someone with the condition.**

	An older carer said: "It can be very hard. Frequently in the middle of the night he calls out. I get out of bed, he puts his arms around my neck and then we rock until he can get to his feet." **Another carer commented:** "I feel embarrassed for him. It triggers Myotonia and people think he's drunk". A carer who is also a patient shared that she felt guilty about being a carrier. **One carer said:** "You feel helpless. I'm always worrying that they'll fall when (they) get a spasm." **Another carer added:** "It's the pain side that you can't help with and you feel really bad because you can't do anything."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	A specialist diagnostic and advisory service for neurological channelopathies is provided through a nationally commissioned service at the MRC Centre for Neuromuscular Diseases in the Queen's Square, London. There are a number of treatments available for this group of conditions and the Queen's Square can supply the following (please note sodium channel blockers include lamotrigine and this is also

provided via the national service:

We can supply the following:

Drug type	Drug name	Effect
Sodium channel blockers	Mexiletine and Carbamazepine	Myotonic disorders - significantly improve symptoms of stiffness
Potassium wasting/sparing	Bendroflumethiazide, Spirinolactone, Amiloride	Periodic paralyses/ATS - reduce the number of paralytic attacks
Carbonic anhydrase inhibitors	Acetazolamide	Can reduce the number of paralysis episodes

Dichlorphenamide is not currently available in the UK but we are working with our Industry Partners to obtain a supply as soon as possible.

Source: https://www.ucl.ac.uk/centre-for-neuromuscular-diseases/patient-services/muscle-services/muscle-channelopathy/diagnosis-and-treatment

Patients' value specialist care: During the channel patient day, patients talked about the support they receive from the Queen's square and the difference this has made to their lives. One said: "I can contact them via email and immediately get a helpful response." Another commented that the team supports their specific needs, for example, by ensuring he has enough medication so that he doesn't have to make such a long journey to London too often, but with support when they need it.

Support locally is difficult to find. **One patient said:** "The team here (Queen's Square) are fantastic but there is no support locally." **Another said**: "No one cares".

One young lady was offered 3 sessions of hydrotherapy because they couldn't organise the transport to get her out of her flat to be able to have more. Her sister (her carer), explained that she is totally house bound and can't leave her flat. She can get half way down or up the stairs (28 stairs in total) and become unable to move. The myotonia gets worse going up the stairs and there's no lift. (paraphrased) The carer also suffers herself from a heart condition. **She said:** "It's really hard."

	Delays in diagnosis: The online survey provided important insights into the challenges patients experience in getting diagnosed. Out of the 27 UK respondents, 70 percent took 5 or my years to receive a diagnosis. Three of these weren't diagnosed for 30 or more years. During the patient day, one patient commented that they had been misdiagnosed with McArdles for 30 years. **Access to medication:** Access to medication was also cited in the online survey as a challenge for patients. Of the 15 patients who have taken Mexiletine nearly half had to travel to see a specialist, 3 had to wait several weeks for prescription to be filled, 3 had side effects but had to wait to next appointment to change medications, nearly half were prescribed medication but couldn't get it from the pharmacy, and 1 had to pay cash for the prescription. Other comments were: 1 patient had to go to a panel for Mexiletine to be prescribed, 1 commented that access was easy and could get it from GP. In response to the same survey, one patient said "I was not prescribed any medication that helped my condition until 8 years after my diagnosis and after seeing 4 specialists. The 5th specialist finally knew what meds to prescribe."
8. Is there an unmet need for patients with this condition?	There is effective treatment for this condition but the benefits are variable and some medicines may be contra-indicated due to co-morbidities. There is no treatment option that is recommended to be taken during pregnancy – a time when symptoms often worsen. Some non-specialist centres are reluctant to prescribe medication or unfamiliar with treatment options. If prescribing a given treatment is considered “complex” or requires a degree of specialist administration this can impair access in non-specialist settings.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Mexiletine currently forms part of the standard of care for the treatment of patients with nondystrophic myotonia and has done for over 10 years. Randomised clinical trials support the efficacy of Mexiletine for the treatment of nondystrophic myotonia with patients reporting a reduction in the average daily reported muscle stiffness (Stunnenberg et al 2018) and improved patient-reported stiffness (Statland et al 2012). **One patient said:** “Mexiletine to me, seems like a wonder drug it controls my aches and pains on a daily basis.”

	Another said: “I wouldn’t have a proper life without it.” **An older patient said:** “It’s the freeing of movement: I can get up out of a chair.” **Another patient agreed saying:** “It’s great not to be dictated to by stiffness.” Patients commented on the benefit of being able to receive a 6 month supply of the drug. Also that it’s easy to take.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The most frequently reported side effect is gastrointestinal, minor tremors have also been reported (Suetterlin et al 2015). During the group discussion, the most talked about side effect was the issue of reflux but patients said that they were ok as long as they took plenty of water and food. **A male patient commented**: “I’ve found out that if you don’t take enough water with the tablets they can get stuck and then you have a painful reflux for most of the day. I now know either to make sure enough water is used or to make sure I eat something to help the tablets go down.” **One patient commented** on the importance of finding the right dose. **Another lady** who enjoys exercise said that she has to take Mexiletine 2 hours before exercise so that it doesn’t wear off. **One patient also said:** “I haven’t found a disadvantage.”

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Generally Mexiletine is beneficial for all forms of non-dystrophic myotonia. There is some evidence that those with myotonia congenita may find it less beneficial or may need higher doses than others but in general terms this group still benefit significantly.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Consideration must be given as to which centres of clinicians are able to prescribe the treatment to ensure equality of access. Access to prescriptions should not, if possible, be limited to one highly specialised service.

Other issues	
13. Are there any other issues that you would like the committee to consider?	The appraisal of Mexiletine provides an opportunity for NICE and NHS England to work with patients and health providers to raise awareness about this group of conditions and to put the right systems in place to ensure swift diagnosis and improved access to treatment for patients. Mexiletine has been standard of care at the national referral service for muscle channelopathies for over 10 years there is a significant group of patients already receiving this medicine long-term (over 100 patients). Any future impaired access to the drug would have a significant impact on this group who are already receiving treatment.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Nondystrophic myotonias are an extremely rare group of muscle disorders which impacts the quality of life of the individual and their family.
- Mexiletine currently forms part of the standard of care for the treatment of patients with nondystrophic myotonia and has done for over 10 years.
- Although not a cure, the treatment has shown to have a big impact on patients and their families, enabling them to enjoy an improved quality of life with improvements in stiffness, pain and discomfort.
- Evidence from randomised control trials support the efficacy of Mexiletine as a treatment of nondystrophic myotonia with reduced stiffness reported in patients.
- Gastrointestinal side effects of Mexiletine have been reported but patients feel that they are manageable.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The ABN is a UK-wide professional organisation whose mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. It is funded by professional member subscription and it's academic journal Practical Neurology (publisher Wiley)**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last	

12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment?	Myotonia affects patients on a daily basis. Non-dystrophic myotonia is not a life-limiting illness in adults and most do maintain employment. However it can have significant impact on quality of life, can influence choice of career and cause significant difficulty in taking public transport. This in turn can limit work and social activity and general independence. As well as the obvious symptom

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	of myotonia it can frequently cause pain and fatigue. Living with a chronic illness can affect mood. Myotonia affecting the leg muscles can lead to falls, and injury. The main aim of treatment with mexiletine is symptomatic improvement i.e. to reduce the severity of myotonia. Reducing myotonia may have an impact on other aspects of health, mobility and quality of life as outlined above.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In the nationally commissioned HSS service for muscle channelopathies a myotonia behaviour score is used to assess response to treatment. This is a 6 point score. Clinical experience suggests an improvement of 1 point or more on the score is clinically meaningful. This score and clinically meaningful improvement of 1 point or more has also been used as an outcome measure in trials of lamotrigine. The antimyotonic effect of **lamotrigine** in non-dystrophic myotonias: a double-blind randomized study. Andersen G, Hedermann G, Witting N, Duno M, Andersen H, Vissing J. Brain. 2017 Sep 1;140(9):2295-2305
8. In your view, is there an unmet need for patients	There are a number of effective treatments for this condition but the benefits are variable and some medicines may be contra-indicated due to co-morbidities or not tolerated due to side effects. There is no treatment option that is recommended to be taken during pregnancy (we don't recommend mexiletine during pregnancy) – a time when symptoms often worsen and there is an unmet need here. In one trial of mexiletine almost a third of participants did not respond adequately to mexiletine so there is a need for

and healthcare professionals in this condition?	alternatives. In our clinical practice we have used lamotrigine with success in a number of individuals who have failed to respond to mexiletine. Some non-specialist centres are reluctant to prescribe medication or are unfamiliar with treatment options. If prescribing a given treatment is considered “complex” or requires a degree of specialist administration this can impair access in non-specialist settings.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Mexiletine is currently first line treatment and standard of care for these disorders. There are other sodium channel blockers that are used. Multiple agents have been reported to have efficacy based on in vitro data, clinical experience, case reports and small series – including but not limited to carbamazepine, flecainide, propafenone and ranolazine. More recently a trial of lamotrigine demonstrated efficacy. At the national service we have used lamotrigine in a number of patients who either cannot tolerate or have failed to respond to mexiletine. We have seen a good response at doses lower than that used in the clinical trial. I know of colleagues in Scotland who have had a similar experience. There has been no head to head study of mexiletine versus lamotrigine in these disorders.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no specific national or international clinical guidelines. At the HSS service we do have our own guidelines for monitoring and prescribing mexiletine.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The majority of patients are managed via the HSS service so approach to treatment is consistent. It is my experience that most neuromuscular specialists managing myotonia patients in the UK outside of this service do also use mexiletine as first line treatment. We routinely provide advice regarding treatment options and monitoring to other specialists who request guidance in situation where patients may not wish or are unable to travel to clinic in London so overall approach in the UK I would consider to be fairly consistent.
• What impact would the technology have on the current pathway of care?	The technology already is standard of care and has been for more than 10 years, until now it has been used off-label or unlicensed.
10. Will the technology be used (or is it already	Yes

used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Before the license acquired by LUPIN mexiletine was an inexpensive treatment. At the HSS service we obtained max dose for one patient for one year at a cost of approx. £1600.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist neurology (ideally where available sub-specialty neuromuscular) clinics.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The only investment required really relates to the cost of the treatment itself. Facilities, training etc. are not required beyond being prescribed by a neurology specialist.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The technology is current care. Alternatives are available and are used in clinical practice e.g. lamotrigine. At the HSS service we have seen good/comparable results with this medicine compared to mexiletine but there have been no formal head to head trials.
• Do you expect the technology to increase length of life more than current care?	The technology is current care.
• Do you expect the	The technology is current care.

technology to increase health-related quality of life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Generally mexiletine is beneficial for all forms of non-dystrophic myotonia. There is some evidence that those with myotonia congenita may find it less beneficial or may need higher doses than others but in general terms this group still benefit significantly.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or	The technology is current care.

healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do	Certain co-morbidities have to be excluded before commencing mexiletine e.g. any history of cardiac disease or abnormal ECG require review by a cardiologist before the drug can be commenced. A pre-existing history of reflux, peptic ulcer may dissuade from taking mexiletine. In the event of planned pregnancy mexiletine needs to be discontinued.

these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Myotonia affects patients on a daily basis. Non-dystrophic myotonia is not a life-limiting illness in adults and most do maintain employment. However it can have significant impact on quality of life, can influence choice of career and cause significant difficulty in taking public transport. This in turn can limit work and social activity and general independence. As well as the obvious symptom of myotonia (muscle stiffness) it can frequently cause pain and fatigue. Living with a chronic illness can affect mood. Myotonia affecting the leg muscles can lead to falls, and injury. Impact on quality of life, mobility, and independence may not be fully captured by a QALY calculation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	There is nothing innovative about this technology – it has been standard of care for more than 10years.

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology	In our experience approximately 50% of patients report side effects although the majority found them to be tolerable. The most common side effect is dyspepsia. This can be reduced by taking the medication with food. A minority of patients require an additional proton pump inhibitor but despite this some will discontinue the drug due to this being an intolerable side effect. Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies.

affect the management of the condition and the patient's quality of life?	Suetterlin KJ, Bugiardini E, Kaski JP, Morrow JM, **Matthews E**, **Hanna** MG, Fialho D. JAMA Neurol. 2015 Dec;72(12):1531-3
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Myotonia is difficult to objectively quantify and most trials have a patient reported primary outcome with other secondary outcomes. I think the patient reported outcomes are most important. I don't think EMG is particularly useful as an outcome measure and there are other objective tests e.g. timed get up and go or sit to stand.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Trials only assessed short term response but we have published a review of "real world" experience using mexiletine and shown long-term benefits. Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies. Suetterlin KJ, Bugiardini E, Kaski JP, Morrow JM, **Matthews E**, **Hanna** MG, Fialho D. JAMA Neurol. 2015 Dec;72(12):1531-3
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Perhaps there would be lack of data on long-term benefits. It depends how review is defined and if e.g. our data above is included.
20. How do data on real-world experience compare with the trial data?	Similar i.e. the majority of patients with myotonia derive benefit although the degree of benefit varies and most side effects are tolerable. There is however a minority (in one trial this was almost a third of participants) who do not find the treatment effective or do discontinue it due to side effects.
Equality	
21a. Are there any potential equality issues that should be taken into account when	If a recommendation were to be made for mexiletine to only be prescribed via the HSS for skeletal muscle channelopathies this could limit access to patients who are unable to travel to the clinic in London, either because of disability (patients with non-dystrophic myotonia often do struggle on public transport and are at risk of falls) or because of inability to afford the cost of travel.

considering this treatment?	
21b. Consider whether these issues are different from issues with current care and why.	Currently a number of patients are managed at other specialist neurology centres across the UK and receive their mexiletine form them. A few patients receive prescriptions from their GP although the monitoring of the condition is usually done by the HSS service or local neurologist.

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Non-dystrophic myotonias are debilitating disorders that require access to effective therapies including mexiletine
- Mexiletine has been standard of care in clinical practice as an off-label or unlicensed product for over 10 years
- Clinical trials have confirmed standard of care to be appropriate
- Not all patients respond to or can tolerate mexiletine and a number of effective alternatives are available in clinical practice
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Fiona Norwood**
2. Name of organisation	**King's College Hospital**

3. Job title or position	**Consultant Neurologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **a specialist in the treatment of people with this condition?** ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **other** (they didn't submit one, I don't know if they submitted one etc.) I have not seen their submission.
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To ameliorate symptoms of non-dystrophic myotonia.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in muscle pain, cramps and stiffness. Better ease of movement.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. In my experience, drug options other than Mexiletine do not provide sufficient benefit for most patients.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Through the use of drugs to reduce the symptoms of non-dystrophic myotonia.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	I am not aware of any formal guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Once the diagnosis is established then the choice of drug is determined by the individual clinician based on personal preference and experience.
• What impact would the technology have on the current pathway of care?	It would provide a licensed drug that would become established as first line therapy.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I already use it.

• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist neuromuscular clinics only in patients in whom the diagnosis is genetically confirmed.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None other than a database of eligible patients.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. I expect the drug to be more efficacious than non-mexiletine drugs.
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No. The only additional requirement is for ECG monitoring before starting treatment and at each dose increase.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Use of standard protocol for initiation and dose increase, including use of ECG as above.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	It provides uniformity of supply. The drug itself is not new.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No: it is an existing drug.
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In my experience patients do not report significant adverse effects.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Please comment on the use of other treatments for NMD other than mexiletine. In	Until the genetic diagnosis is established, my practice is to use other drugs. I usually start with a slow upward titration of carbamazepine, continuing until symptom improvement. There may be limitations to its use through side-effects such as rash, imbalance and so on. I also use carbamazepine in patients aged 16

what circumstances would these be preferred to mexiletine? What would be the expected efficacy of these treatments compared to mexiletine?	and 17. I have used phenytoin in the past and found that largely ineffective. I am aware that a few colleagues use lamotrigine or flecainide but have not used those drugs myself for this group of patients. Lamotrigine could also produce side-effects such as rash and tiredness, and the dose escalation is slow.
24. Please comment on the importance of the dosing schedule and dose titration to overall efficacy of treatment. Is symptom relief dependent on the dose of mexiletine?	My patients report a dose-related improvement of symptoms with mexiletine. Some obtain sufficient relief on 200 mg bd or equivalent but others have commented that their symptoms are significantly improved with the higher dose of 200 mg tds or equivalent.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- I find mexiletine consistently effective for my patients with non-dystrophic myotonia.
- My patients report a dose-related improvement in symptoms.
- I have not yet come across any serious or clinically-meaningful side-effects in my patients treated with mexiletine.
- I have used other drugs but have found these less effective than mexiletine.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**David Lockyer**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Muscular Dystrophy UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Since childhood, I have always been aware that my muscles have felt 'stiff' but this started to have an impact on my life as a teenager – in particular at school where it was most evident when playing sports. As a result this affected my confidence during those years given that I had not received a diagnosis at this point and was very aware of my shortcomings in being able to participate in this area of school life. As I entered my early 20's, the condition appeared to worsen and began to have a more marked effect on my life. I found day to day life compromised eg - I increasingly found it difficult to climb stairs, - I struggled to get in and out of a bath,

	- General movement was compromised eg I found it uncomfortable to sit for long periods given I would get stiff and find it difficult to move. Fighting against this and trying to move would make the situation worse as the muscles 'locked up' until it was possible to 'get going' - My sleep was affected given I would wake up every time I moved position so I because tired and this then made the condition worse. - I got easily fatigued and would have to take time off work on days where this was particularly bad. - I would become anxious that my condition would be noticed (which it often was) and having to come up with excuses eg when shaking hands because my grip would not always let go, sneezing and not being able to open my eyes again, going upstairs alongside someone and becoming 'stuck' or walking very slowly. I began to make compromises in my life to manage around the situation and as a result was unable to do everything I wanted to. - Furthermore, if it affected the muscles in my jaw or mouth, I would find it difficult to speak clearly and could slur words which ran the risk of giving the impression of having consumed alcohol Then I began to suffer falls – my legs would 'lock up' – especially on stairs. This meant that I fell over on a number of occasions – a couple of them quite badly given I could not move easily enough to break my fall. At this point, I then sought medical advice and this resulted in my diagnosis of Myotonia in my mid-late 20's and was prescribed Mexiletine, which I have now been taking for c20 years With Mexiletine, the situation improved considerably and in particular, if I am able to combine with regular exercise, the symptoms are significantly improved. In particular the more serious effects such as falls and complete muscular lock ups have been eliminated altogether. As has the need to take time of work. I am always aware of the condition to some extent due to some low level muscular stiffness and therefore it does still impinge a little upon my ability to do certain physically orientated but I am able to run or cycle regularly as well as go to the gym.

	I still do have occasional days which are worse (often due to tiredness/overwork). On those days I suffer from muscular discomfort/soreness and am increased lack of range of movement etc. That can result in me feeling physically unwell at its very worst but these are rare events now
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I am happy with the treatment and care I currently receive. I am able to access Mexiletine and also feel that through annual consultations, I get the support and monitoring I need. I feel that if I needed to contact someone directly due to a particular issue or a worsening of the condition, I would be able to do so.
10. Is there an unmet need for patients with this condition?	I think that there is a general lack of awareness of the condition – so always have to explain it when I see my local GP about anything else or deal with any health related matters. Eg I had a hernia last year that required surgery and I had to see a number of consultants before I found one willing to operate and even then, they were very cautious and would not undertake a laparoscopic method due to what they considered the increased risk. And then due to concerns about the effects of anaesthetic, I actually had the operation cancelled on the day due to the fact they had said they wanted me to go into ICU post operation but had not planned for a bed to be available. The anaesthetist was not prepared to proceed with the operation.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	I am reliant on mexiletine to help me live my life effectively. Without it, I would find it far more difficult and would experience increased stiffness/soreness/pain. I always know when I have missed a dose because I can feel the effects on my body

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I have to make sure that I take the mexiletine with food to prevent occasional reflux. Given I have Barrett's Oesophagus in any event, I am aware that mexiletine can exacerbate this and have an endoscopy undertaken every two years to monitor this
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not able to comment
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not able to comment

Other issues	
15. Are there any other issues that you would like the committee to consider?	None

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Mexiletine has made a significant difference to my quality of life and to what I can do/achieve
- Awareness and knowledge of the condition is limited
- Untreated, the condition impinges upon many areas of everyday life and can adversely impact confidence/self esteem
- The support provided by the National Neurological Hospital is excellent

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Robert Burley**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Muscular Dystrophy UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered: Through face-to-face discussions with patients and clinicians and through a patient survey which formed the basis of our initial submission.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	In addition to the impact already described in MDUK's initial submission, and to that outlined in David Lockyer's patient expert statement, two patients (one adult patient and her child) describe the impact of the condition in the short eight minute video available at https://www.ucl.ac.uk/centre-for-neuromuscular-diseases/patient-services/muscle-services/muscle-channelopathy/patient-information-and-support. The adult patient describes the impact of the cramping they experience and the regularity of symptom episodes, describing a sense of life "coming to grinding halt". She explains the impact on her ability to

	work and her son explains the impact on his education, with participation in lessons at school hampered by challenges with holding a pen and pencil and muscle cramps affecting participation in play with friends – these experiences are transferrable to adults in the workplace and participating in leisure activities. The adult patient also explains the increased impact of ailments such as stomach bugs because of the prolonged periods of muscle spasms they trigger. The patients also describe some of the benefits they have experienced as a result of taking Mexiletine (see question 11). *Please note that there is a short section of the video discussing participation in a clinical trial, but the conversation returns to the impact of the condition and of taking Mexiletine after this.*
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Nothing to add to previous submissions.
10. Is there an unmet need for patients with this condition?	Nothing to add to previous submissions.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	In the patient video referenced above in answer to question eight, the adult patient describes how Mexiletine greatly reduced the frequency and severity of symptom episodes and that the treatment "makes a huge difference to daily life" particularly as it "takes the pain side of it away".

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Nothing to add to previous submissions.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Nothing to add to previous submissions.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Nothing to add to previous submissions.

Other issues	
15. Are there any other issues that you would like the committee to consider?	Nothing to add to previous submissions.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Myotonia in adults with non-dystrophic myotonic disorders has a significant impact on people's lives, with one patient describing symptom episodes as giving them a sense of life "coming to grinding halt".
- Patients who have taken Mexiletine have experienced significant reduction in the impact of symptom episodes.
- Mexiletine is a treatment that should be made available on the NHS for the treatment of myotonia in adults with non-dystrophic myotonic disorders

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Myotonic (non-dystrophic) disorders - mexiletine Appraisal 1488

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Fiona Marley**
2. Name of organisation	**NHS England**

3. Job title or position	**Head of Highly Specialised Commissioning**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England has published a service specification for a 'Diagnostic service for rare neuromuscular disorders', which can be found here: https://www.england.nhs.uk/wp-content/uploads/2013/06/d04-diagn-serv-rare-neuromusc.pdf This includes reference to myotonic (non-dystrophic) disorders and mexiletine.
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	NHS England commissions a rare neuromuscular diagnostic service from four providers in England, each of whom specialise in the diagnosis of a particular group of rare muscular disorders. Of the four providers, University College London Hospitals NHS Foundation Trust specialised in the treatment of patients with muscular dystrophies and myopathies. This centre provides the specialist diagnostic input and initiates patients on treatment; patients can then be treated within a shared care arrangement at a regional neurosciences centre. Gastric disturbances are common as a side effect, so it is critical to titrate up from a

experience is from outside England.)	low dose to an optimal dose. The mean dose is 400mg per patient. Symptoms generally start in teenage years.
7. What impact would the technology have on the current pathway of care?	The technology is already being used in the NHS but was purchased off-licence for a number of years. The branded version of mexiletine has been funded since license as an interim policy specifically for myotonic (non-dystrophic) disorders The drug is still purchased off-licence from Canada in strengths of 50mg and 100mg at a cost of approximately £1 per capsule to support titration and where the maximum tolerated dose cannot be met by the branded product including use in children where doses are likely to be lower. To note the branded product is only licensed in adults. As recognised practice is to start at a low dose and titrate upwards, the 167mg (equivalent to 200mg of the unlicensed product) licensed product would be more likely to be suitable for stable patients who have reached their optimal dose (average 400mg per patient).
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	An unlicensed (imported) version of the technology was already being used in the NHS.

9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If it is deemed cost effective by NICE it will be made available to suitable patients.
• How does healthcare resource use differ between the technology and current care?	The technology is already being used in the NHS but is purchased at a commercial in confident interim price or an unlicensed version is used.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Mexiletine is a capsule and can be administered (taken) in the patient's home.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None

• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No, all testing is already in place, the main side effect being gastrointestinal disturbance.
10. What is the outcome of any evaluations or audits of the use of the technology?	NHS England is not aware of any evaluations or audits.
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
11b. Consider whether these issues are different from issues with current care and why.	n/a

Thank you for your time.

NICE National Institute for Health and Care Excellence

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Mexiletine for symptomatic myotonia in adults with non-dystrophic myotonic disorders

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors

None.

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Commercial in confidence (CiC) data are redacted throughout the report.

Academic in confidence (AIC) data are redacted throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nasuh Büyükkaramikli acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Hannah Penton, Pim Wetzelaer, Titas Buksnys and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter and Annette Chalker acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report, and provided general health economic guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

Abbreviations

ADM	Abductor digiti minimi
AE	Adverse events
AIC	Akaike information criterion
ANT	Alive no treatment (health state)
AOT	Alive on treatment (health state)
BI	Budget impact
BIC	Bayesian information criterion
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CGI	Clinical global impression
CI	Confidence interval
CLCN1	Skeletal muscle voltage gated chloride channel gene
CMAP	Compound muscle action potential
CMS	Clinical myotonia rating scale
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
DCE	Discrete choice experiment
DSU	Decision Support Unit
ECG	Electrocardiogram
EMA	European Medicines Agency
EMG	Electromyography
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FAD	Final appraisal document
FDA	Food and Drug Administration
HR	Heart rate; Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost effectiveness ratio
INQoL	Individualized neuromuscular quality of life
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
IVR	Interactive voice response
KSR	Kleijnen Systematic Reviews
LYs	Life years
LYG	Life years gained
MA	Marketing authorisation
MC	Myotonia congenita
MeSH	Medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention to treat
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NDM	Non-dystrophic myotonia

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PC	Paramyotonia congenita
PFS	Progression-free survival
PMC	Paramyotonia congenita
PP	Per protocol
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSURs	Periodic safety update reports
PT	Preferred term
QALY	Quality-adjusted life year
QMA	Quantitative myotonia assessment
QoL	Quality of life
RADM	Right abductor digiti minimi
RCT	Randomised controlled trial
RR	Relative risk; Risk ratio
RTA	Right tibialis anterior
SAE	Serious adverse events
SAF	Safety
ScHARR	School of Health and Related Research
SCN4A	Skeletal muscle voltage gated sodium channel gene
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Survey
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	System organ class
STA	Single technology appraisal
TTO	Time trade off
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organization
WTP	Willingness-to-pay

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the scope is: Adults with non-dystrophic myotonic disorders requiring treatment of symptomatic myotonia. The population in the CS is the same; therefore, the population is in line with the scope. However, there is no specific definition for patients 'requiring treatment of symptomatic myotonia'. According to the European Medicines Agency (EMA) in its assessment of NaMuscla "only patients with severe enough myotonia were included in the MYOMEX study", but this "does not necessarily mean these patients suffered from "severe myotonia"; rather, they have clinical symptoms of myotonia that are severe enough to justify treatment with NaMuscla.". In addition, there is no generally recognised and agreed upon definition of myotonia severity according to the company.

No results for mexiletine are presented for patients over 68 years and the number of patients over the age of 65 in the UK is not known according to the company. Therefore, it is unclear whether the trial populations are representative for the UK patient population.

The intervention (mexiletine) is in line with the scope. However, the dosage and administration of mexiletine in UK practice is not the same as in the MYOMEX trial (see Section 3.2 of this report).

The description of the comparators in the NICE scope is as follows: "Established clinical management without mexiletine, including but not limited to: lamotrigine or best support care". The company included only one comparator (best supportive care). This was considered the same as the placebo arms in the trials. Lamotrigine was not included as a comparator.

1.2 Summary of the key issues in the clinical effectiveness evidence

A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The CS provided sufficient details for the Evidence Review Group (ERG) to appraise the literature searches. A good range of database and conference proceedings was searched, including additional grey literature resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

The company identified three randomised clinical trials which evaluated mexiletine and one retrospective review of a UK centre patient database:

- MYOMEX: A double blind, cross-over randomised controlled trial (RCT) (N=26), comparing mexiletine 600 mg/day with placebo, with a duration of 18 days, performed in 2011 to 2014 in France;
- Statland (2012): A double blind, cross-over RCT (N=59), comparing mexiletine 600 mg/day with placebo, with a duration of four weeks, performed in 2008 to 2011 in the USA, Canada, UK, and Italy;
- Stunnenberg (2018): Aggregated, randomised, N-of-1 trials (N=30), comparing mexiletine 600 mg/day with placebo, with a duration of four weeks, performed in 2014 to 2015 in the Netherlands;
- Suetterlin (2015): A retrospective review (N=63), comparing mexiletine up to 600 mg/day with best supportive care; mean length of follow-up: 4.8 years (range: 0.5 to 17.8), performed in the UK.

The four included studies had different designs; therefore, it is not advisable to pool results of individual mexiletine studies (see Section 4.2.4 of the report for details). Patient level data was available solely for the MYOMEX study, and the company described this study as the pivotal study. Therefore, results in

this section will focus on the MYOMEX study. Full results of all studies are reported in Section 4.2.5 of this report.

The MYOMEX trial reported favourable results with mexiletine compared with placebo for the primary outcome of stiffness and secondary outcomes of the time taken to complete a chair test, Clinical global impression (CGI), Clinical myotonia rating scale (CMS) scores and most quality of life domains as measured with the Individualized neuromuscular quality of life (INQoL) tool. This was a crossover trial so each patient received both mexiletine and placebo in a randomised order and the analysis was performed on the within person change from baseline. Patients could have previously received mexiletine treatment and at baseline [redacted] of patients had previously been treated or were treated at screening. Even though the trial was double-blind it is quite likely that, as each patient received both treatments, those who had previously received mexiletine were able to recognise when they were receiving it during the trial particularly if they had previously experienced side effects. If patients can identify which treatment they are taking in each period, the trial is at risk of over-reporting the effectiveness of the intervention.

The results of the analysis of period 1 only, do confirm the analysis of the whole trial period but it should be noted that this was a very small trial, of only 25 patients, and each treatment was received for between 18 and 22 days with a wash-out period of four to eight days.

Although stiffness was the primary efficacy outcome in the MYOMEX trial, it was not used as a measure of effectiveness in the economic model. Treatment effectiveness in the economic model was based on change in health-related quality of life and assessed using eight items from the INQoL scale. The mapping of INQoL items to the appropriate EQ-5D domains is explained by the company in Table 17 of the Response to Clarification and the results for these eight items are presented in Table 18 of the Response to Clarification. The company seems to have used the items most relevant to patient physical functioning. Results of the eight items are in accordance with the other items of the INQoL scale.

A major limitation of all included trials is that the treatment duration was very short (between 18 days and four weeks).

Mexiletine was generally well tolerated in the included studies. Gastrointestinal discomfort was the most common adverse event, and there were no treatment-related serious adverse events.

The company provided a feasibility assessment for conducting an indirect or mixed treatment assessment of mexiletine vs. lamotrigine. In addition to the three mexiletine RCTs described above, the company identified one trial evaluating lamotrigine: Anderson (2017). This is a double blind, eight-week cross-over RCT comparing lamotrigine with placebo. The study was conducted between 2013 and 2015 in Denmark and published in 2017; it included 26 patients. The ERG agrees with the company that there are serious limitations to performing an indirect comparison of mexiletine vs. lamotrigine due to differences in study designs and outcomes reported.

1.3 Summary of the key issues in the cost effectiveness evidence

A single search was undertaken for cost effectiveness, costs and healthcare resource studies, and a separate search was conducted for health-related quality of life (HRQoL) data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings was searched, including additional grey literature resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

The systematic literature review did not identify any relevant evidence and therefore the company developed a de-novo model comparing mexiletine to best supportive care (BSC) in non-dystrophic myotonic (NDM) patients. A lack of evidence on the natural history of the condition led the company to develop a simplistic three state Markov model, where patients could either be alive on treatment (AOT) with mexiletine, alive with no treatment (ANT), where they receive only BSC, or dead. Therefore, patients in the comparator group begin the model in the ANT state and remain there until death. Similarly, patients who discontinue from mexiletine remain in BSC until death, with no subsequent lines of pharmacotherapy considered. This treatment-status focussed model is not able to describe the long-term disease state of patients and leads to a heterogeneous group of patients being assigned the same costs and quality of life. Instead, a more granulated disease model would be preferred, where each health state is fairly homogeneous with regards to costs and quality of life. However, given the lack of data available, the current model structure is difficult to improve on and is considered acceptable.

The baseline patient characteristics applied in the model were based on the patient characteristics from the MYOMEX trial. It is unclear to the ERG how representative the patients included in the MYOMEX trial are of those patients eligible for mexiletine treatment in UK clinical practice. Evidence cited in the submission states that the age of onset of NDM symptoms is typically in infancy or childhood. Therefore, the average baseline age of 44 from the MYOMEX trial might not reflect the average age of patients eligible for mexiletine in clinical practice. Additionally, the ERG is uncertain whether the eligibility criteria used in the MYOMEX trial would be reflective of the disease severity of NDM patients that would be eligible for mexiletine treatment in clinical practice.

Several issues arose regarding interventions and comparators. Firstly, the NICE scope listed lamotrigine as a comparator. However, the company chose to use BSC as the sole comparator. The company excluded the use of lamotrigine as expert opinion elicitation and market research conducted by the company suggested that lamotrigine was not established in clinical practice (received by approximately 3% of patients with NDM). Additionally, lamotrigine is not licensed for this indication and there is a lack of long-term efficacy and safety data or head-to-head evidence with mexiletine in NDM patients. Since it was listed in the final scope as a comparator, the ERG considers that lamotrigine should have been included in the economic model. Therefore, the ERG conducted several exploratory analyses in Section 7, comparing lamotrigine with mexiletine under various assumptions.

Secondly, the company assumed a different dosage for mexiletine in the model than the dosage used in the MYOMEX trial, on which the model efficacy and safety data was based. In the MYOMEX trial, the mexiletine dose was force titrated up to 600 mg daily, at which point efficacy was assessed. However in the company submission, the company assumed a daily dose of 400 mg, as the forced titration would not reflect clinical practice and the 400 mg daily dose was more in line with a UK real world retrospective study from Suetterlin et al., which reported that the mean clinically effective dose of mexiletine used was 416.7 mg daily. However, experts consulted by the company suggested that 400 mg could be considered a minimum dose and given that the efficacy and safety data in the economic model are based on the 600 mg dose, the ERG believe it is inappropriate to cost a lower dose.

Given the assumed lack of impact of mexiletine on survival, the effectiveness of mexiletine in the model was driven by improvements in HRQoL and reductions in health care resource use estimated from the MYOMEX trial. Other clinical inputs implemented in the model were: treatment discontinuation, compliance, mortality and a disease progression differential. In the company base-case treatment compliance was estimated from the MYOMEX trial, while discontinuation was estimated from a study

by Suetterlin et al. The ERG believe it is more appropriate to estimate discontinuation from the MYOMEX study in order to achieve consistency with other efficacy parameters.

In their base-case, the company assumed a disease progression differential of 15%. This was implemented by reducing the HRQoL of patients receiving BSC by 15%, on top of the difference in HRQoL observed between mexiletine and BSC from the MYOMEX trial. This disease progression differential was applied based on the assumption by the company that quality of life in NDM patients decreases over time in the absence of treatment for myotonic symptoms, but that HRQoL would be maintained in patients receiving mexiletine as the treatment would not lose efficacy over time. However, clinical opinion on the long-term progression of NDM and the impact of this on HRQoL was mixed and there was no quantitative evidence for the assumed reduction in HRQoL of 15% in the BSC group on top of the difference in utility observed in MYOMEX and therefore the ERG removed this assumption in their base-case.

The company measured health directly in patients in the MYOMEX trial using the condition-specific Individualized Neuromuscular Quality of Life Questionnaire (INQoL). The company argued that this was the most appropriate measure to use as it was able to best capture the impact of treatment on NDM. However, no psychometric evidence was provided showing that generic measures such as the EQ-5D were invalid or unreliable in this population. No mapping algorithm was available between he INQoL and EQ-5D and the INQoL is not preference based. Therefore, the company had to conduct a valuation study to be able to obtain utility values from the INQoL data collected.

To be amenable for valuation, the INQoL, which contains 45 items each with 6-7 response options, needed to be substantially reduced. The company achieved this by selecting items and response levels which reflected the descriptive system of the EQ-5D, as well as additional items which were considered important to NDM. This reduced the 45 items down to eight items each with four response options included in the valuation exercise. The company presented two separate valuation studies; a discrete choice experiment (DCE), used to value HRQoL in the company base-case, and a vignette study valued using time trade off (TTO) which was given to the ERG just before clarification. Issues were identified for each, as detailed in Section 5.2.8 of this report. However, the ERG believed that the issues in the DCE study were more widespread, including a lack of clear monotonicity in included response options, logical inconsistencies in results, and issues with selecting an appropriate anchor for the DCE results. Therefore, the ERG chose to use the vignette/TTO study to value HRQoL in their base-case.

Regarding resource use and costs, the economic analysis includes drug acquisition costs and cardiac monitoring costs for the AOT health state (i.e. on mexiletine). These costs do not apply for the ANT health state (i.e. on BSC). Furthermore, the cost of genetic testing was included for all patients. To inform further health care costs in the AOT and ANT health states, the company assumed hypothetical associations between levels of resource use and CMS disability scale scores that were categorised as ‘mild’, ‘moderate’, and ‘severe’ for each dimension of disability in patients in MYOMEX that received mexiletine and placebo, respectively. More specifically, patients who experienced problems in handwriting, walking, or ascending/descending stairs were hypothesised to make use of physiotherapy; patients that experienced problems in eating, hygiene, or dressing were hypothesised to make use of occupational health sessions; patients that experienced problems in speech were hypothesised to make use of speech therapy; and patients that experienced problems in walking were hypothesised to make use of mobility aids such as a wheelchair, walking stick and walking frame. Day case attendance was hypothesised to be associated with the categorisations of severity of disability in any of the dimensions of disability mentioned above. In the original company submission (CS), an additional ‘health care resource use multiplier’ of three was used for patients in the ANT health state (i.e. on BSC). This was

justified based on a discrepancy between the opinions of patients and those of clinical experts who typically only see patients once a year. The ERG discarded this threefold multiplication of health care costs in the ANT health state for their preferred base-case as the ERG was not convinced of the plausibility of ANT health care costs being a multiple of the initial estimates, whilst noting that the value of three lacked any foundation.

In general, the key issue in the cost effectiveness analysis was the lack of robust long-term data on both the natural history of NDM and the efficacy and safety of mexiletine and other comparators. This lack of data prohibited the development of a model which could reflect the long-term efficacy of treatment and progression of disease, which could have provided a much clearer estimate of the cost effectiveness of mexiletine compared to relevant comparators. The lack of data also meant many assumptions were used in the submission which could not be substantiated by evidence. This means that important areas of uncertainty remain within the results which cannot be resolved using the current evidence base.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions are described in detail in section 7.1.2 of this report and summarised below:

1. Using utilities calculated from the vignette/TTO study.
2. Incorporating age-adjustment of utilities.
3. Using treatment discontinuation and compliance from the MYOMEX trial.
4. Using adverse events (AE) rates from MYOMEX, including all AEs and not only GI.
5. Assuming no disease progression differential for BSC.
6. Assuming a mexiletine dose in line with the MYOMEX trial (600 mg per day).
7. Assuming no additional multiplier for resource use.

The cost effectiveness results of the ERG preferred base-case are presented in Table 1.1. The assumptions which had the largest impacts on the incremental cost effectiveness ratio (ICER) were the adoption of the mexiletine dosage from the MYOMEX trial and the use of utilities calculated from the vignette/TTO study rather than the DCE study. The base-case ICER (including the patient access scheme (PAS)) in the company submission was [redacted]. The ICER (including the PAS) based on the ERG's preferred assumptions is [redacted].

Table 1.1: ICER resulting from ERG's preferred assumption

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]				

Source: Based on the economic model, updated from the response to the clarification letter.
BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALY = quality-adjusted life year

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG also conducted a probabilistic sensitivity analysis (PSA) and a one-way deterministic sensitivity analysis (DSA) on their preferred base-case assumptions. The probabilistic ICER was [redacted], which was slightly lower, but in line with the deterministic ICER. The majority of simulations ([redacted]) fell in the north-east quadrant of the cost effectiveness plane, with the remaining simulations all falling in the north-west quadrant, where BSC dominates mexiletine. The cost effectiveness acceptability curve

showed that at thresholds of £20,000 and £30,000, the probability that mexiletine is cost effective is [redacted] and [redacted] respectively. The results of the DSA showed that the parameters which have the largest impact on model results are the two utility values (mexiletine alive on treatment and best supportive care alive off treatment), followed by the mexiletine maintenance dose, compliance rate and the assumed disease progression differential.

The ERG considered that there were still key areas (mostly structural) of uncertainty in the model which had not been fully examined within the scenario analyses performed by the company. Therefore, the ERG conducted additional scenarios on parameters which had been shown to have a substantial impact on results or where evidence was lacking. The results of the ERG scenarios, displayed in Table 1.2, show that the model is most sensitive to the exploratory scenario where lamotrigine is considered as the comparator to mexiletine. Due to a lack of direct head-to-head data considering the efficacy and safety of mexiletine compared to lamotrigine in this population, this exploratory scenario assumed the same AE profile, compliance and discontinuation for lamotrigine as mexiletine, while the cost of lamotrigine was identified from the British National Formulary (BNF). Within the scenario various utility values for lamotrigine were examined, which varied between assuming that patients on lamotrigine would have the same utility as patients on BSC and the same utility as patients on mexiletine. Assuming the same utility as BSC for lamotrigine resulted in an ICER of [redacted] for mexiletine compared to lamotrigine, while assuming equivalent utilities between the treatment groups led to an equal amount of QALYs accumulated, but with lamotrigine being cheaper. The other scenarios which were found to have a substantial impact on the ICER were the valuation method to derive the utility values in the model and the assumed dosage of mexiletine.

Table 1.2: Exploratory analyses undertaken by the ERG

Scenario	Section in main ERG report	Mexiletine		BSC		ICER £/QALY
		Costs	QALYs	Costs	QALYs	
Utility values						
DCE (bottom anchor 33333) (Company BC)	7.2.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCE bottom anchor (bottom anchor 23233)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCE bottom anchor (23333)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignettes (ERG BC)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age-adjustment of utilities						
No age adjustment (company BC)	7.2.2.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Equal adjustment both treatments (ERG BC)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier method		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Section in main ERG report	Mexiletine		BSC		ICER £/QALY
		Costs	QALYs	Costs	QALYs	
Utility value of lamotrigine as the comparator (instead of BSC)						
[redacted]	7.2.2.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression differential						
0% (ERG BC)	7.2.2.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5%		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10%		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15% (Company BC)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Healthcare resource use multiplier						
1 (ERG BC)	7.2.2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 (Company BC)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mexiletine dosage						
500 mg (ERG BC)	7.2.2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
333 mg (Company BC)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.
BC = base-case, BSC = best supportive care, DCE = discrete choice experiment; ERG = Evidence Review Group, ICER = incremental cost effectiveness ratio, mex = mexiletine; QALY = quality adjusted life year

2. BACKGROUND

2.1 Critique of company's description of underlying health problem

The company submission (CS) details non-dystrophic myotonia (NDM) and related sub-classifications based on the affected pathway, which differentiate between sodium channelopathies and chloride channelopathies.[1, 2] Common features of NDM are observed as delayed muscle relaxation following a muscle contraction or mechanical stimulation.[2] This delayed muscle relaxation is often characterised by patients as 'stiffness'.[3] The CS notes the most common of NDMs as myotonia congenita (MC). Patients with MC are most symptomatic during rapid voluntary movements following a period of rest.[2, 3]

According to the CS, the prevalence of NDM in England is estimated at 0.75 per 100,000.[2, 4] This equates to 330 adults with NDM in England. The company was unable to provide information regarding NDM incidence.

The company describes the clinical presentation of myotonia, noting the experienced muscle stiffness is caused by genes coding for skeletal ion channels.[2] Myotonia location and severity are noted to differ between clinical phenotypes of NDM.[2] The CS notes that NDM symptoms typically develop during infancy or childhood, as well as during adulthood.[2] The symptoms typically experienced in patients with muscular expressed, pathogenic channelopathies includes muscle stiffness, pain, muscle weakness, fatigue, the inability to relax a tight grip, difficulty with standing or sitting, or are unable to walk fast when needed.[2, 5-8] A myotonic attack can last for a length of time ranging from a few seconds to minutes.[2, 6, 9] The CS provides an example of the potential impact of the condition in the event of swallowing difficulties can increase likelihood of aspiration, which could increase the risk of pneumonia.[2] The company emphasises that the unpredictability of the condition has an impact on patients and their families.[2]

The CS states the diagnosis of NDMs involve an assessment of symptoms, a medical history, a muscle hypertrophy assessment, an examination of the patient and family members, electrodiagnostic testing, and laboratory and genetic testing.[2] The company notes patients often experience delays in seeking help for symptoms and obtaining a diagnosis.[2] The CS notes the time to receive a diagnosis ranged from eight to 12 years, with less than 30% of patients receiving a diagnosis within five years.[6, 10] This can create additional costs to the National Health Service (NHS).[2]

According to the CS, NDM does not affect survival, a significant impact on health-related quality of life (HRQoL) is noted.[2] The company states the evidence is limited regarding NDM patients having a reduced life-expectancy when compared to the general population. However, the symptoms have been noted to impact daily living and mental health.[2] The primary goal of treatment is noted to focus on reducing the involuntary muscle action's potential bursts without blocking the voluntary muscle movement.[2] A component of symptom management is identified as trigger avoidance.[2] Common triggers include cold temperature, stressful situations, and places where there may be stairs.[2] The CS notes that the avoidance of such triggers may be logical, but trigger avoidance may not always be possible.[2] Trigger avoidance is stated to be a component of best supportive care (BSC).[2] The CS emphasises the disability rates in NDM are high and impact daily living, resulting in patients being limited in terms of independence.[2]

ERG comment: The ERG considers the company to have provided an appropriate description of the underlying health problem for this appraisal.

2.2 Critique of company's overview of current service provision

The company states there are no guidelines regarding NDM management or international treatment guidelines.[11] The CS noted that the diagnosis is based on clinical evaluation along with a genetic diagnosis.[2] Afterwards, mexiletine is administered by a neurologist after patient discussion. The patient's symptoms are often considered to be severe enough that avoidance of triggers will no longer be sufficient at this stage.[2] The CS noted that mexiletine is listed as a first-choice treatment from the German Society of Neurology S1 guidelines, the National Hospital for Neurology and Neurosurgery (NHNN) website, Queens Square Centre for Neuromuscular Diseases, London, and based on the advice of clinical experts.[12-14]

The CS reiterated that, despite a statement in the NICE Final Scope that lamotrigine is the most used alternative treatment, it is not considered part of standard care and is not an established treatment in clinical practice in England and Wales.[2, 15] According to market research performed by the company, lamotrigine is not established in practice with less than 3% of patients currently on or having ever received lamotrigine.[16] Therefore, lamotrigine was determined not to be a relevant comparator by the company.

The company did not provide a clear description in the CS of the clinical pathway for NDM patients into which mexiletine might fit. Therefore, we asked the company to provide an outline of such a clinical pathway. In their response to clarification, the company stated that "mexiletine is recognised as a well-established first line choice treatment for Non-Dystrophic Myotonia (NDM) in the UK", and mexiletine "is the first and only licensed medicine."[1] In accordance with the Medicines and Healthcare products Regulatory Agency (MHRA) guidance note 14,[17] mexiletine should be used ahead of any other off licence therapies.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with non-dystrophic myotonic (NDM) disorders requiring treatment of symptomatic myotonia.	As per scope. It is estimated that 50-70% of patients are symptomatic and require treatment,[18] see Appendix M of the CS.	Not applicable	The population is in line with the NICE scope.
Intervention	Mexiletine	Mexiletine	Not applicable	The intervention is in line with the NICE scope. However, the dosage and administration of mexiletine in UK practice and in the economic model is not the same as in the MYOMEX trial.
Comparator(s)	Established clinical management without mexiletine, including but not limited to: • Lamotrigine • Best supportive care	Established clinical management without mexiletine, is placebo (i.e. no treatment) in the base case. Best supportive care is assumed to be received by all patients by the time they require treatment with mexiletine and, according to the NICE Final Scope, include physiotherapy, lifestyle adaptations, mobility aids and occupational assistance. Resource use data in NDM is not available, however, patients in the MYOMEX study were	We agree with the NICE Final Scope that lamotrigine is one of a number of antiarrhythmic and antiepileptic medicines that have been used off-label for the pharmacological treatment of NDM. However, it is not assessed in the base case for the following reasons: • Lamotrigine is not an established treatment in clinical practice in England and Wales. Lupin conducted market research following the Decision Problem meeting with NICE involving eight neurology centres in the England and Wales,	The company included only one comparator, i.e. best supportive care. This was considered the same as the placebo arms in the trials. Lamotrigine was not included as a comparator. In the response to comments on the draft scope,[23] NICE stated that "The marketing authorisation for mexiletine does not specify its use as a first line treatment. During

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		asked to continue with their usual care whilst in the trial. Therefore, it can be assumed that usual care for the study population was best supportive care. It should be noted that best supportive care includes coping strategies developed by patients, regardless of treatment choice, as illustrated in discussions with patients and clinicians (Appendix L and M of the CS) and.[10]	including the National Hospital for Neurology and Neurosurgery (NHNN), Queens Square Centre for Neuromuscular Diseases, London) in November 2019. This showed that lamotrigine is not established in practice with less than 3% of patients currently on or having ever received lamotrigine.[16] In addition, a UK patient survey of 27 NDM patients conducted in November 2019 demonstrated only 4.2% of patients (1 responder) had ever been prescribed lamotrigine,[10] supporting the market research findings that lamotrigine is not established practice in the NHS – see Section B.1.3.7. • Mexiletine is the first-choice treatment – and the most widely used – treatment for myotonic symptoms in NDM patients. • Lamotrigine is not licensed for the indication in this submission in the UK or any other country and no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients. • Lamotrigine is not recommended as first-choice in any guidance[12, 19-21] and when mentioned, listed solely as second-choice therapy – for use	the consultation and workshop, it was noted that lamotrigine is increasingly used as an alternative to mexiletine. The comparators section has been updated to account for this." Therefore, NICE considers lamotrigine a relevant comparator for this appraisal, and it should have been included in the CS.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
			when mexiletine is either contraindicated, ineffective or not tolerated. • There are no randomised/ non-randomised clinical trials, that assess the impact of lamotrigine in comparison with established first-choice treatment for symptoms of myotonia in NDM patients. • The only available evidence for lamotrigine is a recent RCT by Andersen et al which was conducted between 2013 and 2015 and published in 2017. Despite this the market research does not indicate an increase in use in the UK since that could at all suggest established use in the NHS.[22] This trial also lacks common outcome measures and results to enable any indirect treatment comparison with mexiletine NDM RCTs. Some endpoints such as SF-36 were also incomplete and possibly inaccurately reported – this is described in more detail in Section 2.9.1. Efforts were made to contact the lamotrigine trial and other two mexiletine trial authors (Statland et al and Stunnenberg et al) to obtain patient level data but without success.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Outcomes	The outcome measures to be considered include: • muscular symptoms (including stiffness and weakness) • fatigue • motor function • pain • adverse effects of treatment • health-related quality of life.	The outcomes presented listed in the scope are presented where results are available for these outcomes.		The outcomes reported are in line with the NICE scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The economic modelling should include the costs associated with genetic testing for mutations in CLCN-1 and SCN4A gene coding in people	Cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year in this study. The time horizon is lifetime. Costs are considered from an NHS and Personal Social Services perspective. Cost of genetic testing for mutations in CLCN-1 and SCN4A gene coding will be considered, according to the assumption that not all patients currently receiving unlicensed mexiletine are genetically confirmed with NDM. This cost will be added to the first year only to address this.	Genetic testing is already provided as a highly specialised service by the National Hospital for Neurology and Neurosurgery (NHNN), Queens Square Centre for Neuromuscular Diseases – a part of University College London and the national diagnostic centre for NDM. Thus, the infrastructure is already in place for the diagnosis of NDM and funded by NHS England. The economic model includes the costs associated with genetic testing for mutations in CLCN-1 and SCN4A gene coding in people with myotonic disorders in the base case. This cost is removed in scenario analysis. The eligible population are diagnosed NDM patients and the availability of NaMuscla will not drive diagnosis. Only diagnosed patients, as per NHS	The economic analysis is in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	with myotonic disorders who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals		England Standard Contract,[20] are currently offered the option for treatment if symptoms impact quality of life. By this stage patient's symptoms are likely to be severe enough that any strategies they have developed to cope with their condition such as avoiding triggers or performing muscle warming routines (effectively best supportive care) will not be sufficient and the patient may benefit from treatment. Hence, there is no evidence that the rate of diagnosis will change and market research carried out by Lupin that confirms 87% of patients with NDM have been tested.[16] For these reasons, cost of genetic testing need not be accounted for, but it has been done to satisfy the NICE scope.	
Subgroups to be considered	Not addressed in CS			
Special considerations including issues related to equity or equality	Not addressed in CS			

Source: CS, Table 1, pages 9-13.

CLCN1 = Skeletal muscle voltage gated chloride channel gene; NDM = Non-dystrophic myotonia; NHNN = National Hospital for Neurology and Neurosurgery; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SCN4A = Skeletal muscle voltage gated sodium channel gene.

3.1 Population

The population defined in the scope is: Adults with non-dystrophic myotonic disorders requiring treatment of symptomatic myotonia.[15] The population in the CS is the same; therefore, the population is in line with the scope.[1]

The population considered in the CS is in line with the clinical trials for mexiletine, and with the marketing authorisation for mexiletine. Mexiletine was granted marketing authorisation by the European Medicines Agency (EMA) on 18 December 2018.[24] The marketing authorisation is for the 'symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders'. In the response to comments on the draft scope,[23] NICE commented that it was noted in the comments received at consultation and discussion at the scoping workshop that only people with symptomatic myotonia would be treated and it was agreed that this should be represented in the population wording.

Regarding the definition of 'requiring treatment of symptomatic myotonia', we asked the company how this definition was derived. In response to the clarification letter (Question A4),[25] the company stated that the MYOMEX study was sponsored and conducted by the Assistance Publique Hôpitaux de Paris. Patients were recruited from six centres in France. Inclusion criteria in the MYOMEX study included a clinician-based decision about the need to treat, based on the vast experience of the sponsor and its hospital network, as a leading voice in Europe and the world, of treating NDM patients with mexiletine. Therefore, there is no specific definition for patients 'requiring treatment of symptomatic myotonia'. In addition, the company said that the EMA in its assessment of NaMuscla stated "only patients with severe enough myotonia were included in the MYOMEX study";[24] and that this "does not necessarily mean these patients suffered from "severe myotonia"; rather, they have clinical symptoms of myotonia that are severe enough to justify treatment with NaMuscla. There is no generally recognised and agreed upon definition of myotonia severity (Appendices L & M of CS); symptoms may show a high inter- and intraindividual variability. Clinical findings span a continuum from mild to severe, not only between individuals but also, within the same patient, from day to day and even within the same day, depending on factors such as the outside temperature, the level of physical activities, stress, and the diet. Only patients with myotonia symptoms interfering with their daily life will receive treatment which was accepted by the EMA."[25]

Two of the three included mexiletine trials (MYOMEX[18] and Stunnenberg et al. (2018)[26]) included patients aged between 18 and 65 years. In Statland et al. (2012)[27] patients were aged between 16 and 68 years. Therefore, no results for mexiletine are presented for patients over 68 years. In response to the clarification letter, the company stated that "mexiletine has been used for many years as a treatment for NDM patients, and we have not identified anything in the literature that has reported a concern for use in older patients.".[25]

We asked the company what percentage of non-dystrophic myotonia (NDM) disorder patients in the UK are 65 years or older. The company responded that "there is no published natural history set of patients in the UK to refer to which might indicate the number of patients over the age of 65" (Response to clarification, Question A5b).[25] Therefore, it is unclear whether the trial populations are representative for the UK patient population.

3.2 Intervention

The intervention (mexiletine) is in line with the scope.

According to the company,[1] mexiletine blocks channels in muscle cells which allow sodium ions (electrically charged particles) to pass in and out of the cell. Mexiletine blocks sodium channels with a

stronger potency in situations of excessive burst of action potentials (use-dependent block) and/or prolonged depolarization (voltage-dependent block), as occurring in diseased tissues, rather than on physiological excitability (resting or tonic block).[28] These sodium channels play a role in the contraction and relaxation of muscles and are hyperactive in patients with myotonic disorders, causing excessive contractions and stiffness. By blocking these channels, mexiletine reduces the stiffness that occurs when these excessive contractions are prolonged.[24] Mexiletine is, therefore, mostly active on muscle fibres subject to repeated discharges (such as skeletal muscles). It improves myotonic symptoms by decreasing muscle stiffness through reduction of the delay of muscle relaxation);[28] i.e. it reduces the rate of contractions and hence the associated stiffness.

Mexiletine is administered orally. The recommended starting dose, as stated in the summary of product characteristics (SmPC),[29] is one capsule of 167 mg mexiletine base per day (equal to 200 mg mexiletine hydrochloride). Patients are dose titrated up, according to clinical response, after at least one week of treatment, to a daily dose of 333 mg mexiletine daily (i.e. two capsules per day or equivalent to 400 mg mexiletine hydrochloride). After at least one further week of treatment, the dose can be further increased to 500 mg daily (three capsules per day or equivalent to 600 mg mexiletine hydrochloride) based on clinical response. Hence, maintenance dosage is according to the intensity of a patient's symptoms and clinical response can be achieved between a daily dose of 167 mg and 500 mg (i.e. one to three capsules per day). Mexiletine is taken regularly, on a daily basis, to address patient symptoms.[28]

Mexiletine has been used clinically in the UK for at least 10 years and already forms part of the standard of care for the treatment of non-dystrophic myotonia.

ERG comment: Although the intervention (mexiletine) is in line with the scope, the dosage and administration of mexiletine in UK practice is not the same as in the MYOMEX trial. The dosage and administration of mexiletine in UK practice is described above. In the MYOMEX trial mexiletine was started at 200 mg/day (one capsule to be taken at the beginning of the meal) and increased by 200 mg every three days to reach a maximum of 600 mg/day comprised of three capsules taken in one week. Therefore, all patients in the trial received the maximum dose of 600 mg/day, which was achieved within one week; while NDM patients in UK practice receive a maintenance dose which is in accordance with the intensity of a patient's symptoms and clinical response (usually somewhere between 400 and 600 mg/day); and this maintenance dose is achieved within two weeks, rather than one week. In the economic model, a maintenance dose of 400 mg/day was assumed in the company's base-case, with the same effectiveness (impact on QoL) as observed in the trial.

3.3 Comparators

The description of the comparators in the NICE scope is as follows: "Established clinical management without mexiletine, including but not limited to: lamotrigine or best support care".[15]

The company included only one comparator, i.e. best supportive care. This was considered the same as the placebo arms in the trials.

Lamotrigine was not included as a comparator. In the response to comments on the draft scope,[23] NICE stated that "The marketing authorisation for mexiletine does not specify its use as a first-line treatment. During the consultation and workshop, it was noted that lamotrigine is increasingly used as an alternative to mexiletine. The comparators section has been updated to account for this." Therefore, NICE considers lamotrigine a relevant comparator for this appraisal, and it should have been included in the CS.

The company argues that lamotrigine is not an established treatment in clinical practice in England and Wales, with less than 3% of patients currently on or having ever received lamotrigine.[16] In addition, the company states that there are no randomised/non-randomised clinical trials that assess the impact of lamotrigine in comparison with established first-choice treatment for symptoms of myotonia in NDM patients.[1]

ERG comment: Because NICE has clearly stated that lamotrigine is a relevant comparator for this appraisal, it should have been included in the CS. The feasibility of an indirect comparison of mexiletine versus lamotrigine will be discussed in Sections 4.3 and 4.4 of this report.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- muscular symptoms (including stiffness and weakness)
- fatigue
- motor function
- pain
- adverse effects of treatment
- health-related quality of life.

These were all assessed in the trials included in the CS. However, although all three trials assessed stiffness as their primary outcome, different instruments were used to assess the outcome.

3.5 Other relevant factors

According to the company, mexiletine is innovative because it represents the first licensed medicine for NDM that brings access for patients to a highly effective treatment which can dramatically improve HRQoL (CS, Section B.2.12, page 110). However, as stated above, mexiletine has been used clinically in the UK for at least 10 years and already forms part of the standard of care for the treatment of non-dystrophic myotonia; as such it cannot be described as an original or new idea.

A simple discount Patient Access Scheme (PAS) has been submitted to PASLU and NHS England. The PAS discount reported in the CS is equal to [redacted] of the list price for mexiletine (CS, Table 59, Section B.3.5.1, page 148).

According to the company, mexiletine for the treatment of NDM does not meet the criteria for 'life-extending treatment at the end of life' (CS, Section B.2.13.3, page 118).

According to the company, no issues have been identified regarding equality. (CS, Section B.1.4, page 32).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D.1.1 of the CS details a systematic search performed to identify studies investigating the clinical effects and safety of mexiletine for the treatment of adult patients with non-dystrophic myotonia (NDM). Searches were conducted in October 2019, and no language or publication date limits were reported. Databases were searched from date of inception. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

	Resource	Host/Source	Date range	Date searched
Electronic databases	MEDLINE (including MEDLINE daily, MEDLINE ePub ahead of print, MEDLINE In-Process)	Ovid	1946-8.10.19	9.10.19
	Embase	Ovid	1974-8.10.19	9.10.19
	Cochrane CENTRAL	Wiley	Issue 10/12, October 2019	9.10.19
	Cochrane CDSR			
	DARE, NHS EED, HTA	CRD website	All years	15.10.19
Conference proceedings	Annual Meeting of the American Academy of Neurology	Embase/ handsearch	2015-2019	Not reported
	European Neurology Congress	Handsearch	2016-2019	
	World Congress of Neurology	Embase / handsearch	2015, 2017	
	World Muscle Society Congress	Embase / handsearch	2015-2018	
Additional resources	ClinicalTrials.gov	Web search	All years	16.10.19
	Clinicaltrialsregister.eu			
	WHO ICTRP			
	NICE			
	SMC			
	AWSMG			

CENTRAL = Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstract Reviews of Effects; NHS EED = NHS Economic Evaluation Database; HTA = Health Technology Assessment database; WHO ICTRP = WHO International Clinical Trials Registry Platform; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; AWMSG = All Wales Medicines Strategy Group

ERG comment: A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature

resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs are presented in Table 4.2.

Table 4.2: Eligibility criteria used in the clinical and safety review

	Inclusion	Exclusion
Population	Adults with non-dystrophic myotonic disorders requiring treatment of symptomatic myotonia. Adult patients with the following sub-types of NDM will also be eligible for inclusion: • Recessive myotonia congenita (also known as Becker disease) • Dominant myotonia congenita (also known as Thomsen disease or myotonia levior) • Paramyotonia congenita (also known as Eulenburg disease or paralysis periodica paramyotonica) • Sodium channel myotonia (also known as potassium-aggravated myotonia, hyperkalaemia periodic paralysis with myotonia, myotonia fluctuans and myotonia permanens, acetazolamide-responsive myotonia)	• Studies in children will not be eligible • Adult patients diagnosed with myotonia which is not NDM, such as patients with unspecified myotonic dystrophy (DM) will also be excluded
Intervention	• Mexiletine (including all brand names, for example Namuscla®, Mexitil®) • Lamotrigine (including all brand names, for example Lamictal®)	Any other treatment
Comparators	• Placebo/no intervention • Other drug therapy, including lamotrigine • The use of other best supportive care interventions including physiotherapy, lifestyle adaptations, mobility aids and occupational assistance	Any other treatment
Outcomes	Clinical efficacy or effectiveness, including, but not limited to: • Muscular symptoms (including stiffness, weakness and wasting) • Fatigue • Motor function • Exercise capacity • Pain • Adherence and compliance Safety • Adverse effects of treatment • Mortality	Any other outcomes
Study design	• Randomised controlled trials	• Animal studies

		• In-vitro studies • Editorials • Reviews • Letters • Comments • Notes • Erratum • Case studies or case series • Non-randomised controlled studies, including case-control and controlled prospective studies • Non-controlled studies Systematic literature reviews will be included at the abstract review stage, for handsearching of the reference lists, then excluded as primary publications.
Geographical location	No restriction	No restriction
Language	No restriction	No restriction
Publication date	No restriction; any study date	No restriction
Source: Table 8, Appendix D of the CS.[1] NDM = Non-dystrophic myotonia		

ERG comment: According to the inclusion criteria only randomised controlled trials (RCTs) were included. However, the CS mentions that "one retrospective review of a UK centre patient database was identified during the SLR sifting process" (CS, page 33).[1] It is not clear from the CS whether this was based on a systematic search, or a random find. Therefore, we asked the company whether any other relevant observational studies might be available in addition to this study (Clarification Letter, Question A3).[25] The company responded that the retrospective study by Suetterlin et al (2015)[30] is "the most relevant clinical effectiveness evidence source and provided as a significant supportive study in the assessment by the EMA for NaMuscla for the treatment of NDM patients".[25] In addition, the company mentioned the MYOMEX follow-up data[31] reported in the CS, and one other supportive study in the assessment by the EMA which focused on NDM patients, an uncontrolled prospective, open-label study by Monaco et al. (2015).[32] The ERG agrees that uncontrolled prospective, open-label study by Monaco et al. (2015) is less relevant for this appraisal.

4.1.3 Critique of data extraction

Data extraction was completed by two reviewers. One reviewer extracted the data, while the second reviewer checked the extraction. This was considered adequate.

4.1.4 Quality assessment

Quality assessment was completed using the "Revised Cochrane risk of bias tool for randomised trials (RoB 2.0) – Additional considerations for cross-over trials". For the focused N-of-1 trial a quality assessment was completed using the CENT 2015 checklist, which is a modified version of the CONSORT 2010 checklist.

ERG comment: The ERG agrees with the company's quality assessment, with one exception. For all trials blinding was considered inadequate because even though participants, physicians and evaluators

were blinded, there were a number of patients who were taking mexiletine at baseline, and therefore could potentially recognise the side effects of this drug. This is confirmed by the finding in the Statland (2012) trial,[27] where 79% of patients guessed correctly in the second period that they were taking mexiletine, and 80% of patients guessed correctly in the second period that they were taking placebo; indicating that the trial was no longer effectively blinded and patient responses may have been affected by the knowledge of which treatment was being received (see also Section 4.2.5 of this report).

4.1.5 Evidence synthesis

The company concluded that a meta-analysis of the mexiletine trials was not feasible and that any results would be highly uncertain; this is described in Section B.2.8 of the CS.

ERG comment: The ERG agrees that due to differences in study designs, treatment durations, patient populations, definitions of outcomes, and the results reported by the trials, it is not advisable to pool results of individual mexiletine studies.

Regarding the feasibility of an indirect comparison of mexiletine versus lamotrigine, the company starts by stating that they do not believe that lamotrigine is a relevant or appropriate comparator as specified in the NICE Final Scope (see also Section 3.3 of this report). However, they go on to describe the feasibility of such an indirect comparison. A critique of this feasibility study is presented in Sections 4.3 and 4.4 of this report.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

The company identified three randomised clinical trials which evaluated mexiletine and one retrospective review of a UK centre patient database. The studies are described in Table 4.3.

Table 4.3: Mexiletine studies included in the company submission

Study	MYOMEX 2017[18]	Statland 2012[27]	Stunnenberg 2018[26]	Suetterlin 2015[30]
Design (N)	Double blind, cross-over RCT (N=26)	Double blind, cross-over RCT (N=59)	Aggregated, randomised, N-of-1 trials[1] (N=30)	Retrospective review (N=63)
Intervention	Mexiletine 600mg/day	Mexiletine 600mg/day	Mexiletine 600mg/day	Mexiletine up to 600mg/day
Comparator	Placebo	Placebo	Placebo	Best supportive care
Treatment duration	18 days	4 weeks	4 weeks	Mean length of follow-up: 4.8 yrs (range: 0.5 to 17.8)
Trial conduct period	2011-2014	2008-2011	2014-2015	Not reported
Countries	France	USA, Canada, UK, Italy	Netherlands	UK

Source: CS, Table 36, page 94-95; CS, Table 7, page 38 and Suetterlin 2015[30]
Notes: [1]) Aggregated series of N-of-1 trials, multiple periods per patient.

4.2.2 Methodology of the included studies

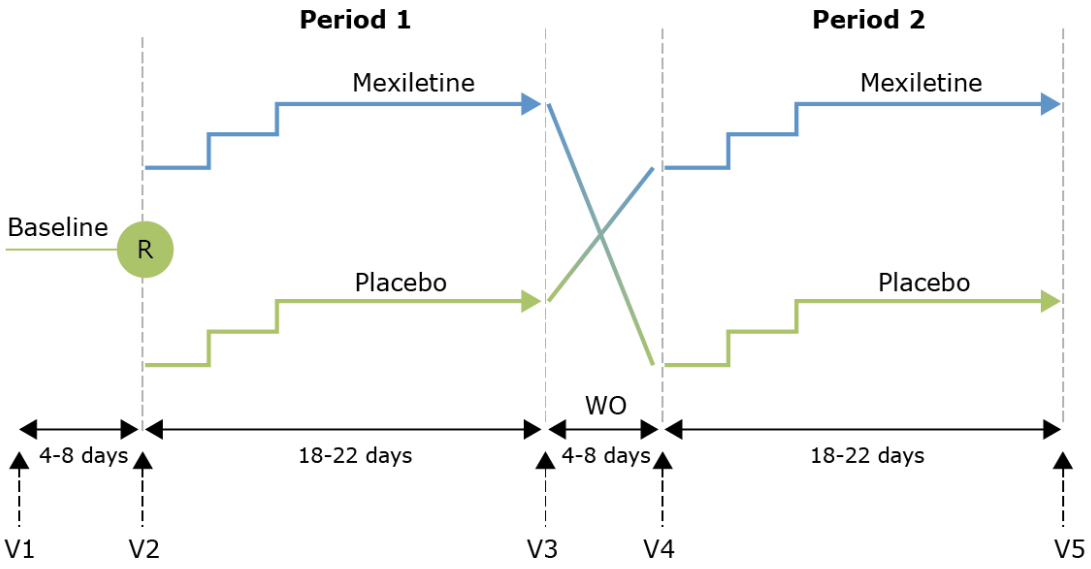
MYOMEX study (NCT02336477)[18]

MYOMEX was a multi-centre, randomised, double-blind, placebo-controlled, crossover (two treatment periods of 18 days), phase III study to evaluate the efficacy and safety of mexiletine for the symptomatic treatment of NDM.

Key inclusion criteria were: Genetically definite myotonia congenita (MC) and paramyotonia congenita (PC); male and female participants, age between 18 and 65 who are able to comply with the study conditions; participants who experience myotonic symptoms severe enough to justify treatment (myotonia that involved at least two body segments (upper limb, lower limb or face) and that had an impact on at least three daily activities). Patients were excluded if they experienced an intercurrent event which could interfere with the muscle function (infection, trauma, fracture); had coincidental renal, hepatic, respiratory, thyroid, other neuromuscular disease or heart disease that would contraindicate mexiletine or interfere with clinical evaluation; used any medications that can interfere with muscle function: diuretics, anti-epileptics (sodium channel blockers), antiarrhythmics, corticosteroids, beta-blockers; or were allergic to mexiletine.

The crossover study design is shown in Figure 4.1. After a baseline period (four–eight days) to eliminate residual mexiletine from any previous treatment, patients were randomised and received either mexiletine or placebo for 18 days (maximum 22 days; period 1). After a wash-out period of at least four days (maximum eight days), patients switched study drug for a period of 18 days (maximum 22 days, period 2). Mexiletine hydrochloride treatment was started at 200 mg per day (equivalent to 167 mg mexiletine) and up titrated in 200 mg increments every three days to reach a maximum total dose of 600 mg mexiletine hydrochloride per day (equivalent to 500 mg mexiletine) in one week, administered as 200 mg mexiletine hydrochloride three times daily (TDS).

Figure 4.1: MYOMEX study design



Source: CS, Figure 10, page 41.
R = randomisation; V1 = screening visit (Day -4); V2 = baseline visit (Day 1; start of Period 1); V3 = visit 3 (Day 18; end of Period 1); V4 = visit 4 (Day 22; start of Period 2); V5 = visit 5 (Day 39; end of Period 2); WO = washout.

The primary efficacy endpoint was the change in stiffness as self-reported by patients on a 100 mm visual analogue scale (VAS) using the endpoints 'no stiffness at all' to 'worst possible stiffness'. The patients' responses were scored on the line to the nearest millimetre (a 100-point scale).

The secondary efficacy endpoints were:

- The percentage of patients with an absolute change from baseline in VAS stiffness score ≥ 50 mm (added after unblinding)
- 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 with the Individualized Neuromuscular Quality of Life (INQoL) scale
- Clinical Global Impression (CGI) Efficacy index
- Preference between the two treatments and willingness to continue the treatment
- Number of intolerable increases in myotonia severity necessitating withdrawal
- Measure of the compound muscle action potential (CMAP) amplitude decline recorded from the abductor digiti minimi muscle after repeated short exercise test at room temperature and after cooling
- Score of a Clinical Myotonia rating Scale (CMS). This scale comprises two 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 endpoints included adverse event (AE) frequency and severity; changes in clinical laboratory values; changes in vital signs; ECG and CGI Tolerability index.

After completion of the MYOMEX study, patients had the opportunity to immediately continue treatment with mexiletine at a dosage adapted to their clinical response and tolerance to the drug. Long-term data on the patients treated at site 01 (Hôpital La Pitié Salpêtrière Paris), has been collected for up to 94 months after the completion of the study.[31]

Statland et al (NCT00832000)[27]

This was a randomised, double-blind, placebo-controlled crossover phase II study, conducted at seven neuromuscular referral centres in four countries – USA, Canada, England, and Italy and included participants with genetically confirmed NDM or patients who had clinical features of NDM but negative myotonic dystrophy DNA testing. The objective was to determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDM.

Eligible participants were aged at least 16 years, had genetically confirmed NDM or clinical symptoms or signs of NDM but negative myotonic dystrophy DNA testing, and had myotonic potentials on EMG. Patients taking anti-myotonic agents were required to discontinue medications for a washout period equal to seven times the half-life of elimination before their baseline visit.

Patients already taking anti-myotonic treatments were first required to complete a washout period. Participants were randomised to mexiletine hydrochloride 200 mg capsules (corresponding to 167 mg mexiletine) three times a day (TID) or placebo capsules TID for four weeks. After a one-week washout period, they were placed on the opposite intervention for four weeks. Patients were randomly assigned the order of the two treatments in a 1:1 ratio, stratified by institution.

The primary endpoint was stiffness severity score reported by patients 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 symptoms were assigned a score of 0 for analysis).

The secondary endpoints required participants to assess symptoms were:

- Patient-reported pain, weakness, tiredness. Measured daily over the third and fourth weeks of treatment period using the IVR
- Clinical myotonia bedside assessment of eyelid and fist function measured five times in sequence at each clinic visit using a stopwatch to measure response times, participants were asked to:
- Squeeze their eyes closed for five seconds then rapidly open them
- Make a tight fist for five seconds then rapidly open
- Handgrip myotonia: Using a commercially available grip dynamometer and computerised capture system, the maximum voluntary contractions 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
- The maximal post-exercise decrement in CMAP after short and long exercise
- Myotonia on needle electromyography was graded on a 1+ to 3+ scale in the right abductor digiti minimi (hand muscle) and right tibialis anterior (lower leg muscle)
- Health-related quality of life using the SF-36 and the INQoL

The safety endpoint was the number of adverse events.

Stunnenberg et al. (NCT02045667)[26]

This was a series of aggregated, double-blind, randomised, placebo-controlled N-of-1 trials, performed in a single academic referral centre in adults with clinical phenotype and genetically confirmed diagnosis of NDM, without cardiac or psychiatric comorbidity or co-medication, selected from the Dutch neuromuscular database.

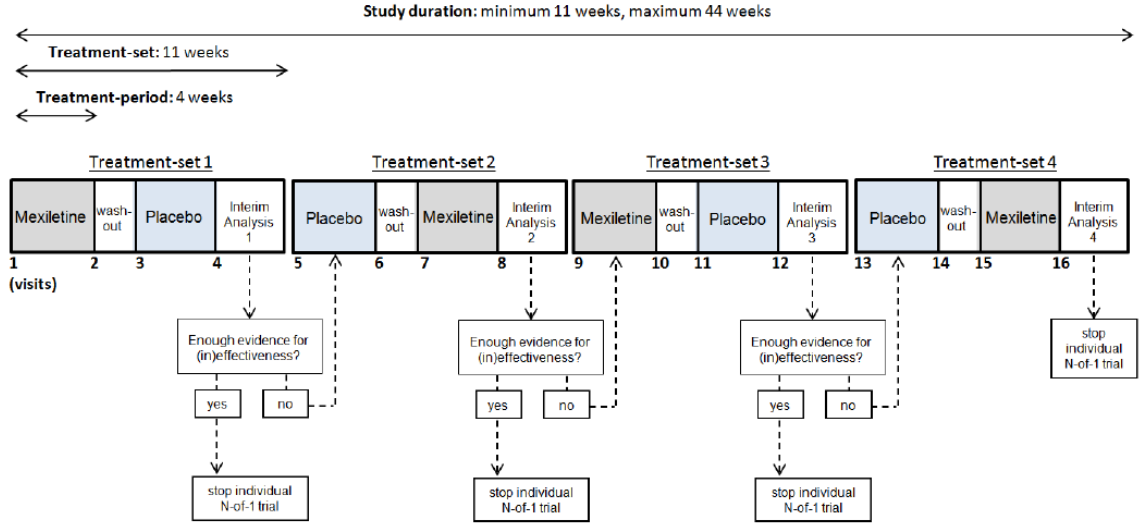
Eligible patients were at least 18 years of age with a genetically confirmed diagnosis of NDMs. Other neurological conditions that might affect the assessment of the study measurement were excluded; as were patients with genetically confirmed myotonic dystrophy; existing cardiac conduction defects, evidenced on ECG including but not limited to the following conditions: malignant arrhythmia or cardiac conduction disturbance (such as second-degree AV block, third-degree AV block, or prolonged QT interval >500ms or QRS duration >150msec); current use of the following antiarrhythmic medication for a cardiac disorder: flecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone or mexiletine; women who are pregnant or lactating; currently on medication for myotonia such as phenytoin and flecainide acetate within five days of enrolment, carbamazepine and mexiletine within three days of enrolment, or propafenone, procainamide, disopyramide, quinidine and encainide within two days of enrolment; or renal or hepatic disease, heart failure, history of myocardial infarction, or seizure disorders

Patients were randomly assigned to receive mexiletine hydrochloride 200 mg capsules (equivalent to mexiletine 167 mg), or placebo capsule, three times per day. Those receiving anti-myotonic treatment underwent a two-week washout period before baseline.

Each N-of-1 trial consisted of one to four treatment sets, comprising 11 weeks each; a four-week period of mexiletine and a four-week period of placebo treatment, block-randomised, with a one-week washout in between and two weeks for statistical interim analysis at the end (See Figure 4.2). Each patient had

between four and 16 study visits, depending on the number of treatments sets necessary to draw conclusions regarding the treatment effect. The trial used a Bayesian analysis which was conducted after completion of each treatment set and patients were advised to stop the trial if the posterior probability of a meaningful treatment effect was higher than 0.8 or lower than 0.2. Results from the multiple treatment sets were combined using a Bayesian hierarchical model.

Figure 4.2: Study Design - Stunnenberg et al. 2018



Source: CS, Figure 11, page 49.

The primary outcome measure was the mean daily self-reported stiffness severity score reported with an IVR diary. Patients noted if they experienced symptoms during the previous 24 hours and rated the severity of the symptoms on an ordinal scale (1-9, with 9 being the worst ever experienced).

Secondary outcomes included mean daily self-reported (using the IVR) severity scores for pain, weakness, and tiredness; the INQoL questionnaire composite score (0-100 scale; a higher score indicates greater disease severity) and 36-Item Short-Form Health Survey (Dutch version) mental and physical component scores (both 0-100 scales; lower score indicates greater disease severity) the first, fifth, and mean of five attempts of myotonic bedside tests: eyelid closure and handgrip muscle relaxation times after forceful muscle contraction for five seconds; and the Timed Up & Go test, which measures the time in which the patient rises from a chair, walks three metres, turns around, walks back, and sits down again, at a self-selected speed.

Adverse events were ascertained by active surveillance during trial visits and passive surveillance. Determination of the relationship between an adverse event and mexiletine treatment was performed by a data and safety monitoring board together with the trial pharmacologist.

The trial used a Bayesian statistical approach. The statistical analysis plan included the aggregation (analyses of prespecified genotype subgroup and total NDM patient groups) to obtain patients' mean effect sizes which were modelled, assuming a normal distribution around the genotype subgroups. Of the 27 patients who completed their individual N-of-1 trial, 23 underwent a single treatment set and four completed a second treatment set; thus, in total, 31 treatment sets from 27 patients were analysed. For the outcome assessments, 773 of 868 (89%) telephone calls to assess the primary outcome were completed and 2,676 of 2,728 (98%) possible outcome measures for the secondary outcomes were collected at the in-person visits. Since the amount of missing data was relatively small and assumed missing at random, multiple imputation was not performed.

Suetterlin et al. 2015[30]

This was a retrospective review of a large skeletal muscle channelopathy patient cohort in the United Kingdom. The study assessed all patients with genetically confirmed NDM prescribed mexiletine hydrochloride with a minimum of 6 months follow-up.

This study presents long term effectiveness and also enables the calculation of an average effective treatment dose in clinical practice (which aligns with that seen in the MYOMEX study and expert feedback), long-term discontinuation rate, as well as adverse event rates which were incorporated into the economic model. Therefore, the results of this study enabled the extrapolation of the outcomes over the model's time horizon.

According to the submission the following outcomes were reported: Adverse event rates (base-case); Efficacy as determined by patient report; Average effective dose (scenario analysis); Discontinuation rates (base-case); Electrocardiograms (ECGs). However, in Section B.2.6.4 (Clinical effectiveness results of Suetterlin et al. 2015) only one of the outcomes was reported, i.e. mean effective daily dose of mexiletine.

4.2.3 Baseline characteristics of the included studies

Baseline characteristics of the study populations of the three RCTs are shown in Table 4.4. In the MYOMEX study[18], more mexiletine naïve patients received the placebo-mexiletine treatment sequence, compared to the mexiletine-placebo treatment sequence. Randomisation between groups was balanced in the Statland et al. (2012) study,[27] with the exception of more men in the placebo- mexiletine group. In the Stunnenberg et al. (2018) study,[26] IVR stiffness scores (higher in patients with CLCN1 genotype), IVR pain scores (higher in patients with SCN4A genotype), and eyelid closure action myotonia scores (higher in patients with SCN4A genotype) differed between the two genotype subgroups at baseline. The Suetterlin et al. (2015) study[30] included 63 patients. The mean length of follow-up was 4.8 years (range 6 months - 17.8 years). No baseline characteristics were reported in the CS for this study.

Table 4.4: Baseline demographic and disease characteristics

Demographics/ characteristics	MYOMEX			Statland		Stunnenberg	
	Treatment sequence		All patients (mITT) (n=25)	Treatment sequence		Genotype	
	Placebo-mexiletine (n=13)	Mexiletine-placebo (n=12)		Mexiletine – placebo (n=29)	Placebo – mexiletine (n=30)	CLCN1 (N=16)	SCN4A (N=11)
Mean (SD/range) age, years	[redacted]	[redacted]	[redacted]	41.10 (16–66)	44.70 (22–68)	50 (24–65)	38 (19–64)
Diagnosis, n (%)							
Myotonia congenita	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Paramyotonia congenita	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Gender, n (%)							
Male	[redacted]	[redacted]	[redacted]	13 (44.8)	20 (66.7)	13 (81)	7 (64)
Female	[redacted]	[redacted]	[redacted]	16 (55.2)	10 (33.3)	3 (19)	4 (36)
Mean (SD) BMI, kg/m2	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Mean (SD) SBP (mmHg)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Mean (SD) DBP (mmHg)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
Mexiletine treatment, n (%)							
Treated at screening	[redacted]	[redacted]	[redacted]	7 (24.1)	6 (20.0)	2 (13)	0
Previously treated (before screening)	[redacted]	[redacted]	[redacted]				
Treatment naïve	[redacted]	[redacted]	[redacted]	19 (65.6)	23 (76.7)	7 (43)	6 (54)

Source: CS, Tables 12-14, pages 52-58

BMI = body max index; CLCN1 = skeletal muscle chloride channel gene; DBP = diastolic blood pressure; mITT = modified intention-to-treat; SBP = Systolic blood pressure; SCN4A = skeletal muscle sodium channel gene; SD = standard deviation.

Table 4.5: Statistical methods

	MYOMEX	Statland	Stunnenberg
Sample size calculation	24 patients (12 of each diagnosis) were required to detect a 50% reduction in stiffness VAS score with mexiletine compared with placebo. To achieve this up to 40 patients had to be screened.	54 patients with primary outcome measurements for both treatment periods provided at least 93% power to detect an effect size of 0.25 SD in stiffness score with a 2-sided, 5% significance level. This was based on computer simulation using 500 Monte Carlo simulations, a mean score of 3 on placebo, a within patient SD of 1.5 and a between patient SD between 1.5 and 3.0.	The sample size was based on simulation and assumed that 0.75 was a clinically relevant mean difference between mexiletine and placebo (corresponding to a 20% change and an effect size of 0.34). One thousand simulations were performed using the following steps: a random sample was drawn from the prior distribution of the mean treatment effect; 30 N-of-1 trials were simulated; each simulated dataset was analysed using Bayesian analyses; the resulting posterior distributions were used to estimate the posterior probability of substantial treatment effect (>0.75). Thirty patients with an estimated treatment effect of 1.75 provided a power of 69%.
Analysis populations	ITT: all randomised patients mITT: all randomised patients with at least one primary outcome evaluation or with a VAS at visits 3 or 5 Per protocol: all randomised without a major protocol deviation, no intercurrent event which could interfere with the primary outcome evaluation and who completed the two study periods.	mITT: patients with missing IVR scores in either period were excluded.	All patients who completed at least one treatment set (27/30 (90%)).
Analysis methods Primary outcome	The change from baseline in stiffness VAS score was analysed using a mixed effect linear regression model on ranks including: Baseline value, diagnosis, treatment, period, treatment sequence and the	Stiffness IVR scores measured in weeks 3 and 4 of each treatment period were analysed using mixed effects linear regression model using patients as a random effect. A Wald test was used to evaluate the significance of the treatment	Bayesian analysis: Results from each patient were combined using a Bayesian hierarchical model to obtain a sample mean and variance assuming a normal distribution around each patient's true mean. All patients with at

	MYOMEX	Statland	Stunnenberg
	diagnosis-treatment interaction as fixed effects Patient as a random effect (to allow for multiple results within each patient) The carry-over effect was tested using the significance of treatment sequence (if $p > 0.05$ there was no carry-over). If there was a significant carry-over effect ($p \leq 0.05$) then the mixed model was not used and treatments were compared using a Wilcoxon test for each period separately.	sequence group variables (testing for carry-over). The carry-over effect was considered significant if $p < 0.10$. If there was evidence of a carry-over effect results were reported separately for each treatment period. Most 95% CI were calculated using the standard method but for outcomes which were skewed and required a log transformation the CI were estimated using bootstrapping. The standardised effect size was calculated as the treatment effect divided by the within patient SD.	least one treatment sequence were included in the analysis. Frequentist analysis: A mixed effects linear regression model was used for the IVR stiffness score adjusting for treatment, genotype, mean baseline stiffness score, randomisation order and treatment period and genotype x treatment interaction. A variance components model was used and variables were selected using $p < 0.10$.
Secondary outcomes	The change from baseline (visit 2) in the chair test results was compared between treatments using a Wilcoxon test. Changes from baseline in INQoL scores were compared between treatments using a linear mixed model including treatment, baseline value, and period as fixed effects and patients as random effects. The CGI efficacy index was evaluated by the investigator at visits 3 and 5 using a 4-point scale. This was converted to a binary variable (efficient [good and fair] vs. not efficient [poor and none]) and compared between treatments using McNemar's test. The percentage of patients with an absolute change from baseline in VAS stiffness score ≥ 50 mm was summarised but not analysed.	All secondary outcomes were analysed using the same analysis methods as the primary outcome with the exception of 2 needle electromyographic tests which were analysed using a Wilcoxon test because it was not a continuous variable and the assumption of normality was not justified.	Secondary IVR outcomes (tiredness, pain and weakness) were also analysed using a mixed effects linear regression model using the same method as for stiffness. For other secondary outcomes which were normally distributed dependent t-tests were used to calculate mean treatment effects, significance levels and confidence intervals.

Source: MYOMEX CSR,[18] Statland[27] and Stunnenberg[26]

INQoL = Individualized neuromuscular quality of life; ITT = intention to treat, mITT = modified intention to treat, SD = standard deviation, VAS = visual analogue scale.

4.2.4 Statistical analyses of the included studies

The statistical methods of the included RTCs are summarised in Table 4.5.

ERG comment: The four included studies had different designs. Two were randomised crossover trials where patients received both mexiletine and placebo and the order was determined by randomisation. The treatment periods were 18 days with a washout of four days, and 28 days with a washout of seven days respectively. The third study was a randomised N-of-1 design where each patient received both mexiletine and placebo in a random order for four weeks with a one-week washout. Each patient could receive multiple treatment sets which was different from the other two crossover trials where each patient only received each treatment once. The trial design and analysis used Bayesian methods, which also differed from the two other crossover trials which used standard design and analysis methods. The design and statistical analysis methods of the two crossover trials were appropriate and both tested for evidence of a carryover effect (whether the effect of treatment differed by period (whether or not it was the first treatment). The statistical analysis used methods which accounted for the within patient design (every patient received both treatments). However, although both trials had stiffness as their primary outcome they were measured in different ways.

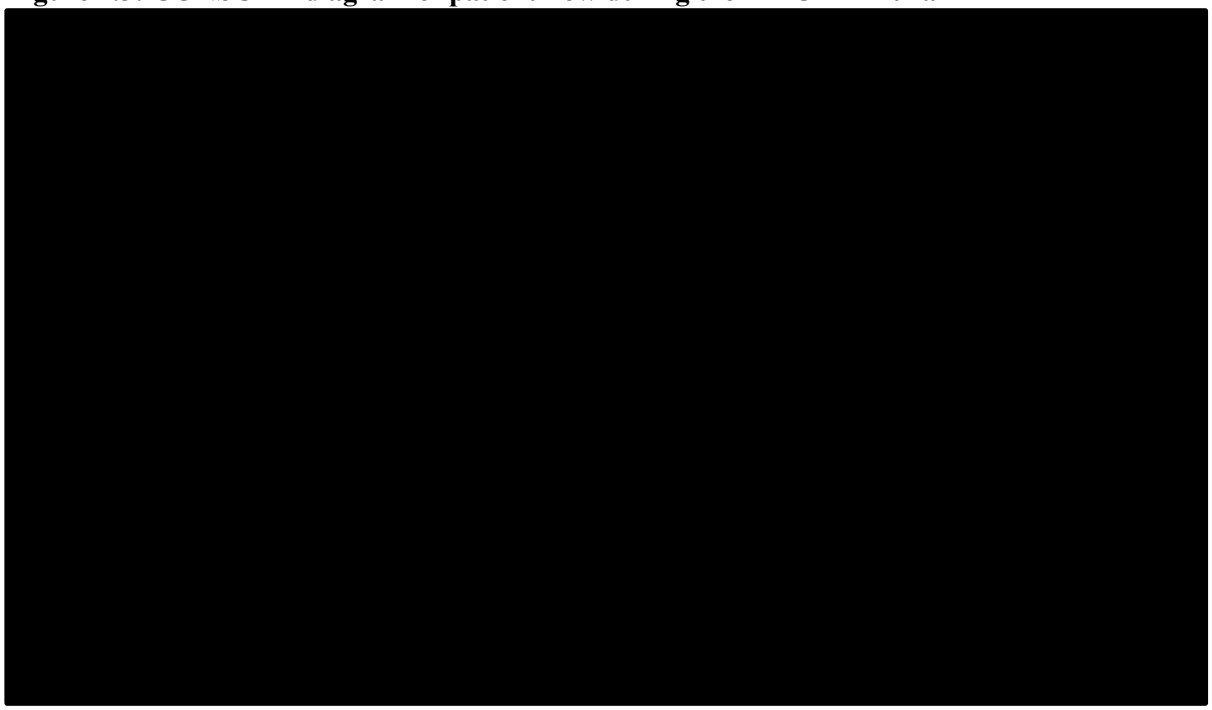
The aggregated N-of-1 trials study (Stunnenberg) performed a Bayesian analysis after the completion of each treatment set in each patient, and if the posterior probability of a meaningful clinical treatment effect was > 0.80 or < 0.20 they were advised to stop trial treatment. Twenty-three patients (85%) had one treatment set and four (15%) had two. Due to the differences in design this study is not comparable to MYOMEX and Statland. However, it did also report results from an analysis using frequentist methods using the same type of mixed effect linear regression used in the other two studies. The frequentist results are reported in Section 4.2.5. The fourth study (Suetterlin) had a retrospective observational design.

4.2.5 Results of the included studies

MYOMEX study (NCT02336477)[18]

In the MYOMEX study, a total of 26 patients were included, one withdrew consent prior to treatment and did not receive any study treatment. This patient was included in the intention-to-treat (ITT) population but excluded from the modified ITT (mITT) and safety populations. The CONSORT diagram is shown in Figure 4.3.

Figure 4.3: CONSORT diagram of patient flow during the MYOMEX trial



Source: CS, Figure 12, page 52.
MC = myotonia congenita; PC = paramyotonia congenita; mITT = modified intention-to-treat; PP = per protocol; pt = patient; SAF = safety; V2 = visit 2.

MYOMEX results

The primary efficacy criterion of this study was the stiffness as assessed by the patient on a visual analogue scale (VAS). The primary analysis was performed in the modified intention to treat (mITT) and per protocol (PP) populations. Absolute changes from baseline at the end of each period were assessed by treatment. The results of the MYOMEX trial are shown in Table 4.6 and results for INQoL are in Table 4.7. The ERG requested treatment effect estimates and measures of variability for each treatment period separately and for the whole trial period and these were provided in the response to clarification (Question A10).[25]

For the primary outcome of the change from baseline in stiffness VAS score there was no evidence of a carry-over effect (for treatment sequence) and the mixed effects model results are based on both periods combined. There was a significant difference ( ) between mexiletine and placebo with mexiletine having a greater median reduction in stiffness of) compared to a median increase of) with placebo.

After mexiletine treatment the time taken to perform the chair test was significantly shorter with a median reduction of) compared to) with placebo (Wilcoxon signed rank test).

For the CMS severity and disability global scores there were significant differences between mexiletine and placebo for both outcomes) with mexiletine having a greater median reduction in score compared with placebo (Table 4.6).

Table 4.6: MYOMEX main results

Median (range) absolute change	MYOMEX	
	Treatment	
	Placebo (N=13)	Mexiletine (N=12)
Primary outcome: stiffness VAS score (mm)		
Period 1	[redacted]	[redacted]
Period 2	[redacted]	[redacted]
Whole trial period (N=25)	[redacted]	[redacted]
Secondary outcomes: chair test (s)		
Period 1	[redacted]	[redacted]
Whole trial period (N=25)	[redacted]	[redacted]
CMS scores: severity global score		
Period 1	[redacted]	[redacted]
Whole trial period (N=25)	[redacted]	[redacted]
CMS scores: disability global score		
Period 1	[redacted]	[redacted]
Whole trial period (N=25)	[redacted]	[redacted]

Sources: MYOMEX CSR[18] and Response to Clarification[25]
Global severity score ranges from 0 to 104 and disability score from 0 to 27 (0 is normal)
CMS = clinical myotonia rating scale

Results for health-related quality of life measured using the INQoL scale are presented in Table 4.7. There was a significant period effect for fatigue, overall quality of life, social relationships, emotions, independence and activities ([redacted]) indicating that there were differences in these outcomes between periods one and two. However, in the clarification response to question A10 the company stated that the term for treatment sequence in the mixed effect linear model was not significant [redacted]) in any of the analyses indicating that there was no evidence of a carry-over effect.[25] Results for period 1 and the whole trial period were provided. All quality of life domains showed a significant difference between mexiletine and placebo in the change from baseline score ([redacted]) apart from the expected treatment effect ([redacted]).

Table 4.7: MYOMEX – INQoL results

Median (range) absolute change	MYOMEX	
	Treatment	
	Placebo	Mexiletine
Weakness		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Locking		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Pain		

Median (range) absolute change	MYOMEX	
	Treatment	
	Placebo	Mexiletine
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Fatigue		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Activities		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Independence		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Social relationships		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Emotions		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Body image		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Overall quality of life		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Perceived treatment effects		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]
Expected treatment effects		
Period 1	[redacted]	[redacted]
Whole trial period	[redacted]	[redacted]

Sources: MYOMEX CSR[18] and Response to Clarification[25]
INQoL = Individualized neuromuscular quality of life.

Results for the clinical global impression of efficacy (CGI) are presented in Table 4.8. This was a dichotomous outcome categorised as efficient (good or fair) or not efficient (poor or none) and analysed using McNemar's test. For both CGI as judged by the investigators and as judged by the patients mexiletine treatment was judged to be more efficient than placebo ([redacted]).

Table 4.8: MYOMEX - CGI results

	MYOMEX	
	Treatment	
	Placebo	Mexiletine
CGI judged by investigators (N (%))		
Efficient	[redacted]	[redacted]
Not efficient	[redacted]	[redacted]
CGI judged by patients		
Efficient	[redacted]	[redacted]
Not efficient	[redacted]	[redacted]
Source: MYOMEX CSR[18]		

Other outcomes reported were CMAP amplitude which was reported descriptively without supporting data. In patients with myotonia congenita (MC) the mean CMAP amplitude decreased after the first short exercise then returned to normal. At room temperature CMAP amplitudes recovered after repeated exercise and approached normal values but after cold exposure the decrease in CMAP amplitudes remained more pronounced (cold-aggravated). In patients with paramyotonia congenita (PMC) it was aggravated with repeated exercises and with cold. In both groups the decrease in CMAP amplitudes was less pronounced with mexiletine than with placebo.

Long-term data from site 01 (Hôpital La Pitié Salpêtrière Paris) was available for eight patients with follow-up for up to 94 months after the completion of the study.[31] Mexiletine treatment was associated with long-term benefit for all eight patients, who reported improved stiffness scores as determined on a VAS and/or perceived efficacy after several years of treatment. All patients wished to continue their mexiletine treatment. Mexiletine long-term treatment is generally well tolerated; the most frequently observed side effect, epigastralgia, could be alleviated by decreasing mexiletine dose. All reported adverse events had already been experienced during the MYOMEX study.

ERG comment: The MYOMEX trial reported favourable results with mexiletine compared with placebo for the primary outcome of stiffness and secondary outcomes of the time taken to complete a chair test, CGI, CMS scores and most quality of life domains as measured with the INQoL tool. This was a crossover trial so each patient received both mexiletine and placebo in a randomised order and the analysis was performed on the within person change from baseline. Patients could have previously received mexiletine treatment and at baseline[redacted] of patients had previously been treated or were treated at screening. Even though the trial was double-blind it is quite likely that, as each patient received both treatments, those who had previously received mexiletine were able to recognise when they were receiving it during the trial particularly if they had previously experienced side effects.

The primary outcome of stiffness was a self-reported outcome and the median change from baseline with mexiletine during period 1 was greater than in period 2 with a reduction of [redacted] mm compared to [redacted] mm. The ERG requested results for periods 1 and 2 and these were provided for stiffness but not for other outcomes where only results for period 1 and the whole trial period were provided. The company stated that "The only "true" confirmation of the absence of a carry-over effect is by analysing results for the first period, and we have conducted an analysis of all efficacy endpoints for Period 1. All results obtained through this analysis in the first period only confirmed those initially presented for both periods combined, demonstrating the efficacy of mexiletine. Therefore, no mixed effect linear model has been applied for period 2" (Response to Clarification, Question A10c).[25]

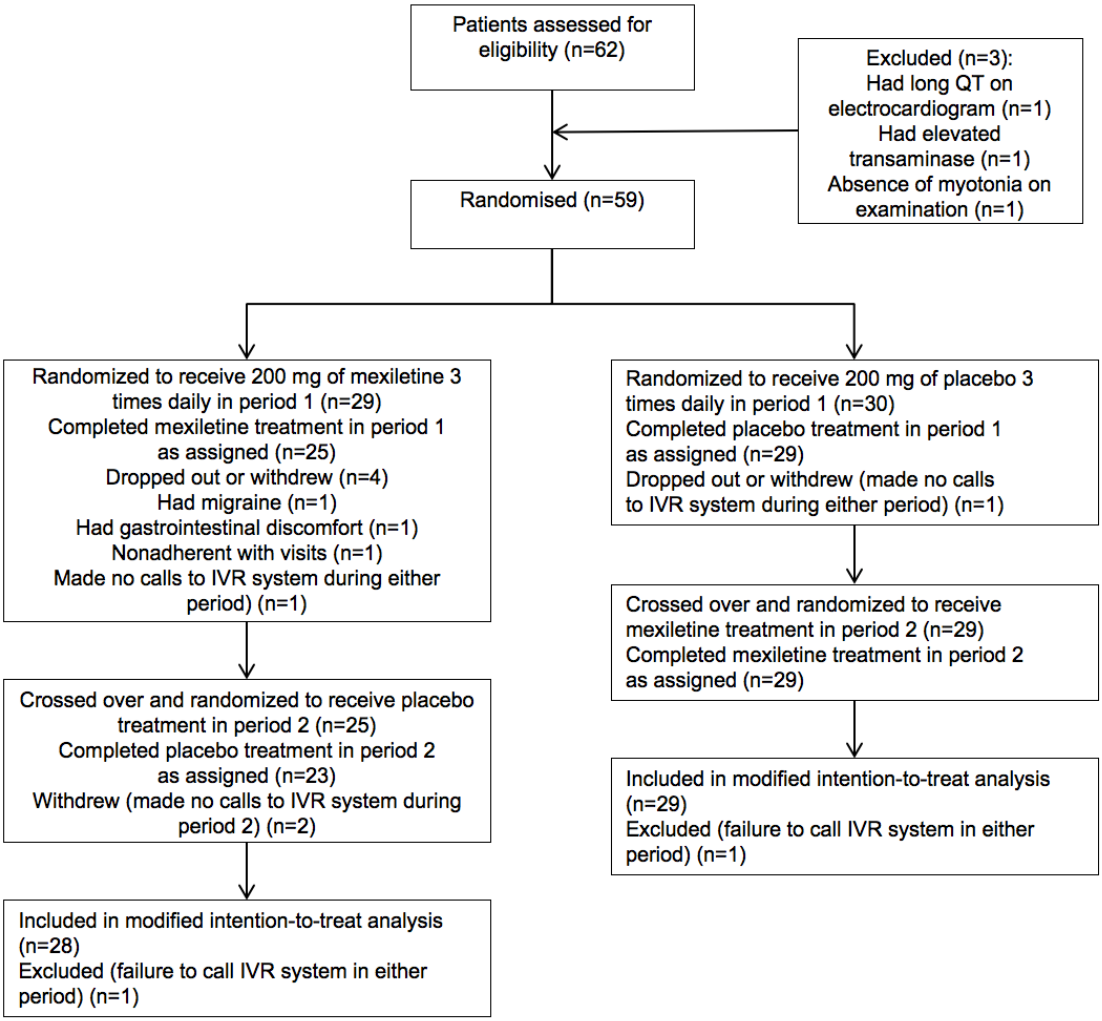
The results of the analysis of period 1 only do confirm the analysis of the whole trial period but it should be noted that this was a very small trial, of only 25 patients, and each treatment was received for between 18 and 22 days with a wash-out period of four to eight days

Although stiffness was the primary efficacy outcome in the MYOMEX trial, it was not used as a measure of effectiveness in the economic model. Treatment effectiveness in the economic model was assessed using eight items from the INQoL scale. The mapping of INQoL items to the appropriate EQ-5D domains is explained by the company in Table 17 of the Response to Clarification; and the results for these eight items are presented in Table 18 of the Response to Clarification.[25] The company seem to have used the items most relevant to patient physical functioning. Results of the eight items are in accordance with the other items of the INQoL scale.

Statland et al (NCT00832000)[27]

In the Statland et al. (2012) study, 59 patients were randomised. Two patients (one in each group) were not included in the mITT population due to failure to call the IVR system in either period. An overview of patient disposition is shown in Figure 4.4.

Figure 4.4: CONSORT diagram of patient flow during the Statland trial



Source: CS, Figure 13, page 54.
IVR = interactive voice response

The company notes that up to 25% of outcome data for the IVR, nearly 50% for some domains of the INQoL and around 10% of SF-36 data were missing, but it was not reported how these missing data were interpreted.

Primary efficacy endpoint - stiffness

The treatment effect was estimated separately for each period because the treatment sequence variable in the model was significant (p=0.04) indicating a carry-over effect. In both periods mexiletine had a significantly lower stiffness score at the end of the treatment period compared with placebo with a mean difference of −1.68 (95% CI, −2.66 to −0.706; p<0.001) in period 1 and −3.68 (95% CI, −3.85 to −0.139; p=0.04) in period 2 (See Table 4.9).

Table 4.9: IVR stiffness results

Outcome	N	Mexiletine	Placebo	Treatment Effect	Effect size	P value
Interactive voice response stiffness						
Period 1 Mean (95% CI)	57	2.53 (1.80 to 3.17)	4.21 (3.40 to 5.20)	-1.68 (-2.66 to -0.706)	-1.36	<0.001
Period 2 Mean (95% CI)	57	1.60 (1.04 or 2.20)	5.27 (4.44 to 6.27)	−3.68 (−3.85 to −0.139)	-2.97	0.04

Source: CS, Table 27, page 84.
IVR = Interactive voice response; N = Number of participants.
Note: Higher scores represent more stiffness. Effect size = mean difference divided by within patient SD

Secondary efficacy endpoints - IVR pain, weakness and tiredness; exercise and myotonia on needle electromyography

Results for IVR assessments of pain, weakness and tiredness were analysed for the whole trial overall, not by period, and these are shown in Table 4.10. Mexiletine significantly reduced pain (mean difference [MD] -1.63, 95% CI -2.00 to -1.26), weakness (MD -1.26 (95% CI -1.67 to -0.861) and tiredness (MD -0.92, 95% CI -1.30 to -0.53), respectively (all p<0.001).

Electrophysiological measures of myotonia showed a mixed response. Mexiletine significantly improved the severity of graded myotonia on electromyography (right abductor digiti minimi (RADM): MD, −0.568; 95% CI, −0.812 to −0.325; p<0.001; Table 4.10). There were no statistically significant differences between mexiletine and placebo in electrophysiological exercise testing.

Table 4.10: IVR pain, weakness and tiredness and exercise and needle electromyography results

End Point	No. of Participant	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
Interactive voice response						
Pain, overall	48	1.54 (0.924 to 2.13)	3.17 (2.43 to 3.93)	-1.63 (-2.00 to -1.26)	-1.36	<0.001
Weakness, overall	44	1.96 (1.43 to 2.63)	3.22 (2.52 to 3.98)	-1.26 (-1.67 to -0.861)	-0.994	<0.001
Tiredness, overall	49	2.9 (2.12 to 3.68)	3.82 (3.03 to 4.53)	-0.918 (-1.30 to -0.532)	-0.709	<0.001
Exercise (% baseline)						
Short, overall	56	83.1 (77.5 to 88.4)	78.6 (71.9 to 84.7)	4.54 (-0.680 to 9.75)	0.347	0.09

End Point	No. of Participant	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
Prolonged, overall	56	81.8 (76.8 to 87.0)	80.1 (74.7 to 86.4)	1.69 (-3.34 to 6.73)	0.134	0.50
Needle, electromyography						
RADM, overall	56	2.05 (1.75 to 2.33)	2.62 (2.39 to 2.86)	-0.568 (-0.812 to -0.325)	-0.947	<0.001
RTA, overall	56	2.07 (1.73 to 2.37)	2.54 (2.28 to 2.76)	-0.464(-0.675 to -0.254)	-0.900	<0.001
Source: CS, Table 28, pages 84-85. RADM = right abductor digiti minimi; RTA = right tibialis anterior.						

Quality of life was measured using SF-36 and INQoL. The results of SF-36 showed variation across the dimension with regard to significance levels (Table 4.11). Most results were reported for the overall study period but some component results were reported separately for periods 1 and 2. Over the whole study, physical function (MD 5.00, 95% CI 2.81 to 7.20), role physical (MD 7.23, 95% CI 4.55 to 9.92), bodily pain (MD 7.78, 95% CI 5.08 to 10.5) and social function (MD 5.27, 95% CI 2.69 to 7.85) and the physical composite score (MD 5.58, 95% CI 3.44 to 7.72) were all significantly improved with mexiletine compared with placebo (p<0 .001).

Table 4.11: SF-36 results

End Point	N	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
SF-36						
Physical function, overall	57	42.8 (40.1 to 46.1)	37.8 (34.9 to 41.3)	5.00 (2.81 to 7.20)	0.904	<0.001
Role physical, overall	57	46.5 (43.6 to 49.2)	39.2 (35.7 to 42.6)	7.23 (4.55 to 9.92)	1.07	<0.001
Bodily pain, overall	57	49.8 (46.4 to 52.6)	42.0 (38.6 to 45.5)	7.78 (5.08 to 10.5)	1.14	<0.001
General health, overall	57	45.5 (41.9 to 48.7)	44.5 (41 to 47.7)	0.977 (−0.659 to 2.61)	0.240	0.24
Vitality, first period	57	45.5 (41.1 to 49.6)	43.7 (39.7 to 48.1)	1.76 (−4.34 to 7.85)	0.211	0.57
Vitality, second period	57	51.9 (48.1 to 55.5)	40.0 (35.1 to 45.0)	11.9 (−0.307 to 20.5)	1.43	0.06
Social function, overall	57	47.1 (44.4 to 49.8)	41.9 (38.5 to 44.9)	5.27 (2.69 to 7.85)	0.809	<0.001
Role emotional, first period	57	46.2 (42.0 to 50.3)	45.5 (41.2 to 49.4)	0.764 (−5.68 to 7.21)	0.102	0.81
Role emotional, second period	57	49.9 (46.2 to 53.1)	39.1 (33.5 to 45.0)	10.8 (−1.51 to 21.6)	1.45	0.09
Mental health, first period	57	47.3 (43.6 to 51.0)	47.3 (43.7 to 50.6)	0.016 (−5.24 to 5.27)	0.00258	0.99
Mental health, second period	57	53.3 (50.2 to 56.2)	44.4 (39.8 to 48.7)	8.84 (−0.572 to 18.2)	1.42	0.07

End Point	N	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
Physical composite, overall	57	44.8 (41.9 to 47.4)	39.2 (35.9 to 41.9)	5.58 (3.44 to 7.72)	1.04	<0.001
Mental composite, first period	57	47.4 (44.0 to 50.2)	47.7 (44.2 to 51.3)	−0.351 (−5.87 to 5.17)	-0.0539	0.90
Mental composite, second period	57	53.1 (50.3 to 55.8)	42.7 (36.8 to 48.3)	10.4 (0.941 to 20.6)	1.60	0.03
Source: CS, Table 29, pages 85-86.						

All dimensions in the INQoL questionnaire significantly improved with mexiletine compared with placebo, with the exception of weakness. The summary QoL score showed a significant improvement with mexiletine (MD −2.69, 95% CI −4.07 to −1.30; p<0.001), Table 4.12 shows INQoL scores for the overall trial period.

Table 4.12: INQoL results

End Point	N	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
INQoL						
Weakness, overall	35	45.7 (37.7 to 52.6)	49.3 (41.7 to 57.3)	-3.56 (−9.54 to 2.43)	-0.290	0.24
Muscle locking, overall	43	40.0 (33.1 to 46.7)	53.8 (46.4 to 61.1)	−13.7 (−20.4 to −7.03)	-0.888	<0.001
Pain, overall	32	39.9 (30.6 to 49.0)	48.2 (39.2 to 57.1)	−8.32 (−13.8 to −2.87)	-0.782	0.004
Fatigue, overall	35	48.4 (40.9 to 56.6)	58.3 (50.6 to 66.0)	−9.96 (−17.0 to −2.93)	-0.678	0.007
Activity, overall	51	34.2 (26.7 to 43.0)	47.1 (40.1 to 55.5)	−12.9 (−18.3 to −7.43)	-0.950	<0.001
Independence, overall	51	17.8 (12.3 to 23.3)	22.5 (17.2 to 28.1)	−4.74 (−8.14 to −1.35)	-0.561	0.007
Social relations, overall	51	18.9 (13.5 to 24.5)	25.9 (18.0 to 35.2)	−7.02 (−13.4 to −0.671)	-0.440	0.03
Emotions, overall	51	27.7 (22.0 to 34.4)	33.8 (27.1 to 41.5)	−6.13 (−10.1 to −2.15)	-0.619	0.003
Body image, overall	51	24.2 (17.3 to 31.0)	29.4 (22.0 to 36.5)	−5.27 (−10.4 to −0.105)	-0.408	0.05
QoL, overall	51	14.0 (11.6 to 16.5)	16.7 (14.0 to 19.4)	−2.69 (−4.07 to −1.30)	-0.780	<0.001
Perceived treatment effect, overall	51	36.6 (27.1 to 45.8)	21.7 (12.7 to 31.1)	14.9 (7.43 to 22.3)	0.797	<0.001
Expected treatment effect, overall	51	36.1 (26.9 to 47.0)	23.1 (14.5 to 33.6)	13.0 (4.18 to 21.8)	0.585	0.005
Source: CS, Table 30, pages 86-87. INQoL = Individualized Neuromuscular Quality of Life Questionnaire; QoL = Quality of Life.						

Table 4.13 shows that mexiletine significantly improved all clinical assessments compared with placebo. Mexiletine improved myotonia as measured on clinical examination by overall handgrip times

(MD −0.33 seconds, 95% CI −0.633 to −0.142; p<0.001) and overall QMA (MD −0.109 seconds, 95% CI −0.177 to −0.0560; p<0.001).

Table 4.13: Clinical assessment results

End Point	N	Mexiletine	Placebo	Treatment Effect Estimate	Effect size	P value
Clinical assessment, overall, seconds						
Eye closure	57	0.161 (0.0704 to 0.314)	0.474 (0.261 to 0.871)	−0.313 (−0.602 to −0.149)	-0.888	<.001
Handgrip	57	0.164 (0.0858 to 0.294)	0.494 (0.281 to 0.872)	−0.330 (−0.633 to −0.142)	-0.748	<.001
QMA handgrip	54	0.321 (0.274 to 0.370)	0.429 (0.365 to 0.517)	−0.109 (−0.177 to −0.0560)	-0.518	<.001

Source: CS, Table 30, pages 86-87.
QMA = quantitative myotonia assessment.

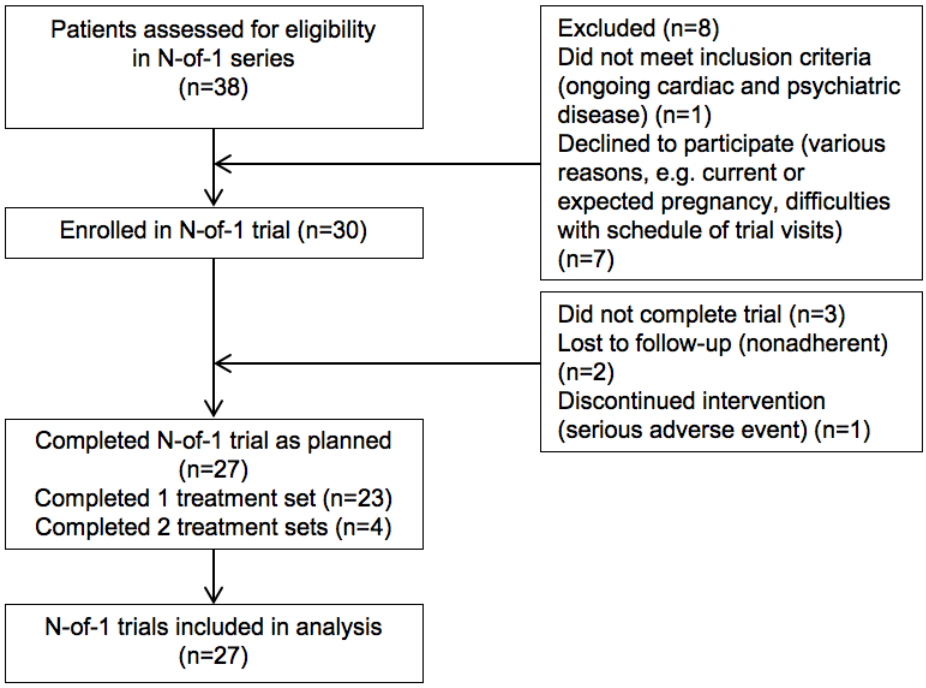
ERG comment: Similar to MYOMEX this was also a crossover trial and at risk of unblinding if patients can identify which treatment they are taking in each period which can lead to over-reporting of effectiveness. In this trial fewer patients were taking mexiletine before the trial start (22%). The primary outcomes were patient reported on the interactive voice response system and a survey was conducted after each study period asking patients to guess which treatment they were taking in the previous period, The percentages of patients who guessed correctly in the second period were high at 79% for mexiletine and 80% for placebo indicating that the trial was no longer effectively blinded and patient responses may have been affected by the knowledge of which treatment was being received.

The stiffness results indicate that the effectiveness of mexiletine was greater (lower score) in the second period compared to the first period although the second period results were less variable (narrower confidence interval). The analysis of stiffness also indicated presence of a carry-over effect so the periods were analysed separately and not combined. This was a larger trial than MYOMEX (n=59) and the treatments were given for longer (four weeks with a one-week washout period). Mexiletine was found to have statistically significant benefits compared with placebo for stiffness and most other outcomes apart from some SF-36 components.

Stunnenberg et al. (NCT02045667)[26]

In the Stunnenberg et al. (2018) study, 30 patients were randomised and received study medication. There were three dropouts: two patients did not complete study visits, and for one patient the individual N-of-1 trial was stopped because of a serious adverse reaction. An overview of patient disposition is shown in Figure 4.5.

Figure 4.5: CONSORT diagram of patient flow during the Stunnenberg trial



Source: CS, Figure 14, page 56.

Results for the primary outcome of stiffness recorded on IVR showed that mexiletine had a significantly lower stiffness score compared with placebo (MD -3.12, 95% CI -3.78 to -2.46). Mexiletine also had significantly lower pain, weakness and tiredness scores compared with placebo, all results are shown in Table 4.14. These are results for the whole trial period as this trial used a different design and did not report results separately for each treatment period.

Table 4.14: IVR stiffness, pain, weakness and tiredness results

IVR Outcome	Mexiletine Mean (SD)	Placebo Mean (SD)	Treatment Effect Mean (95% CI)	P value
Stiffness	2.42 (1.81)	5.55 (2.09)	-3.12 (-3.78 to -2.46)	<0.001
Pain	1.37 (2.13)	2.08 (2.10)	-0.70 (-1.23 to -0.18)	0.01
Weakness	1.49 (1.66)	2.96 (2.75)	-1.56 (-2.06 to -1.05)	<0.001
Tiredness	2.41 (2.53)	3.65 (2.51)	-1.27 (-1.95 to -0.58)	0.001

Source: Stunnenberg 2018[26]
Results from a mixed effect linear regression model of scores during each treatment adjusted for treatment, genotype, mean baseline treatment, randomisation order, period and genotype x treatment interaction.
CI = confidence interval, IVR = interactive voice response, SD = standard deviation.

Results for HRQoL and other outcomes are shown in Table 4.15. This trial only reported results for the overall INQoL composite score and not the individual components and found a significantly greater improvement (reduction in score) with mexiletine compared with placebo (MD -14.22, 95% CI -24.71 to -3.74). Significant improvements were also seen in the physical and mental component scores on SF-36, in the Timed Up and Go test and in handgrip dynamometry measurements.

Table 4.15: Quality of life and other secondary outcome results

Change from baseline	Mexiletine Mean (95% CI)	Placebo Mean (95% CI)	Treatment Effect Mean (95% CI)	P value
Health-related quality of life				
SF-36 Physical component	8.66 (5.94 to 11.38)	1.04 (-0.60 to 2.96)	7.81 (4.72 to 10.88)	<0.01
SF-36-Mental component	4.77 (0.67 to 8.48)	-1.85 (-4.81 to 1.11)	6.78 (1.64 to 11.92)	0.001
INQoL composite score	-7.22 (-14.5 to -0.29)	-21.44 (-30.90 to -11.95)	-14.22 (-24.71 to -3.74)	0.01
Timed Up and Go[a]				
Mean of all attempts	-1.05 (-1.48 to -0.62)	0.07 (-0.67 to 0.01)	-1.12 (-2.07 to -0.18)	0.02
Eyelid closure action				
Mean of all attempts	-2.54 (-4.15 to -0.93)	-0.43 (-1.24 to 0.37)	-2.11 (-3.94 to -0.28)	0.03
Handgrip dynamometry measures				
Relaxation time	-0.05 (-0.10 to 0.00)	-0.07 (-0.33 to 0.19)	0.02 (-0.25 to 0.28)	0.91
Peak force	29.90 (5.74 to 54.05)	-3.85 (-25.84 to 18.14)	37.23 (10.19 to 64.28)	0.009
Transient paresis, fifth attempt (%)	-8.56 (-17.26 to 0.14)	0.73(-3.63 to 5.09)	-12.25 (-22.04 to -2.47)	0.02
Myotonic discharges on needle EMG (grading)				
Mean (SD)	1.85 (1.13)	2.52 (0.89)	-0.67 (-1.11 to -0.23)	<0.001

Source: Stunnenberg 2018[26]
Results from a mixed effect linear regression model of scores during each treatment adjusted for treatment, genotype, mean baseline treatment, randomisation order, period and genotype x treatment interaction.
a) Measures time taken to rise from a chair, walk 3 metres, turn around, walk back and sit down again at a self-selected speed.
CI = confidence interval, INQoL = Individualized neuromuscular quality of life, SD = standard deviation, SF-36 = short form 36.

ERG comment: The trial by Stunnenberg used a different design to the other two mexiletine trials. It was a series of aggregated, placebo-controlled N-of-1 trials, designed and analysed using Bayesian methods, although results were also reported for a frequentist analysis which have been included in this report. Patients could receive multiple sets of mexiletine and placebo each for four weeks duration with a one-week wash-out period in between. Each patient could receive between one and four treatment sets (11 weeks comprising mexiletine treatment, a wash-out, placebo treatment and an interim analysis period) which is different from MYOMEX and Statland where each patient could only receive mexiletine and placebo once. Although stiffness was measured by all trials, the outcome measures used for analysis were different. Stunnenberg analysed the mean daily stiffness score, MYOMEX analysed the mean change from baseline and Statland analysed the mean score during weeks three and four of each treatment period. MYOMEX performed an analysis of ranks as the change from baseline in stiffness was skewed and the results were reported as median and range, the other two trials reported treatment effects using means and 95% confidence intervals. Due to differences in the study designs,

analysis methods and effect sizes used in reporting the results of these trials are not comparable and should not be pooled in meta-analysis.

Suetterlin et al. 2015[30]

Suetterlin et al. 2015 is a retrospective review of a cohort of patients with skeletal muscle channelopathy (n=63) and a mean length of follow-up of 4.8 years (range, 6 months to 17.8 years).

Efficacy was based on subjective patient report, documented by the clinician where the mean effective daily dose of mexiletine across the study population was 416.7 mg. Twelve patients were refractory to mexiletine treatment. No other effectiveness results were reported.

4.2.6 Adverse events

In MYOMEX,[18] 25 patients received at least one dose of mexiletine (safety population). The mean mexiletine treatment duration was 19.0 days (SD 2.4 days), representing an exposure of 1.4 patient-years. No patient withdrew due to intolerable increase in myotonia severity. [redacted]) prematurely discontinued the study medication following occurrence of an adverse event.

The severity of the majority of adverse events was [redacted] mild and [redacted] moderate experienced by the participants receiving mexiletine. One adverse event in the mexiletine group was deemed to be severe (tachycardia), and the patient discontinued treatment. The most frequent treatment-related adverse events were upper abdominal pain, vertigo and insomnia. While mexiletine may induce an arrhythmia or accentuate a pre-existing arrhythmia, no marked variations in ECG parameters were observed between baseline and the end of the treatment period when tested on NDM patients. An overview of adverse events is reported in Table 4.16.

Table 4.16: Overview of adverse events in the MYOMEX trial (safety population)

	Mexiletine (N=25)		**Placebo (N=25)**	
	Event	Patient (%)	Event	Patient (%)
Any AEs	[redacted]	[redacted]	[redacted]	[redacted]
Related AE	[redacted]	[redacted]	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
AE requiring concomitant medication	[redacted]	[redacted]	[redacted]	[redacted]

Source: MYOMEX CSR[18]
AE = Adverse event; N = Number of patients; Patient = Number of patients with at least one AE; % = Percentage of patients with at least one AE.

In the MYOMEX study, [redacted] out of 25 patients ([redacted]%) reported [redacted] adverse events. The most common side effects of mexiletine were gastrointestinal disorders, nervous system disorders and infections and infestations (see Table 4.17).

Table 4.17: Adverse events by SOC and PT – SAF

	Mexiletine (N=25)		Placebo (N=25)	
	Event	Patient (%)	Event	Patient (%)
TOTAL POPULATION	[redacted]	[redacted]	[redacted]	[redacted]
INFECTIONS AND INFESTATIONS	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]
NERVOUS SYSTEM DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Radicular pain	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]
GASTROINTESTINAL DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]
BLOOD AND LYMPHATIC SYSTEM DISORDERS – Lymphadenopathy	[redacted]	[redacted]	[redacted]	[redacted]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]
Eczema	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]
CARDIAC DISORDERS - Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
EAR AND LABYRINTH DISORDERS – Vertigo	[redacted]	[redacted]	[redacted]	[redacted]
EYE DISORDERS - Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]

	Mexiletine (N=25)		Placebo (N=25)	
	Event	Patient (%)	Event	Patient (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS – Fall	[redacted]	[redacted]	[redacted]	[redacted]
MUSCOSKELETAL AND CONNECTIVE TISSUE DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]
Muscle contracture	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
PSYCHIATRIC DISORDERS	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]		[redacted]	[redacted]
REPRODUCTIVE SYSTEM AND BREAST DISORDERS – Dysmenorrhea	[redacted]	[redacted]	[redacted]	[redacted]
VASCULAR DISORDERS	[redacted]		[redacted]	[redacted]
Flushing	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 40, pages 103-104.
AE = Adverse event; N = Number of patients; Patient = Number of patients with at least one AE; % = Percentage of patients with at least one AE.

In Statland et al. (2012),[27] 58 patients received at least one dose of mexiletine. The most common adverse event was gastrointestinal in nine participants in the mexiletine group and in one participant in the placebo group (Table 4.18). There were two reported cardiac adverse events both found incidentally on electrocardiogram at the end of week four (one patient had bradycardia in the mexiletine group that resolved on follow-up electrocardiogram and one patient had premature ventricular complexes in the placebo group). Neither necessitated stopping the study. There was one serious adverse event determined to be not study related (narcotic withdrawal).

Table 4.18: Adverse reactions in Statland et al. (2012)

Adverse reactions No. (%); N=58	Mexiletine	Placebo
Cardiac	1 (2%)	1 (2%)
Constitutional	3 (5%)	0
Dermatologic/skin	1 (2%)	2 (3%)
Gastrointestinal	9 (16%)	1 (2%)
Infection	1 (2%)	3 (5%)
Lymphatics	0	1 (2%)
Musculoskeletal/soft tissue	0	2 (3%)
Neurologic	5 (9%)	1 (2%)
Pain	4 (7%)	0
Total:	24	11

Source: Statland et al. (2012)[27]

In Stunnenberg et al. (2018),[26] the most common adverse event was gastrointestinal discomfort, which occurred in 21 of 30 patients (70%) during mexiletine treatment periods (Table 4.19). These symptoms

were controlled in most patients with lifestyle advice. One serious adverse event – a reversible urticaria-like rash – was determined to be mexiletine-related, and that patient was excluded from the trial. No clinically relevant electrocardiographic rhythm abnormalities or cardiac conduction interval changes were observed during the course of the trial.

Table 4.19: Adverse reactions in Stunnenberg et al. (2018)

Adverse reactions No. (%); N=30	Mexiletine	Placebo
Gastrointestinal discomfort (Reflux, dyspepsia, nausea, diarrhoea and flatulence)	21 (70%)	1 (3%)
Tremor	2 (7%)	0 (0%)
Palpitations	2 (7%)	0 (0%)
Headache	1 (3%)	1 (3%)
Insomnia	1 (3%)	0 (0%)
Any	27 (90%)	2 (6%)
>1 adverse reaction	2 (7%)	0 (0%)
>2 adverse reactions	0 (0%)	0 (0%)
Causing study withdrawal	1 (3%)	0 (0%)
Leading to dosage reduction	3 (10%)	0 (0%)
Leading to additional therapy	2 (7%)	0 (0%)
Serious adverse reactions:		
Allergic skin reaction (toxicodermia)	1 (3%)	0 (0%)
Source: Stunnenberg et al. (2018)[26]		

Suetterlin et al. (2015)[30] was a retrospective review of 63 patients treated for six months or greater with mexiletine. A total of 33 of 63 patients (52.4%) reported one or more adverse events. Sixteen of the 23 patients (69.6%) who reported dyspepsia required dyspeptic therapy, despite which four stopped taking mexiletine.

Patients with CLCN1-missense mutations required significantly more mexiletine than those with SCN4A mutations. Eight of 11 patients (72.7%) who stopped mexiletine previously because of inefficacy or intolerable adverse events found it effective and tolerable on retrial. Twelve patients were refractory to mexiletine treatment.

No serious adverse events were reported. Further, paired assessment of ECG parameters while not taking mexiletine and at the highest dose at which an ECG was recorded for each individual revealed no significant change in heart rate (71 beats per minute vs 71 beats per minute; p=0.97), PR interval (154 milliseconds vs 166 milliseconds; p=0.23), QRS duration (89 milliseconds vs 89 milliseconds; p=0.52), automatically calculated QTc (406 milliseconds vs 405 milliseconds; p=0.88), or manually calculated QTc (386 milliseconds vs 392 milliseconds; p=0.30). All 16 patients referred to cardiology because of cardiac concern were advised it was safe to start or continue mexiletine.

Post-marketing safety

Following the approval in 2010 of mexiletine for the symptomatic treatment of myotonic disorders in France, four periodic safety update reports (PSURs) have summarised the long-term safety and

tolerability of mexiletine (Mexiletine hydrochloride AP-HP 200 mg capsules) in patients with myotonic disorders.[33-36]

Between November 2010 and October 2012, 18 treatment-related adverse events were reported over two years of treatment with mexiletine in France, including the MYOMEX study (15 treatment-related adverse events). Treatment-related adverse events reported outside of the MYOMEX study were drug exposure during pregnancy and foetal exposure during pregnancy.[34-36]

In addition to the 25 patients treated in the MYOMEX study, a mean number of 372 patients with myotonic disorders were treated with mexiletine (based on a posology of two capsules per day, with 407,300 capsule units for treatment over the period). During the period covered by these PSURs, there were no reported serious adverse events, no dose modifications and no modifications of the formulation for safety reasons.[33-36]

The analysis of safety data collected between 2010 and 2012 did not reveal evidence of any new safety issues with the use of mexiletine in France. As such, the benefit-risk profile was considered favourable.[33-36]

Safety data are now available since the marketing authorisation of mexiletine (NaMuscla) for NDM for the period 18 December 2018 to 17 June 2019.[37] No new risk has been identified during the review period. The signals of drug interaction between sacubitril/valsartan and mexiletine causing proarrhythmogenic effect, fatal Drug Reaction and Eosinophilia with Systemic Symptoms (DRESS), fatal Pulmonary fibrosis were identified, which will be subject for close monitoring and discussion in future PSUR. In all cases mexiletine had been prescribed for a cardiac indication rather than for NDM.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company provided a feasibility assessment for conducting an indirect or mixed treatment assessment of mexiletine vs. lamotrigine in Section B.2.9.1 of the CS. This assessment resulted in four relevant studies, three for mexiletine (MYOMEX (2017),[18] Statland (2012)[27] and Stunnenberg (2018)[26]) and one for lamotrigine (Andersen (2017)[22]).

The mexiletine studies are discussed in Section 4.2 of this report, the study by Anderson (2017)[22] is a double blind, eight-week cross-over RCT comparing lamotrigine with placebo. The study was conducted between 2013 and 2015 in Denmark and published in 2017; it included 26 patients.

Baseline characteristics for all four trials are presented in Table 4.20 below. The trial populations are broadly similar in terms of age and all required genetic confirmation of NDM in the inclusion criteria apart from the Statland trial. In the Statland trial, the inclusion criteria stated eligible patients could have genetically confirmed NDMs, or clinical features of NDMs but negative myotonic dystrophy DNA testing. This could introduce some uncertainty that all the patients recruited into the trial definitely had NDM.

Table 4.20: Trial baseline demographic and disease characteristics

Characteristic	Andersen 2017[22]	MYOMEX 2017[18]	Statland 2012[27]	Stunnenberg 2018[26]
Trial design type	Double blind, cross-over RCT	Double blind, cross-over RCT	Double blind, cross-over RCT	Double blind, cross-over RCT[3]
Study treatments	Lamotrigine Placebo	Mexiletine 600mg/day Placebo	Mexiletine 600mg/day Placebo	Mexiletine 600mg/day Placebo
Treatment duration	8 weeks	18 days	4 weeks	4 weeks
Trial conduct period	2013-2015	2011-2014	2008-2011	2014-2015
Countries	Denmark	France	USA, Canada, UK, Italy	Netherlands
Number of patients analysed	26	25	59	27
Patient level data available?	N	Y	N	Y[2]
Genetically confirmed NDM	Y	Y	Y/N[9]	Y
Efficacy subgroups	None	MC/PC	None	Genotype
Age (years)[1]	45	43	43	43
Male (%)	61	68	56	73[8]
BMI (kg/m^2) [1]	28	25	NR	NR
MC (%)	54	52	NR	NR
PC (%)	46	48	NR	NR
Stiffness assessment type[4]	MBS (0-5)	VAS (0-100)	VAS (1-9)	VAS (1-9)
Baseline stiffness[5]	3.2 (1.2)	76 (20)	4.26 (2.71)	6.65 (1.78)
Eyelid closure action myotonia (s)	4.8	NR	0.49[7]	3.50
Hand grip relaxation time (s)[7]	4.3	NR	0.86[7]	2.02

Source: CS, Table 36, page 94.[1]
NDM = Non-dystrophic myotonia; BMI = Body mass index; MC = Myotonia congenita; PC = paramyotonia congenita; RCT = Randomised Controlled Trial.
Notes: [1]) Mean/median. [2]) IPD available for limited baseline and primary endpoint (mean daily stiffness severity score). [3]) Aggregate N-of-1 design, multiple period per patient. [4]) Patient self-reported. [5]) Mean (SD). [7]) Geometric mean. [8]) Incorrectly reported as 22% in the abstract of the publication. [9]) Inclusion criteria stated patients could have genetically confirmed NDMs or had clinical features of NDMs but negative myotonic dystrophy DNA testing.

The company presents a complete list of all outcomes reported in the four trials (CS, Table 37, pages 96-98). This table shows that all trials measured stiffness as their primary outcome. However, different outcome measures were used, the Myotonia Behaviour Scale in Andersen 2017,[22] a VAS stiffness severity score in MYOMEX 2017[18] and patient-reported stiffness on the interactive voice response (IVR) diary in Statland 2012[27] and Stunnenberg 2018[26]. The company consulted clinical experts regarding the possible clinical interchangeability of the MBS and VAS/IVR scales. it was concluded that it would not be appropriate to conduct ITC of this outcome given the variability in the measures used to assess stiffness.

Clinical measures of myotonia of the eye, hand or leg and health-related quality of life (HRQoL), namely SF-36 were also assessed in the lamotrigine trial and at least one of the mexiletine trials. After consultation with clinical experts, it was concluded that it would not be appropriate to conduct an ITC using clinical measures of myotonia of the eye, hand or leg, because of lack of a consensus on minimally clinically important difference and lack of precision of the tests. Regarding the SF-36 assessments, the company states that there are doubts about the validity of the SF-36 overall score in the lamotrigine trial as well as there being insufficient data to inform a meaningful ITC for this outcome.

ERG comment: The ERG agrees that there are serious limitations to performing an indirect comparison of mexiletine vs. lamotrigine. The most informative comparison would be based on the primary outcome in the mexiletine and lamotrigine trials, i.e. stiffness. However, clinical experts consulted by the company stated that the MBS (lamotrigine trial[22]) was different to the VAS (MYOMEX trial[18]) and IVR (Statland[27] and Stunnenberg[26] trials) as it not only measured stiffness but also impact on function. Some clinical experts also noted the scale had been developed in a very small study and had not been validated. In addition, stiffness was measured using different scales in the mexiletine trials (0 to 100 in MYOMEX, 1 to 9 in Statland and Stunnenberg) and different outcomes (change from baseline in MYOMEX, mean during the third and fourth week of treatment in Statland, and mean of the daily scores in Stunnenberg). The statistical analysis methods were also different as MYOMEX performed a mixed effects linear regression model on ranks as the stiffness scores were not normally distributed and reported medians and ranges for change. The other two mexiletine trials also used the same type of model but analysed mean stiffness scores rather than change from baseline and reported results as means with 95% CI. This means that it would not be possible to statistically pool the results of the three mexiletine trials for use in an ITC. The lamotrigine trial did not report summary statistics for the within-patient difference in MBS on each treatment so could not be used in an ITC.

For HRQoL the trials used different tools. MYOMEX reported results for all domains of INQoL, Statland also reported INQoL but as a different measure (mean scores during last two weeks of treatment rather than change from baseline), Stunnenberg only reported the overall INQoL score and the lamotrigine trial used SF-36 but did not report the results in a format suitable for analysis (there were 95% CI but no means). An ITC comparison of HRQoL outcomes would not be possible and, the ERG agrees with the company that ITC of mexiletine vs. lamotrigine would not be informative.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

As stated above, given the available evidence presented in the published studies, the ERG agrees with the company that an indirect comparison of mexiletine vs. lamotrigine would not be informative or possible for stiffness.

However, Anderson et al. (2017) "estimated the standardized effect size of MBS data (effect size/baseline SD) with confidence interval (CI), to compare the effect of mexiletine (Statland et al., 2012) and lamotrigine".[22] As stated by Anderson et al. (2017), "Mexiletine is the only drug with proven

effect for treatment of non-dystrophic myotonia, but mexiletine is expensive, has limited availability and several side effects. There is therefore a need to identify other pharmacological compounds that can alleviate myotonia in non-dystrophic myotonias. Like mexiletine, lamotrigine is a sodium channel blocker, but unlike mexiletine, lamotrigine is available, inexpensive, and well tolerated." Therefore, Anderson et al. investigated the potential of using lamotrigine for treatment of myotonia in patients with non-dystrophic myotonias. According to Anderson et al. (2017), "lamotrigine has a benign side effect profile, is easy to obtain and costs ~10% of the price of mexiletine";[22] and that was in 2017, before the recent mexiletine price increase by Lupin Healthcare. Anderson et al. (2017) conclude that "the standardized effect size of lamotrigine was 1.5 (CI: 1.2–1.8) and of mexiletine 1.4 (CI: 0.6–2.2) and 3.0 (CI: 0.1–3.1). Thus, the standardized effect size was in the range of the other treatment's CI, indicating a similar treatment effect of mexiletine and lamotrigine".[22] It needs to be taken into account that Anderson et al. compare MBS scores with IVR stiffness scores, which may not be comparable according to clinical experts consulted by the company. Therefore, the results of this analyses need to be interpreted with considerable caution.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The population defined in the scope is: Adults with non-dystrophic myotonic disorders requiring treatment of symptomatic myotonia. The population in the CS is the same; therefore, the population is in line with the scope. However, there is no specific definition for patients 'requiring treatment of symptomatic myotonia'. According to the EMA in its assessment of NaMuscla "only patients with severe enough myotonia were included in the MYOMEX study", but this "does not necessarily mean these patients suffered from "severe myotonia"; rather, they have clinical symptoms of myotonia that are severe enough to justify treatment with NaMuscla.".[24] In addition, there is no generally recognised and agreed upon definition of myotonia severity according to the company.

No results for mexiletine are presented for patients over 68 years and the number of patients over the age of 65 in the UK is not known according to the company. Therefore, it is unclear whether the trial populations are representative for the UK patient population.

The intervention (mexiletine) is in line with the scope. However, the dosage and administration of mexiletine in UK practice is not the same as in the MYOMEX trial (see Section 3.2 of this report).

The description of the comparators in the NICE scope is as follows: "Established clinical management without mexiletine, including but not limited to: lamotrigine or best support care".[15] The company included only one comparator (best supportive care). This was considered the same as the placebo arms in the trials. Lamotrigine was not included as a comparator.

The company identified three randomised clinical trials which evaluated mexiletine and one retrospective review of a UK centre patient database:

- MYOMEX: A double blind, cross-over RCT (N=26), comparing mexiletine 600 mg/day with placebo, with a duration of four weeks, performed in 2011 to 2014 in France;
- Statland 2012: A double blind, cross-over RCT (N=59), comparing mexiletine 600 mg/day with placebo, with a duration of 18 days, performed in 2008 to 2011 in the USA, Canada, UK, and Italy;

- Stunnenberg (2018): Aggregated, randomised, N-of-1 trials (N=30), comparing mexiletine 600 mg/day with placebo, with a duration of four weeks, performed in 2014 to 2015 in the Netherlands;
- Suetterlin (2015): A retrospective review (N=63), comparing mexiletine up to 600 mg/day with best supportive care; mean length of follow-up: 4.8 years (range: 0.5 to 17.8), performed in the UK.

The four included studies had different designs; therefore, it is not advisable to pool results of individual mexiletine studies (see Section 4.2.4 of the report for details). Patient level data was available solely for the MYOMEX study, and the company described this study as the pivotal study. Therefore, results in this section will focus on the MYOMEX study. Full results of all studies are reported in Section 4.2.5 of this report.

The MYOMEX trial reported favourable results with mexiletine compared with placebo for the primary outcome of stiffness and secondary outcomes of the time taken to complete a chair test, CGI, CMS scores and most quality of life domains as measured with the INQoL tool. This was a crossover trial so each patient received both mexiletine and placebo in a randomised order and the analysis was performed on the within person change from baseline. Patients could have previously received mexiletine treatment and at baseline 56% of patients had previously been treated or were treated at screening. Even though the trial was double-blind it is quite likely that, as each patient received both treatments, those who had previously received mexiletine were able to recognise when they were receiving it during the trial particularly if they had previously experienced side effects. If patients can identify which treatment they are taking in each period, the trial is at risk of over-reporting the effectiveness of the intervention.

The results of the analysis of period 1 only, do confirm the analysis of the whole trial period but it should be noted that this was a very small trial, of only 25 patients, and each treatment was received for between 18 and 22 days with a wash-out period of four to eight days

Although stiffness was the primary efficacy outcome in the MYOMEX trial, it was not used as a measure of effectiveness in the economic model. Treatment effectiveness in the economic model was assessed using eight items from the INQoL scale. The mapping of INQoL items to the appropriate EQ-5D domains is explained by the company in Table 17 of the Response to Clarification; and the results for these eight items are presented in Table 18 of the Response to Clarification.[25] The company seem to have used the items most relevant to patient physical functioning. Results of the eight items are in accordance with the other items of the INQoL scale.

A major limitation of all included trials is that the treatment duration was very short (between 18 days and four weeks).

Mexiletine was generally well tolerated in the included studies. Gastrointestinal discomfort was the most common adverse event, and there were no treatment-related serious adverse events.

The company provided a feasibility assessment for conducting an indirect or mixed treatment assessment of mexiletine vs. lamotrigine. In addition to the three mexiletine trials described above, the company identified one trial evaluating lamotrigine: Anderson (2017).[22] This is a double blind, eight-week cross-over RCT comparing lamotrigine with placebo. The study was conducted between 2013 and 2015 in Denmark and published in 2017; it included 26 patients. The ERG agrees with the company that there are serious limitations to performing and indirect comparison of mexiletine vs. lamotrigine due to differences in study designs and outcomes reported.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

Appendix G of the CS details systematic searches of the literature used to identify studies investigating economic evaluations or cost and healthcare resource use associated with the treatment of NDM. Searches were conducted in October 2019, and no language or publication date limits were reported. Databases were searched from date of inception. A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review (as reported in CS)

	Resource	Host/Source	Date range	Date searched
Electronic databases	MEDLINE (including MEDLINE daily, MEDLINE ePub ahead of print, MEDLINE In-Process)	Ovid	1946-7.10.19	8.10.19
	Embase	Ovid	1974-7.10.19	8.10.19
	Cochrane CENTRAL	Wiley	Issue 10/12, October 2019	8.10.19
	Cochrane CDSR			
	EconLit	Ovid	1886-26.9.19	8.10.19
	DARE, NHS EED, HTA	CRD website	All years	15.10.19
Conference proceedings	Annual Meeting of the American Academy of Neurology	Embase/ handsearch	2015-2019	Not reported
	European Neurology Congress	Handsearch	2016-2019	
	World Congress of Neurology	Embase / handsearch	2015, 2017	
	World Muscle Society Congress	Embase / handsearch	2015-2018	
Additional resources	ClinicalTrials.gov	Web search	All years	16.10.19
	Clinicaltrialsregister.eu			
	WHO ICTRP			
	NICE			
	SMC			
	AWSMG			

CENTRAL = Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstract Reviews of Effects; NHS EED = NHS Economic Evaluation Database; HTA = Health Technology Assessment database; WHO ICTRP = WHO International Clinical Trials Registry Platform; NICE

= National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; AWMSG = All Wales Medicines Strategy Group

Appendix H of the CS details systematic searches of the literature used to identify studies investigating the health state utility values associated with the treatment of NDM. Searches were conducted in October 2019, and no language or publication date limits were reported. Databases were searched from date of inception. A summary of the sources searched is provided in Table 5.2.

Table 5.2: Data sources for the HRQoL systematic review (as reported in CS)

	Resource	Host/Source	Date range	Date searched
Electronic databases	MEDLINE (including MEDLINE daily, MEDLINE ePub ahead of print, MEDLINE In-Process)	Ovid	1946-7.10.19	8.10.19
	Embase	Ovid	1974-7.10.19	8.10.19
	Cochrane CENTRAL	Wiley	Issue 10/12, October 2019	8.10.19
	Cochrane CDSR			
	EconLit	Ovid	1886-26.9.19	8.10.19
	DARE, NHS EED, HTA	CRD website	All years	15.10.19
	ScHARRHUD	ScHARR website	All years	8.10.19
Conference proceedings	Annual Meeting of the American Academy of Neurology	Embase/ handsearch	2015-2019	Not reported
	European Neurology Congress	Handsearch	2016-2019	
	World Congress of Neurology	Embase / handsearch	2015, 2017	
	World Muscle Society Congress	Embase / handsearch	2015-2018	
Additional resources	ClinicalTrials.gov	Web search	All years	16.10.19
	Clinicaltrialsregister.eu			
	WHO ICTRP			
	NICE			
	SMC			
	AWSMG			

CENTRAL = Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstract Reviews of Effects; NHS EED = NHS Economic Evaluation Database; HTA = Health Technology Assessment database; WHO ICTRP = WHO International Clinical Trials Registry Platform; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; AWMSG = All Wales Medicines Strategy Group

ERG comment: A single search was undertaken for cost effectiveness, costs and healthcare resource studies, and a separate search was conducted for HRQoL data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were

searched, including additional grey literature resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

5.1.2 Inclusion/exclusion criteria used in the study selection

The predefined eligibility criteria for the cost effectiveness, HRQoL and cost/resource use SLRs were provided in detail, in Table 23 (Appendix G, for cost effectiveness and costs/resource use SLRs), and Table 34 (Appendix H, for the HRQoL SLR) of the CS respectively.[38] The inclusion/exclusion criteria were based on the PICOS criteria, to identify the population and disease, interventions, comparators, outcomes, and study designs of interest, as well as geographical location, publication dates and language. There were no exclusions based on the intervention, comparator, geographical setting of studies, language and the publication date in the SLRs.

The title-abstract and full-text screening were conducted by two independent reviewers. Disagreements were discussed and a third reviewer was involved if required.

ERG comment: The ERG finds the eligibility criteria and search strategy to be transparent and plausible. However, it is unclear how the trials reporting HRQoL outcomes (with generic preference-based utilities) as outlined in Section 4.2.5 of this report were not identified in the SLRs conducted in Appendix H

5.1.3 Identified studies

No studies containing economic evaluations or cost and resource use data were identified. There were also no studies identified with utility data. The PRISMA diagrams and the list of excluded articles with their reasons of exclusion were given in Appendix H and Appendix G of the CS, for the economic evaluation/cost and resource use SLRs and HRQoL SLR, respectively.[38]

5.1.4 Interpretation of the review

The review was generally well reported however no cost effectiveness, HRQoL, cost/resource use evidence relevant to the indication and intervention was detected. Therefore, the development of a new economic model by the company was considered to be plausible by the ERG.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.3.

Table 5.3: Summary of the company submission economic evaluation

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Model	Three state cohort-based Markov model. The states are "alive on treatment", "alive no treatment" and death.	A lack of evidence of the natural history of the disease in the literature and from clinical experts when questioned led to the use of a simple Markov model where patients could be in one of two health states, 'alive on treatment' (AOT) or alive with no treatment (ANT), with the final absorbing state 'death'.	Section 5.2.2
States and events	Patients start in the "alive on-treatment" state, where they remain until treatment discontinuation or death. Upon treatment discontinuation, patients either remain in the "alive no treatment" state, or they die.	The company claimed that the Markov model was built in line with the NICE reference case and enabled the extrapolation of costs and benefits across the lifetime of an NDM cohort.	Section 5.2.2
Comparators	Base-case comparator is the best supportive care. Lamotrigine was not considered as a relevant comparator.	The company did not consider lamotrigine as a comparator based on expert opinions (Appendix M of CS)[39], market research[40] and UK patient survey[41].	Section 5.2.4
Natural history	The natural history of the disease is unknown. In the economic model, only the treatment patterns of the patients were modelled (with and without mexiletine) therefore the only events in the model were mexiletine discontinuation and death. Under mexiletine and BSC treatment, the utility and the cost inputs remain constant over time. Upon mexiletine treatment discontinuation, it was assumed that the patients' HRQoL and costs would be the same as the patients' HRQoL and costs, under BSC.	The detailed natural history and determinants of morbidity have yet to be prospectively studied[42] and therefore the underlying disease progression is unknown, but the company claimed that the disease severity worsens over time.	Section 2 and Section 5.2.2
Treatment effectiveness	The clinical effectiveness outcomes from the MYOMEX trial and other trials in the literature were not directly used in the economic model. It was assumed that the mexiletine treatment would have an impact on the HRQoL as well as the on the resource use of the patients. General population mortality was assumed for the NDM patients.	The benefit of mexiletine treatment was reflected in terms of increased HRQoL and reduced healthcare resource use. The underlying disease progression is unknown.	Section 5.2.6

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Adverse events	The effects of AEs were captured by applying cycle-based costs for the adverse events. In the economic model the only included adverse events were 1. The joint probability of suffering a gastrointestinal disturbance whilst on mexiletine and being treated for dyspepsia associated with this gastrointestinal disturbance. 2. Treatment specific fracture probabilities No additional disutilities due to AEs were applied in the model.	The GI disturbance probabilities were obtained from the Suetterlin et al. study.[43] in the base case, whereas the treatment specific fracture probabilities were based on UK Advisory Board.[44]	Section 5.2.7
Health-related QoL	The company measured health directly in patients in the MYOMEX trial using the condition-specific INQoL. No mapping algorithm was available between the INQoL and EQ-5D and therefore a valuation study had to be conducted to be able to obtain utility values from the INQoL data. Two general population valuation studies were conducted: a discrete choice experiment (DCE) and a vignette study with time trade off (TTO) valuation. The INQoL was reduced for valuation. Items were selected for inclusion in the valuation based on conceptual overlap with the EQ-5D and importance to NDM. Alternative utility values were derived from the DCE study, using a variety of assumptions to anchor the results to a utility scale (in the base-case DCE results were rescaled to fit the range of the EQ-5D-3L (1.0 to -0.59)). The vignette/TTO study provided participants with INQoL health state vignettes covering the same INQoL items as the DCE study and asked participants to value those states using a TTO exercise.	Generic HRQoL data was not collected in the MYOMEX trial. In the CS, it was argued that generic HRQoL tools such as SF-36 would not be able to capture the disease characteristics that impact the HRQoL of NDM patients. Given that no mapping algorithms were available, the company had to conduct its own valuation study.	Section 5.2.8

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Resource utilisation and costs	The economic analysis was performed from the NHS and PSS perspective. The following state-specific costs were included: • Drug acquisition costs (AOT only) • Treatment-related AEs costs (AOT only) • Cardiac evaluation and monitoring costs (AOT only) • Genetic testing costs • Costs of physiotherapy, occupational therapy, speech therapy, day case attendance, and mobility aids • Costs of treatment of fractures resulting from falls (incl. A&E attendance) •	Healthcare unit costs were obtained from the PSSRU 2018[45], 2018 NHS reference costs,[46] 2017 UK Genetic Testing Network,[47] and the NHS.uk website.[48] Genetic testing costs were inflated using the HCHS index from PSSRU 2018.[45] The frequency of the healthcare resource use is dependent on the disease severity categorisations using clinical experts' and patients' opinions as well as the Clinical Myotonia Scale (CMS) disability scale scores collected from the MYOMEX trial. Drug costs were taken from the BNF 2019.[49] The dose information was based on company assumptions (400 mg daily dose) and a mean dose intensity of 94.82% was derived from the MYOMEX trial.	Section 5.2.9
Discount rates	Cost and health outcomes discounted at 3.5%	As per NICE reference case	Section 5.2.5
Sensitivity analysis	Probabilistic, deterministic one-way sensitivity analysis and scenario analyses were conducted	As per NICE reference case	Section 6.2.1

AE = adverse event; AOT = alive on treatment; ANT = alive with no treatment; BNF = British National Formulary; CS = company submission; DCE = discrete choice experiment; GI = gastrointestinal; HRQoL = health-related quality of life; INQoL = Individualized Neuromuscular Quality of Life Questionnaire; NDM = non-dystrophic myotonia; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; PSSRU = Personal Social Services Research Unit; TTO = time trade off; UK = United Kingdom

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Direct health effects for patients included.
Perspective on costs	NHS and PSS.	NHS and PSS perspective taken.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	Cost-utility analysis with fully incremental analysis undertaken.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The model time horizon of 57 years is appropriate for a lifetime horizon as the starting age of the treatment in the economic model was 44 years.
Synthesis of evidence on health effects	Based on systematic review.	Systematic review conducted to identify evidence on health effects. However, none of the effectiveness data were used in the model. The treatment effect of mexiletine vs. BSC was estimated based on: 1. a difference in health state utilities, 2. an assumption regarding difference in disease progression, and 3. an assumption regarding resource consumption.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects expressed in QALYs. HRQoL was measured using the INQoL, a condition-specific measure. The INQoL was valued using both a DCE study and a vignette/TTO study. In both cases the INQoL had to be reduced to be amendable for valuation. The company made some effort to align the reduced INQoL more closely to the EQ-5D descriptive system and to anchor DCE results to the utility range of the EQ-5D-3L. However, this does not mean that the resulting utilities are equivalent as many differences still exist between the measures.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	HRQoL (INQoL) was reported by NDM patients in the MYOMEX trial.

Element of health technology assessment	Reference case	ERG comment on company's submission
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Two valuation studies were conducted. A DCE was conducted in 508 members of the UK general population and a vignette/TTO study was conducted in 200 members of the general population. Attempts were made to make sure these samples were representative.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Costs were sourced from NHS Reference Costs 2017–18,[46] PSSRU 2018,[45] the BNF,[49] 2017 UK Genetic Testing Network,[47] and the NHS.uk website.[48]
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Costs and health effects are discounted at 3.5%. In scenario/sensitivity analyses different discount rates were considered.
BNF = British National Formulary; DCE = discrete choice experiment; HRQoL = health-related quality of life; INQoL = Individualized Neuromuscular Quality of Life Questionnaire; NHS = National Health Service; PSS = personal social services; PSSRU = Personal Social Services Research Unit; QALYs = quality-adjusted life years; TTO = time trade off		

5.2.2 Model structure

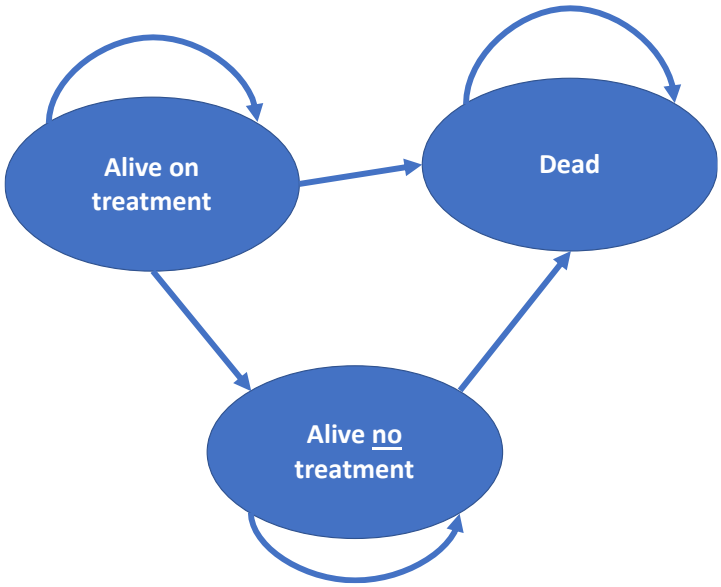
A Markov cohort model was created within Microsoft Excel® to evaluate the cost effectiveness of mexiletine for the treatment of patients with NDM in comparison to the BSC. The Markov model enabled the extrapolation of costs and benefits across the lifetime of an NDM cohort.

In the economic model, only the treatment patterns of the patients were modelled (with and without mexiletine) therefore the only events in the model are mexiletine discontinuation and death. Under mexiletine and BSC treatment, the utility and the cost inputs remain constant over time. Upon mexiletine treatment discontinuation, it is assumed that the patients' HRQoL and costs would be the same as the patients' HRQoL and costs, under BSC.

The model consists of three health states, 'alive on treatment' (AOT), 'alive with no treatment' (ANT), and the final absorbing state 'death', as illustrated in Figure 5.1 below. Patients on mexiletine treatment started the model from the AOT state, whereas patients receiving BSC start the model from the ANT state and remain there until death.

After treatment discontinuation, patients receiving mexiletine are assumed to be in the BSC until death. A cycle length of one year was considered and half-cycle correction was also applied. A lifetime horizon was chosen, capping the maximum survival at age 100 years. The utility and resource use inputs for the AOT and ANT states were derived from the individual patient data from the MYOMEX trial.

Figure 5.1: Markov model structure



Source: Figure 25 from CS.[2]

ERG comment: The model presented in the CS is not a disease model, as it does not attempt to describe the course of the disease but merely the treatment status of a patient. This leads to a heterogeneous group of patients being assigned the same costs and quality of life. Instead, a more granulated model would be preferred, where each health state is fairly homogeneous with regards to costs and quality of life. However, the ERG concedes that given the current level of data available the current model structure is difficult to improve upon and can be regarded as adequate.

The model is based on time cycles and half cycle correction is applied to reflect that patients will move from one state to another evenly throughout that time cycle. However, the half cycle correction was incorrectly implemented as the first cycle was not incorporated into the calculations of costs and QALYs. This has been rectified by the ERG (see Section 7.1.2), and the impact on the ICER was small.

The ERG has several concerns that the current model structure might not reflect the UK clinical practice of NDM patients.

In the model, NDM patients are considered to receive only one line of treatment. However, the ERG considers that it might be plausible that NDM patients receive additional lines of treatment after they discontinue from their assigned first-line treatments. Therefore, in the clarification letter, the ERG asked the company to incorporate health state(s) for "2nd and further line treatments" into the model structure, so that the patients after discontinuing from mexiletine or "best supportive care without pharmacological treatment" would be able to receive further lines of pharmacological treatment in their lifetime.[25]

The company argued that even if patients discontinue mexiletine in the first-line, their second-line of treatment would be most probably mexiletine again, based on the findings from Suetterlin et al. study, where eight out of the 11 patients who stopped mexiletine found mexiletine effective or tolerable on retrial.[43] In addition, the company referred to the NDM clinical management research that they conducted among NDM treatment centres.[40] In their research, they mentioned that out of the 265 identified patients who have ever been treated for NDM, 132 still remained on their first-line treatment and 78 of the patients were reported to receive a second line therapy at the moment of contact with the treatment centres. It was also stated that the most common medicines used to treat NDM in second-line

were phenytoin, flecainide and acetazolamide, which were not licensed for NDM, and therefore not part of the BSC, in line with the original scope. Hence, the company did not incorporate additional health state(s) for second/later line therapies after first-line treatment discontinuation, and also argued that this was a conservative choice, since the additional health state(s) would increase the costs in the BSC arm with no efficacy/safety evidence in comparison to mexiletine.

The ERG considers that the arguments provided by the company did not justify the exclusion of the health state(s) for second/further line treatments. In the NDM clinical management research, more than half (n=78) of the patients who discontinued first-line treatment (n=265-132=133) received another line of therapy. Even though there is a scarcity of evidence on treatment efficacy/safety for further line therapies, the ERG disagrees that not including those would be conservative, since these costs and effects will be included in both arms and, the impact on incremental costs and effects would highly depend on the utility and cost input assumptions for those states.

Secondly, the ERG has concerns regarding the assumptions by the company that the resource use and utility of each health state in the economic model would remain constant over time. Since the natural history of the disease is not known, there is a scarcity of evidence on whether the utility and the resource use in each health state would remain unchanged. Despite the issues elaborated above, the model still can be considered as fit for the purpose of decision making.

5.2.3 Population

The company stated that the population considered in the economic evaluation is adults with NDM who require symptomatic treatment of myotonia. It was considered that the patients from the MYOMEX trial were representative of the NDM patients eligible for mexiletine treatment in the UK clinical practice. In the UK, once the diagnosis is made, mexiletine treatment is initiated by a neurologist after discussion with the patient at either the National Hospital for Neurology and Neurosurgery in Queen Square, London or one of the neurology centres commissioned by NHS England as a specialised service.[50, 51] The company claimed that at the diagnosis stage, patient's symptoms would be severe enough that any strategies they have developed to cope with their condition, such as avoiding triggers or performing muscle warming routines (effectively BSC), would not be sufficient and the patient would require treatment.[2] Since the patients entering the MYOMEX trial had disease severe enough to warrant drug therapy, (as described in Section 4.2 of the ERG report), the company claimed that the baseline population of the MYOMEX trial reflected UK clinical practice. The baseline characteristics of the patients from the MYOMEX trial were used in the model and are given in Table 5.5 below.

Table 5.5: Baseline characteristics of the patients in the MYOMEX trial

Demographics/ characteristics	Treatment sequence		All patients (n=25)
	Placebo-mexiletine (n=13)	Mexiletine-placebo (n=12)	
Mean (SD) age, years	[redacted]	[redacted]	[redacted]
Diagnosis, n (%)			
Myotonia congenita	[redacted]	[redacted]	[redacted]
Paramyotonia congenita	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]

Demographics/ characteristics	Treatment sequence		All patients (n=25)
	Placebo-mexiletine (n=13)	Mexiletine-placebo (n=12)	
Mean (SD) BMI, kg/m^2	[redacted]	[redacted]	[redacted]
Mexiletine treatment, n (%)			
Treated at screening	[redacted]	[redacted]	[redacted]
Previously treated (before screening)	[redacted]	[redacted]	[redacted]
Treatment naïve	[redacted]	[redacted]	[redacted]

Source: Based on Table 12 from the CS.[2]
BMI: body max index; SD: standard deviation

ERG comment: The ERG has doubts about whether the patients from the MYOMEX trial were representative of the NDM patients eligible for mexiletine treatment in UK clinical practice. Since age of onset of NDM symptoms is typically in infancy or childhood,[52] the average baseline age of patients in the MYOMEX trial, 43, might not reflect the average age of the mexiletine eligible patients.

Additionally, the ERG is uncertain whether the eligibility criteria that were used in the MYOMEX trial would be reflective of the disease severity of the NDM patients that are eligible for mexiletine treatment in UK clinical practice. The claims of the company on the symptom severity of NDM patients at the diagnosis stage (that would be similar to the baseline symptom severity of the patients in the MYOMEX trial) were not substantiated with evidence.

5.2.4 Interventions and comparators

The cost effectiveness model in the company submission compares mexiletine against no pharmacological therapy for the treatment of NDM. It is assumed that all patients also receive BSC regardless of treatment choice. BSC consists of supportive nonpharmacological treatment as well as any strategies the patients have developed to cope with their condition, such as avoiding triggers or performing muscle warming routines. The company claimed that the placebo arm of the MYOMEX trial reflected the BSC in UK clinical practice.

Mexiletine is taken daily, on a regular basis, to address patient symptoms. Mexiletine is administered orally with water and in an upright position, preferably at mealtimes to reduce the risk of digestive intolerance. The recommended starting dose, as stated in the summary of product characteristics (SmPC), is one capsule of 167 mg mexiletine base per day. Then, based on the clinical response after at least one week of treatment, the dose of the patients may be titrated up, to a daily dose of 333 mg mexiletine. After at least one further week of treatment, the dose can be further increased to 500 mg daily (three capsules per day or equivalent to 600 mg mexiletine hydrochloride) based on clinical response.[53]

The company considered that the use of the clinical dose of 400 mg daily dose as the base-case would be more appropriate, since, patients in all mexiletine trials were force titrated to achieve a dose of 600 mg mexiletine hydrochloride daily at which point efficacy was assessed. This would represent an artificial situation rather than what would happen in clinical practice. The company claimed that the 400 mg daily dose would be more in line with the long-term follow-up of the MYOMEX trial, as well as the UK real world retrospective study from Suetterlin et al., which reported that the mean clinically effective dose of mexiletine used was 416.7 mg daily.[43]

ERG comment: The ERG noted that lamotrigine was not included as a comparator in the economic model, even though it was listed in the final scope issued by NICE.[54] After a request for clarification, the company reiterated its position on the exclusion of lamotrigine as a comparator in the economic model, due to the following reasons:

- Based on the clinical experts (Appendix M of company submission) and 2019 market research conducted by the company, lamotrigine is not established in clinical practice with less than 3% of patients currently on or having ever received lamotrigine.[39, 40]
- Lamotrigine is not licensed for the indication to treat NDM patients in the UK or any other country and no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients.
- No randomised/non-randomised evidence for head to head comparison of lamotrigine against mexiletine, and lack of common outcomes from the trials to perform an indirect treatment comparison including lamotrigine and mexiletine trials.[55]

Even though the ERG acknowledges the lack of evidence to populate the economic model for including lamotrigine as a comparator, the ERG disagrees with the company that lamotrigine can be excluded as a comparator. Since it was listed in the final scope as a comparator, the ERG considers that lamotrigine should be included in economic model. Therefore, the ERG conducted several exploratory analyses in Section 7, comparing lamotrigine with mexiletine under various assumptions.

Regarding the daily dose of mexiletine, the ERG considers that assuming a daily dose of 600 mg per day in the model (the force titrated dose in the MYOMEX trial), would be more rational, since the efficacy and safety inputs of the economic model were also obtained from the MYOMEX trial, hence reflecting the efficacy and safety of mexiletine, when it was administered with a dose of 600 mg per day. Additionally, among the clinical experts, there was no consensus that the average daily dose for mexiletine would be 400 mg per day; in Appendix M of the CS, a clinical expert stated that "400 mg is minimum. Some males may need higher doses such as 500 or 600 mg daily".[39] (p6, Appendix M of the CS) Due to the fact that the efficacy data used in the economic model is based on the MYOMEX trial, for the sake of consistency, the ERG also prefers the force titrated daily dose in the MYOMEX trial, which is 600 mg per day, in its base-case.

5.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from the perspective of the NHS and Personal Social Services (PSS). The model has a time horizon of 58 years, which is considered appropriate as a lifetime horizon given that the baseline age of patients in the model is 44 years. Costs and QALYs were discounted at 3.5% per annum according to the NICE method guidance. A lower discount rate (1.5% rather than 3.5%) was used in the scenario analysis based on the most recent UK HM Treasury Green Book.[56]

5.2.6 Treatment effectiveness and extrapolation

In the economic model, the potential treatment benefit of mexiletine was mostly reflected in treatment specific HRQoL and the healthcare resource use, derived from the MYOMEX trial, which will be elaborated on in Sections 5.2.8 and 5.2.9, respectively. Other clinical inputs required in the model were: treatment discontinuation, compliance, mortality and disease progression differential.

Treatment discontinuation and compliance

The transition probability of moving from the AOT health state to the ANT health state in the Markov model was informed by the discontinuation rate of patients from the mexiletine arm of the retrospective

chart review by Suetterlin et al. study.[43] In this study, the mean follow-up was 4.8 years and 15 out of 63 patients discontinued treatment. The probability of discontinuation in this study was converted to an annual discontinuation rate (using the formula: rate=(-ln(1-probability))/t), which resulted in an annual discontinuation rate of 5.15%.

Mean compliance was calculated according to the number of capsules taken by each individual during the mexiletine arm of the MYOMEX study, [redacted] in the base-case. This figure was used to calculate the annual number of capsules taken by an individual in the model, under the clinical effective dose assumed by the company (400 mg daily), which in turn informed mexiletine drug cost calculations.

Alternative sources of mexiletine compliance and discontinuation are given in Table 5.6 below.

Table 5.6: Sources of mexiletine compliance and discontinuation probabilities

Study	Compliance rate	Discontinuation rate
MYOMEX study[57]	[redacted] (base-case)	[redacted]
Statland et al (2012)[58]	90.2%	7%
Stunnenberg et al (2015)[59]	94%	3%
Suetterlin et al (2015)[43]	Not reported	5.15% (base case)

Source: Based on Table 48 from the CS.[2]

ERG comment: The ERG considers using treatment discontinuation rate obtained from the MYOMEX trial to be more consistent, since other model inputs were also obtained from the MYOMEX trial. The ERG acknowledges though that this preference for consistency comes at the cost of a shorter follow-up duration used in the estimation of the rate, Additionally, the ERG requested that the company include an option in the economic model to choose pooled discontinuation/compliance values from all mexiletine trials. However, the company only provided the arithmetic mean on the discontinuation rates from the trials, which would not be appropriate to use in the model, since the weight of the estimate from each trial should reflect the precision of the corresponding rates while pooling these estimates.

Mortality

The company assumed that there was no reduced life expectancy in NDM patients in comparison to the general population, therefore the mortality from the UK life tables were used in the economic model.[60]

Disease progression differential

The company assumed a disease progression differential in the model, based on the assumption that quality of life in NDM patients decreases over time in the absence of treatment for myotonic symptoms. This disease progression differential was implemented by reducing the utility value for ANT by 15% for patients receiving BSC or discontinuing from mexiletine. This introduced a differential effect between mexiletine treatment and BSC, on top of the treatment effect observed from the MYOMEX trial, based on the assumption that the disease severity worsens over time when untreated with mexiletine, but that QoL is maintained on mexiletine treatment as the treatment does not lose effectiveness over time. This assumption was based on findings from the literature, UK patient survey, patient elicitation interviews and clinical expert opinions.[2, 41, 52]

ERG comment: Firstly, the implementation of the disease progression differential in the model does not match the intended reasoning by the company. The disease progression differential applied in the model simply lowered the ANT utility by 15%. It did not lead to utility decreasing over time. The only time a patient's utility decreased in the model was when a patient discontinued from mexiletine. Therefore, the differential applied by the company did not solve the issue of the expectation that the quality of life of NDM patients would decrease over time in the absence of treatment for myotonic symptoms.

The ERG acknowledges that substantial uncertainty exists regarding the long-term HRQoL of patients with NDM given the lack of long-term data on both treatment effectiveness as well as the natural course of the disease. This uncertainty applies both to patients who are left untreated as well as to patients that continue treatment with mexiletine. Indeed, the disease may progressively worsen over time, and differences may exist in this regard between patients treated with mexiletine versus BSC. The uncertainty surrounding this issue has also been captured in the opinions from clinical experts (Appendix M in the CS), and patients (Appendix L in the CS). Appendix M shows a lack of consensus on the presence of disease progression differential (whereby patients on mexiletine maintain their QoL and the QoL of patients on best supportive care declines). Clinical experts suggested that "1) the patients tend to learn to live with condition over time so although condition may be getting worse they compensate for this. 2) No data for whether patients experience a decline in QoL over time. They tend to adapt to their situation in older age. 3) Some older patients may improve over time as they get used to it (NDM the condition – complain a lot less) and practise avoidance of triggers." (p 6 of Appendix M of the CS).[39]

In the article by Trip et al., 2009[52] 17 out of 30 patients with NDM characterised by sodium channelopathies (who were untreated at the time of the study, but eight had received treatment before the study) indicated increasing severity over time, and 10 indicated their disease as being stable over time. However, it is unclear to what extent the patient population in that study is comparable to the current target population, to what extent severity would increase in the presence of treatment, and how increased severity of symptoms translates to reduced HRQoL.

Results from a patient survey that were provided by the company indicated that a substantial proportion of patients experienced increased stiffness (87.5%), weakness (70.8%), and pain (45.8%) over time since their original diagnosis.[41] But again, it is unclear to what extent this translates into reduced HRQoL, and whether such worsening would not have happened if these patients had received treatment.

In light of the overall uncertainty regarding this aspect, as well as the lack of data to inform relevant parameters in the model, the ERG considers a conservative approach as most appropriate. Therefore, the ERG's preferred base-case does not make use of a disease progression differential. The ERG has addressed the potential impact of a difference in disease progression as assumed in the company's base-case by performing a scenario analysis that does make use of a, rather arbitrary, disease progression differential of 15% (i.e. assuming a 15% reduction in HRQoL in patients who do not receive mexiletine).

5.2.7 Adverse events

The effects of AEs were captured by applying cycle-based costs for the AEs. The utility decrements associated with these AEs were not included in the model separately, as it was argued that these utility decrements would be captured in the utility estimates, which were derived from the MYOMEX trial.

In the economic model the only included AEs were:

1. The joint probability of suffering a gastrointestinal disturbance whilst on mexiletine and being treated for dyspepsia associated with this gastrointestinal disturbance.
2. Treatment specific fracture probabilities

The GI disturbance and dyspepsia treatment probabilities were obtained from the Suetterlin et al. study.[43] in the base-case, whereas the treatment specific fracture probabilities were based on UK Advisory Board.[44] In Table 5.7 below, the AE probabilities that were used in the economic model are given.

Table 5.7: Adverse event probabilities incorporated into economic model

GI disturbance		
Study	**Probability of disturbance under mexiletine**	**Probability of dyspepsia treatment**
MYOMEX study[57]	[redacted]	Not reported
Statland et al (2012)[58]	0.32	Not reported
Stunnenberg et al (2015) [59]	0.70	Not reported
Suetterlin et al (2015) [43]	0.33	0.70
Fractures		
Study	**Probability of fractures under mexiletine**	**Probability of fractures under BSC**
UK Advisory Board[44]	0.1	0.2

Source: Based on Table 49 and Table 50 from the CS.[2]
GI=gastrointestinal

ERG comment: It was unclear to the ERG why only GI disturbance was included in the economic model as the only treatment-related AE. In its response to the clarification letter, the company mentioned that in its base-case, the Suetterlin et al. study was used as the data source for AE rates in the model, and there were no serious/economically impactful AEs observed in the Suetterlin et al. study.[43, 55]

The ERG considers using the AE rates from the MYOMEX trial would be more plausible, since it would be consistent with other inputs (e.g. utility and resource use inputs) used in the economic model. Therefore, the ERG requested from the company to include all relevant AEs observed in the MYOMEX trial, which are provided in Table 5.8 below. After the inclusion of these AEs, the company mentioned that the incremental results did not change significantly. Even though the ERG concurs with the company on the minor impact on the incremental results, it would prefer the AE rates, for all AEs observed, from the MYOMEX trial in its base-case.

Finally, it was not clear to the ERG how the treatment specific probability of falls with fractures were derived from the clinical experts consulted during the advisory board, since in the UK Advisory Board summary, the Key Opinion Leaders (KOLs) estimated the risk of falls with fractures to be between 0 and 20% for patients on BSC and between 0 and 10% for patients on mexiletine. In its response to the clarification letter, the company provided additional scenarios with different fracture risks, demonstrating that the impact of this assumption was minor on incremental results.[55] The ERG concurs

with the company about the impact of this assumption on incremental results and no change was implemented on the company base case, given the lack of more plausible evidence.

Table 5.8. Adverse events included in updated economic model

Adverse event category	Events	Patients	%	Source
Gastrointestinal disorders (Abdominal pain, Nausea, Abdominal pain upper)	[redacted]	[redacted]	[redacted]	MYOMEX
General disorders and administration site conditions (Fatigue, Chest pain, Asthenia, Chest discomfort, Malaise)	[redacted]	[redacted]	[redacted]	
Nervous system disorders (Headache, Somnolence, Paraesthesia)	[redacted]	[redacted]	[redacted]	
Respiratory, Thoracic and Mediastinal disorders (Dyspnoea)	[redacted]	[redacted]	[redacted]	
Cardiac disorders (Tachycardia)	[redacted]	[redacted]	[redacted]	
Ear and Labyrinth disorders (vertigo)	[redacted]	[redacted]	[redacted]	
Musculoskeletal and connective tissue disorders (Pain in extremity)	[redacted]	[redacted]	[redacted]	
Injury, Poisoning and Procedural complications	[redacted]	[redacted]	[redacted]	
Skin and subcutaneous tissue disorders (Acne)	[redacted]	[redacted]	[redacted]	
Vascular disorders (Flushing, Hypotension)	[redacted]	[redacted]	[redacted]	
Total	[redacted]	[redacted]	[redacted]	

Source: Table 19 of the response to the clarification letter.[55]

5.2.8 Health-related quality of life

5.2.8.1 Measurement of HRQoL

HRQoL was measured in the MYOMEX trial using the Individualized Neuromuscular Quality of Life Questionnaire (INQoL). HRQoL was measured in each patient in each phase of the MYOMEX cross-over trial. Therefore, each patient provided HRQoL data for on treatment and off treatment.

The INQoL is a condition-specific patient-reported outcome measure describing the disease-related impact of neuromuscular diseases on patients.[61] The INQoL is made up of 45 items, split amongst the following four main domains and subdomains: Symptoms (subdomains: muscle weakness, muscle 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); Overall QoL (overall INQoL-QoL is an aggregation of parts of five subdomains (activities, independence, social relationships, emotions, and body image). Responses options are provided on a six to seven-point Likert scale. Raw data can be converted to a score of 0–100 for every subdomain, with higher scores indicating a greater impact on QoL.

The company chose to measure HRQoL using the INQoL, citing previous research which suggested that generic measures of HRQoL, such as the SF-36 were unable to effectively capture muscle weakness and muscle locking and would therefore not represent the true impact of NDM on the HRQoL of patients. The INQoL was the only validated QoL questionnaire identified that referred specifically to the presence and impact of myotonic symptoms. The company justified their choice by citing previous research from Sansone et al., which concluded that INQoL was an appropriate measure because "it can quantify the impact of muscle symptoms that are specific to this group of patients (e.g. myotonia, muscle pain)".[62] An additional study by Trivedi et al. described INQoL as "a more relevant instrument for determining symptom impact on quality of life in non-dystrophic myotonia compared with the generic SF-36".[63] The company also argued against the use of the SF-36 as some of its items are considered not relevant to muscle disease and could easily be influenced by other factors.[61] Lastly the company reported that the clinical experts consulted unanimously agreed that INQoL was more relevant and appropriate to capture the impact on the quality of life of NDM patients compared to SF-36.[39]

ERG comment: The evidence referred to and provided by the company does not demonstrate that generic measures such as the EQ-5D or SF-36 are unable to measure the HRQoL of patients with NDM. The evidence shows that INQoL may be more sensitive in assessing differences in NDM channelopathies but does not show that generic measures are inappropriate. Disease specific measures are often found to be more sensitive to assessing specific symptoms of the condition and this is to be expected. The justification adopted by the company against the use of the SF-36 because some of its items are considered not relevant to muscle disease and could easily be influenced by other factors, is in fact one of the benefits of using generic measures as they are able to capture broader aspects of health such as comorbidities and the impact of AEs, which can be missed by condition-specific measures. Therefore, the ERG does not believe that the evidence presented represents psychometric evidence that generic measures are invalid or unreliable in this population and the ERG believes that a generic measure should have been included in line with the NICE reference case.

5.2.8.2 Valuation of HRQoL

As no generic preference-based measure of HRQoL was collected in the MYOMEX and no mapping studies exist between the INQoL and such generic measures, the company had to conduct a valuation study for the INQoL, in order to obtain preference-based utility values for the model. The company conducted two separate studies for the valuation of HRQoL. The first was a discrete choice experiment (DCE) and the second was a vignette study with time trade off (TTO) valuation. At 45 items, the INQoL is far too long for all items to be included within a DCE choice task or vignette/TTO exercise. The INQoL items also feature too many response levels (6-7) to be precisely and feasibly covered within a DCE or vignette/TTO study. Therefore, the company had to choose how to select INQoL items and response levels for inclusion. Here the company attempted to more closely align itself with the NICE reference case by selecting items from the INQoL which conceptually overlapped with the items of the EQ-5D. The conceptual mapping process, which applies to both valuation studies will be described first, followed by each of the valuation studies.

Conceptual mapping

The conceptual mapping process aimed to reduce the number of INQoL items and response levels and align the measure more closely to the EQ-5D descriptive system and the NICE reference case. The conceptual mapping was informed by one-to-one discussions with three clinical experts and one health economics expert.[2] First, INQoL domains which conceptually related to EQ-5D domains were identified. Then appropriate items within these INQoL domains were selected and the most similar response levels of those INQoL items were mapped to the response levels of EQ-5D items. Please note here that statistical methods were not used to inform this mapping. Here mapping refers to conceptual mapping.

Three INQoL domains were identified as conceptually overlapping with concepts covered by the EQ-5D. These were pain, emotions (anxiety and depression), and activities (daily activities such as washing and dressing, and leisure activities). In addition to these three domains, clinical experts agreed that muscle weakness and muscle locking, assessed by two separate INQoL domains, would be appropriate to include. These domains were considered to conceptually overlap with the mobility domain of the EQ-5D as they impact patient's mobility. The symptoms of muscle locking and muscle weakness were considered to be independent of each other as patients can experience one without the other. Finally, it was observed in the literature that fatigue had an important impact on NDM patients' assessment of their HRQoL and that fatigue is among the most frequent complaints reported by patients with chronic illnesses.[52, 58, 63-65] Experts agreed, and fatigue was also included in the conceptual mapping. A single item was selected from each of these six INQoL domains. In keeping with the levels of the EQ-5D, which describe the severity of issues experienced for each domain, INQoL items which quantified the degree to which the respondent was affected by the issue were selected. This conceptual mapping process reduced the 45 items of the INQoL to eight items for the DCE exercise. The included items and response levels are displayed in Table 5.9.

Table 5.9: Results of the conceptual mapping of the INQoL items to the EQ-5D-5L descriptive system

EQ-5D domain	INQoL item	INQoL response options
Mobility	• How much weakness would you say you have in the muscles affected by your condition? • How much muscle locking would you say you have at the moment?	Very little Some A moderate amount An extreme Amount
Self-care (washing and dressing)	• At the moment does your muscle condition affect your ability to do daily activities e.g. washing, dressing & housework?	Not at all Slightly Moderately Extremely
Usual activities (leisure, work, social activities)	• At the moment does your muscle condition affect your ability to do leisure activities?	Not at all Slightly Moderately Extremely
Pain/ discomfort	• How much pain would you say you have at the moment? • How much tiredness/fatigue would you say you have at the moment	Very little Some A moderate amount An extreme Amount

EQ-5D domain	INQoL item	INQoL response options
Anxiety/ depression	• At the moment does your muscle condition make you feel anxious/worried? • At the moment does your muscle condition make you feel depressed?	Not at all Slightly Moderately Extremely
Source: Table 52 of the Company submission[2]		

The number of INQoL response levels also needed to be reduced to enable the development of a practical and feasible DCE, as including all response levels would have resulted in the DCE requiring 144 choice questions per participant.[2] Each INQoL items features a six or seven-point Likert scale. The company decided, in consultation with a clinical expert, to reduce this down to four response levels within the DCE. The best and worst levels were retained for each item as well as two other response levels within the range which closely matched the response levels of the EQ-5D-5L. This resulted in included levels of "extreme", "moderate", "some" or "slight" and "very little" or "not at all".

ERG comment: The ERG agrees that the INQoL needed to be substantially reduced to be amenable for valuation. The company chose to focus the reduction of items and levels by conceptually mapping with the EQ-5D, in order to more closely align with the NICE reference case. Several items included in the reduced INQoL mapped reasonably well to EQ-5D items, such as pain, anxiety and depression and self-care. However, INQoL items chosen to reflect the mobility and usual activities domains were less closely related to the original EQ-5D items. The INQoL usual activities item asks solely about leisure activities rather than work, study, housework, family and leisure activities. The INQoL items chosen to reflect the mobility are very disease specific, focusing on muscle weakness and muscle locking rather than issues in walking about as on the EQ-5D. It is not clear how well these two mobility items reflect the EQ-5D mobility item. Additionally, fatigue was identified to be important in the literature and was also added. This item does not conceptually map to the EQ-5D. The focussing of INQoL items on patients' "muscle condition" also limits the conceptual overlap. By adopting a strategy where the company try to include both items that conceptually map with the EQ-5D as well as additional items which are considered important to the specific disease, leads to a middle point which does not fully meet either criterion. The content validity of the INQoL can also no longer be fully argued as the substantially reduced INQoL for valuation misses several domains from the full INQoL entirely, with other domains greatly reduced.

The selection of response levels was also chosen to reflect the levels of the EQ-5D-5L. Following the reduction, some included items were left with response options "Not at all", "Slightly", "Moderately" and "Extremely", which approximate the response levels of the EQ-5D-5L fairly well, with only "severe" problems being missed. The remaining included items were left with response options "Very little", "Some", "A moderate amount" and "An extreme amount". These less closely reflect the EQ-5D-5L response levels. There is no equivalent to no problems, altering the top anchor. There is also no "severe" option, reflecting an option between moderate and extreme problems, but instead there is an extra mid-range option of "some" problems, which is intended to sit between "very little" and "moderate" problems. Clear monotonicity in response options is very important in both measurement and valuation of health, particularly in valuation where respondents are required to trade off consistently between levels. When all responses are shown on a questionnaire in order, it is easy for participants to observe the intended order of levels. However, in a valuation task this visual ordering is lost, and so it is vital that the ordering of the labels is clearly understood. The monotonic ordering of "some" and "moderate" is not at all clear and would probably cause issues for valuation results.

Discrete choice experiment

In their first study attempting to value the HRQoL data collected in the trial, the company carried out a DCE in a representative sample of the UK general population. A published fractional factorial method was used to design the DCE.[2] This method minimised participant burden, whilst representing the different included response levels of the eight INQoL items in a balanced and statistically efficient way.[2] The orthogonal design combined questions and response choices with zero correlation, assuming that the items informing the choice sets were independent. The company justified this assumption by stating that the developers of the INQoL items scored domains describing these items separately. The orthogonal design required 32 choice questions. The order of questions was randomised, and half of the participants completed questions 1-16 and the other half 17-32. An example of a choice question can be seen in Figure 5.2.

Figure 5.2: Example DCE scenario

	Treatment A	Treatment B
*How much **muscle weakness** you would have*	A moderate amount	An extreme amount
*How much **'locking' (seizing up)** of your muscles you have*	A moderate amount	An extreme amount
*Your muscle condition affects your ability to do daily activities e.g. **washing, dressing & housework***	Moderately	Extremely
*Your muscle condition affects your **ability to do leisure activities***	Extremely	None at all
*How much **pain** you have*	Slight	Moderate
*How much **tiredness or fatigue** you have*	A moderate amount	An extreme amount
*Your muscle condition makes you feel **anxious***	Extremely	None at all
*Your muscle condition makes you feel **depressed***	Moderately	Extremely
Which treatment is best? *Please tick A or B*	A ❑	B ❑

Source: Figure 26 Company submission[2]
DCE = discrete choice experiment

The DCE was conducted online in 508 members of the UK general population. The company state that the second choice in each of the 32 questions was determined by folding over the first choice.[2] The fold over method is described in the literature as constructing the second scenario within a choice question by assigning the opposite levels to those displayed in the first scenario. So for example, if choice A of a choice question with eight attributes and four levels can be represented by levels 12341234, then choice B would be represented by 43214321 using the fold over method.[66] Quota sampling was used to balance geographic distribution, gender, and ethnicity, as shown in Table 53 of the company submission.[2]

Data was analysed using a conditional logit model to estimate a linear function. Results are presented below in Table 5.10. Results showed that each item was a significant predictor of choice and each level of each attribute was statistically significant.[2] It would be expected within each item that the order of magnitude of coefficients would follow the same pattern as the ordering of severity of the response levels. For example, compared to "extreme" problems, "moderate" problems would have a positive impact on HRQoL, "some" problems would have a larger positive impact on HRQoL and "very little" problems would have an even larger positive impact on HRQoL as people would prefer to have very

little problems than moderate and would prefer moderate problems to extreme problems. However, there were some logical inconsistencies in the resulting preference weights, listed as follows:

- Some muscle weakness preferred to very little muscle weakness
- Some muscle locking equivalent to a moderate amount of muscle locking
- Slight problems washing, dressing or doing housework preferred to no problems
- Moderate problems doing leisure activities preferred to slight problems
- Some problems with tiredness preferred to very little problems
- Slightly depressed preferred to not at all depressed

Table 5.10: Conditional logit outputs

Attributes and levels	Coefficients	SE	z	P>|z|	95% CI		Odds ratios	95% CI	
Muscle weakness									
An extreme amount	-	-	-	-	-	-	-	-	-
A moderate amount	0.23	0.045	5.13	**<0.001**	0.142	0.318	1.259	1.153	1.374
Some	0.266	0.051	5.2	**<0.001**	0.166	0.366	1.305	1.18	1.442
Very little	0.265	0.045	5.91	**<0.001**	0.177	0.353	1.304	1.194	1.424
Locking									
An extreme amount	-	-	-	-	-	-	-	-	-
A moderate amount	0.282	0.047	5.97	**<0.001**	0.189	0.374	1.325	1.208	1.454
Some	0.282	0.052	5.45	**<0.001**	0.18	0.383	1.325	1.198	1.467
Very little	0.346	0.044	7.87	**<0.001**	0.26	0.432	1.414	1.297	1.541
Washing, dressing, housework									
Extremely	-	-	-	-	-	-	-	-	-
Moderately	0.398	0.046	8.72	**<0.001**	0.309	0.488	1.49	1.362	1.629
Slightly	0.412	0.051	8.01	**<0.001**	0.311	0.513	1.51	1.365	1.671
Not at all	0.358	0.044	8.07	**<0.001**	0.271	0.445	1.43	1.311	1.56
Leisure activities									
Extremely	-	-	-	-	-	-	-	-	-
Moderately	0.149	0.046	3.26	**0.001**	0.059	0.239	1.161	1.061	1.27
Slightly	0.122	0.051	2.39	**0.017**	0.022	0.223	1.13	1.022	1.25
Not at all	0.221	0.043	5.11	**<0.001**	0.136	0.306	1.248	1.146	1.359
Pain									
An extreme amount	-	-	-	-	-	-	-	-	-
A moderate amount	0.647	0.046	13.96	**<0.001**	0.556	0.737	1.909	1.743	2.09
Some	0.767	0.051	14.9	**<0.001**	0.666	0.867	2.153	1.946	2.381
Very little	1.115	0.042	26.25	**<0.001**	1.031	1.198	3.048	2.805	3.313
Tiredness									
An extreme amount	-	-	-	-	-	-	-	-	-
A moderate amount	0.321	0.046	7.03	**<0.001**	0.232	0.411	1.379	1.261	1.508
Some	0.41	0.051	8	**<0.001**	0.31	0.511	1.507	1.363	1.667
Very little	0.339	0.044	7.7	**<0.001**	0.253	0.425	1.404	1.288	1.53
Anxious/worried									
Extremely	-	-	-	-	-	-	-	-	-
Moderately	0.212	0.044	4.8	**<0.001**	0.126	0.299	1.237	1.134	1.349
Slightly	0.266	0.051	5.18	**<0.001**	0.166	0.367	1.305	1.18	1.443
Not at all	0.302	0.044	6.84	**<0.001**	0.216	0.389	1.353	1.241	1.475
Depressed									
Extremely	-	-	-	-	-	-	-	-	-
Moderately	0.528	0.048	10.96	**<0.001**	0.434	0.623	1.696	1.543	1.864
Slightly	0.748	0.052	14.46	**<0.001**	0.646	0.849	2.113	1.909	2.338
Not at all	0.704	0.044	16.09	**<0.001**	0.618	0.789	2.021	1.855	2.202

Source: Table 54 from the Company submission[2]

Where inconsistencies were identified, the inconsistent value was altered in the scoring algorithm to be the same as the better level (the level signifying less HRQoL impairment).[2] Logical inconsistencies also occurred whereby people preferred 'some' or 'slight problems' to the upper anchor of "very little" problem/ "not at all". Where this occurred, those disutilities for 'some' or 'slight' were adjusted to 0. These adjustments were considered as conservative approaches by the company.

The coefficients for the worst level of each INQoL item were summed to calculate a scoring range. However, this then needed to be anchored to an appropriate range for utility values, Therefore the coefficients were rescaled so that the maximum DCE score was 1 and the minimum was -0.594, in line with the full range of the UK valuation tariff for the EQ-5D-3L.[67] An expert on utilities suggested that the company explore different assumptions regarding the value for the worst health state in the INQoL measure, as the worst state in the EQ-5D could be considered worse than the worst state in the INQoL given differences in item wording and response levels.[2] Therefore, the company tested an alternative bottom anchor for their scoring range of -0.291. This value represents the utility value of state 23233 (extreme problems/unable to for self-care, pain/discomfort and anxiety/depression and moderate problems with mobility and usual activities). This alternative bottom anchor state was chosen because it was considered that extreme muscle locking and muscle weakness may not equate to the worst mobility state in the EQ-5D-3L, confined to bed and similarly, unable to complete usual activities could be considered more severe than the matching item in the INQoL, extreme impact on your ability to complete leisure activities.[2] This alternative bottom anchor was used to rescale DCE utility coefficients in a scenario analysis.

The DCE provides information about the relative importance of each of the included INQoL items, as well as the relative impact on HRQoL of each of the included levels. These preference data were assumed to take the form of a linear function with no interaction effects. The utility function is shown below.

Tot = 1 + Uweak + Ulock + Upain + Utired + Uwash + Uleis + Uanx + Udep

Where Total is an individual's utility score, 1 is full health and Uweak-Udep are the utility weights (disutilities) associated with the selected response level for each of the included INQoL items. The DCE exercise provided utility decrements for four out of six or seven response levels of the included INQoL items. The scores without associated disutilities were imputed using linear interpolation. The rescaled and interpolated utility decrements for each item, for each worst health state value assumption (-0.594 or -0.291) are displayed in Table 57 of the CS.[2]

ERG comment: The number of logical inconsistencies in the results of the DCE are a concern for the ERG. Logical inconsistencies, where a worse level of problems was preferred to a lower level of problems, were observed in six out of eight items included in the DCE. This suggests a widespread issue in the DCE. The cause of such issues could be that: the levels were not sufficiently different to force participants to make consistent trade-offs; participants did not understand the ordering of response levels in the same way as intended; participants did not fully understand the DCE task or participants did not fully engage with the DCE task (taking heuristic shortcuts or making choices without properly considering the states provided) or there could be issues present in the design of the DCE (too many attributes for patients to properly consider or an inefficient design). Three of these six logical inconsistencies involve the levels "some" and either "moderate" or "very little". Issues with these levels were anticipated by the ERG and one of the experts consulted by the company as they are not clearly monotonic.[68] Clear monotonicity becomes particularly important when response options are not presented in a clear order, as they would be in a questionnaire where a respondent can observe the intended ordering and adjust their interpretation of the levels according to the context provided. As shown in Figure 5.2, in a DCE exercise, no ordering of response options is shown and therefore the choices made and the resulting ordering of coefficients depends entirely on the respondents' interpretation of the levels. Additionally, a lack of monotonicity means that these levels may be viewed as very similar by participants which will not encourage strong trade-offs, which may lead to very similar coefficients and level mis ordering. Examination of the draft DCE provided by the company

with the clarification response shows that, out of 32 choice tasks, 21 included at least one attribute including the choice between some and moderate problems.[69, 70] Therefore this lack of clear monotonicity could have had a widespread impact on results.

Perhaps more concerning are the three logical inconsistencies in which the coefficients for "no problems" and either "slight" or "moderate" problems are mis ordered. These level comparisons are clearly monotonic and therefore suggest deeper issues with participant understanding of the task or attention to the task or DCE design. In the clarification phase, the ERG asked whether any quality control checks were carried out on the data to investigate issues with participant understanding or attention. Regarding checks of respondent understanding, the company responded that "only completed surveys were included within the final results and therefore any participants that dropped out prior to completing the full survey due to their understanding of the task were excluded from the final analysis."[55] However, the ERG would argue that participants can misunderstand the task and still complete it, whether or not they are aware that they have misunderstood and therefore this represents a poor check for understanding. The ERG also asked for details of any other quality control checks that were built into the DCE, such as the identification of participants: who preferred a clearly inferior state within a choice task; who always (or too often) selected either A or B; who completed the task too quickly to have properly considered the choices. The company responded that no participants always answered A or B, which is encouraging in suggesting that everyone was engaging at least somewhat with the task.[55] The company stated that the survey was purposefully designed so that no state within a choice was clearly inferior and therefore this test of respondent attention/understanding was not possible. Additionally, no analysis was conducted on time taken to complete the task, but the company did not expect that this would make a significant difference to the results, as the number of respondents would have reduced any such results to white noise. The ERG argue that this would depend on the number of respondents who were flagged for this issue. Overall, the ERG would have felt more confident in the results of the DCE if such checks had been performed.

Additionally, several elements of the DCE design caused concern. The DCE contained eight attributes, which all varied simultaneously within each choice task. This is a lot of attributes for respondents to keep in mind. Recent methods to improve the study designs of DCEs which contain many domains have recommended including overlap within the choice pairs, so that some attributes stay constant within the choice pair, while overs vary.[71] This overlap allows participants to focus on those attributes which vary within the choice set, reducing the chances that participants make heuristic shortcuts, by ignoring some attributes in the face of a complex choice with many variables. This technique has been shown to be effective in reducing task complexity which reduces dropout rates and increases choice consistency.[71] This type of design requires a larger sample or more choice tasks but can help to improve the data quality obtained and may have improved the quality of the data and results in this study.

Lastly the anchoring of the DCE results to the EQ-5D-3L utility scale of 1 to -0.594 implies that the best and worst health states described by the reduced eight item INQoL are equivalent in terms of severity or utility to the best and worst health states described by the EQ-5D-3L. Table 5.11 compares the best and worst states described by the INQoL and the best and worst states described by the EQ-5D-3L. At the top end of the utility scale, the best response option for some of the INQoL items is described by "very little" problems instead of "no problems" on the EQ-5D-3L. Therefore, the best state described by the INQoL could be considered worse than the best state on the EQ-5D-3L. At the bottom end of the utility scale, the worst level for mobility in the EQ-5D-3L is given the label "confined to bed". This is likely to reflect a worse state of mobility than the "extreme amount" of muscle weakness and muscle locking described by the INQoL. Additionally, the worst level of the usual activities item on the EQ-5D-3L represents extreme problems with work, study, housework, family or leisure activities

is likely to describe a worse state than the equivalent item on the INQoL which describes extreme problems with leisure activities. Additionally, the INQoL state asks about fatigue which is not covered by the EQ-5D-3L. This item will impact the appropriateness of the anchor, but the direction of the impact cannot be determined. Lastly, the focussing effects of the INQoL items, which ask about issues caused by "the muscles affected by your condition" will also likely affect the appropriateness of the anchor, but again the direction is unclear. The company tested a range of alternative bottom anchors to account for the issues with the worst levels of mobility and usual activities and included these options within the model. However, the other elements of concern surrounding the top anchor and the impact of the addition of fatigue and focussing effects remain as areas of uncertainty.

Table 5.11: Comparison of the best and worst health states described by the INQoL and the EQ-5D-3L

Health state	INQoL	EQ-5D-3L
Best	Very little muscle weakness in the muscles affected by your condition Very little muscle locking at the moment	No problems in walking about
	Muscle condition affects ability to do daily activities e.g. washing, dressing & housework not at all	No problems with self-care
	Muscle condition affects ability to do leisure activities not at all	No problems with performing usual activities
	Very little pain Very little tiredness or fatigue	No pain or discomfort
	Not at all anxious Not at all depressed	Not anxious or depressed
Worst	Extreme amount of muscle weakness in the muscles affected by your condition Extreme amount of muscle locking at the moment	Confined to bed
	Muscle condition affects ability to do daily activities e.g. washing, dressing & housework extremely	Unable to wash or dress
	Muscle condition affects ability to do leisure activities extremely	Unable to perform usual activities
	Extreme amount of pain Extreme amount of tiredness or fatigue	Extreme pain or discomfort
	Extremely anxious Extremely depressed	Extremely anxious or depressed
INQoL = Individualized Neuromuscular Quality of Life Questionnaire		

Additional issues noted by the ERG related to the DCE are:

- Some of the response options in Figure 5.2 and in the draft DCE choice sets provided in Appendices B and C of the clarification response do not exactly match the INQoL response options.[69, 70] The best INQoL response option for washing, dressing and housework; leisure activities; anxiety; and depression should be "not at all". However, in the DCE examples they are displayed as "none at all". It is not clear whether the final DCE included the correct response options.
- The company submission states that 508 participants were recruited to participate in the DCE.[2] The clarification response refers to participant drop-out during the DCE task, but no numbers are provided.[55] It is not clear to the ERG how many of the 508 respondents dropped out and were therefore not included in the DCE results. The drop-out rate could be important when considering how confident we can be in the final results. Drop-out rate can be a signal of how engaged patients were with the task and how well they understood, as well as providing important information on the final sample size on which the model was fitted and the results are based.
- The company described that the second alternative within each choice question was developed using the fold over technique, but the choice sets in Figure 5.2 and the draft DCE choice sets provided in Appendices B and C of the clarification response have not been developed using the fold over method (as it is described in the literature).[2, 69, 70] This provides another example of inconsistencies between reporting and the documentation provided to the ERG for the DCE study.

These additional issues increase the ERGs concern about the conduct and design of the DCE study.

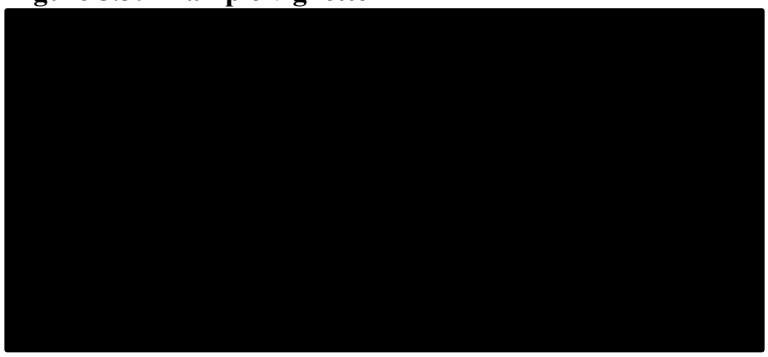
Vignette/TTO study

Just prior to the clarification stage, the company also provided the details and results of a vignette and TTO study conducted to value the INQoL data obtained in the trial.[72] In this report, the company stated that this additional study was conducted with the aim of validating the DCE results, at the suggestion of NICE and the ERG in the Decision Problem Meeting, prior to submission.[72]

The vignette study incorporated the same eight INQoL items included in the DCE study and therefore all explanation of content mapping and item selection is also relevant for this study. Similar to the DCE study, it was not feasible to include all INQoL response levels and so only four were included in the vignettes: "very little", "a fair amount", "a considerable amount" and "an extreme amount". Again, linear interpolation was used to estimate utility weights for those levels not included.[72]

These eight items were incorporated into vignettes describing various health states using an orthogonal design to ensure that there was no correlation between items in their severity. Half of the DCE choice sets (choice A for each question) were included as vignettes in the TTO valuation task. An example vignette is displayed in Figure 5.3 below.

Figure 5.3: Example vignette



Source: Figure 3 in the Lupin Vignette Utilities Report[72]

Two hundred members of the UK general population valued these vignettes using a TTO exercise in one-to-one interviews.[59] These TTO exercises required participants to consider a choice between living in the health state described in the vignette for 10 years or living for 10 minus x years in full health, with x being varied until patients were indifferent between the two choices. Participants were asked to perform this exercise for a series of 16 health state vignettes. This number of TTO exercises is quite a burden for participants, so the interview was simplified. Participants did not assess the states using a visual analogue scale (VAS) or ranking task, as is often done as a warmup exercise. Instead, the TTO task was explained in detail to participants and the interview consisted of simply completing the 16 TTO exercises as well as some additional background questions.

Linear regression was used to estimate the impact of included response levels on utility. Several adaptation methods were considered for handling insignificant coefficients (p-value > 0.05) and mis ordered weights, signalling logical inconsistencies with the ordering of response level severity.[59] In Adapted Model 1, insignificant coefficients were set to zero and mis ordered weights were estimated by linear interpolation from adjacent significant coefficients. In Adapted Model 2, where the regression weights for the INQoL measure included significant and non-significant coefficients, linear interpolation was used only for missing levels. The vignettes model without adaptation was applied in the economic model as a scenario. Resulting utility weights from alternative models considered in the DCE and Vignette studies for each item are compared in Table 5.12.

Table 5.12: Comparison of DCE and vignettes utility weights

INQoL item	DCE 33333 Worst Health State	DCE 23233 Worst Health State	Vignettes	Vignettes adapted model 1	Vignettes adapted model 2
Muscle weakness - very little	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle weakness – some	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle weakness - a fair amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle weakness - a moderate amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle weakness - a considerable amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle weakness - a lot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle weakness - an extreme amount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

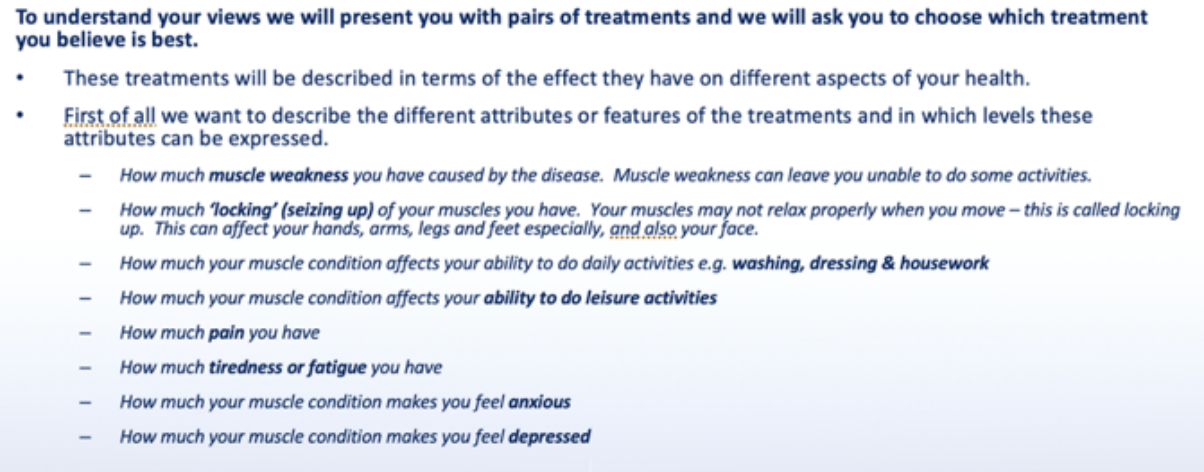
Locking - very little	[redacted]				
Locking- some	[redacted]				
Locking - a fair amount	[redacted]				
Locking - a moderate amount	[redacted]				
Locking - a considerable amount	[redacted]				
Locking - a lot	[redacted]				
Locking - an extreme amount	[redacted]				
Pain - very little	[redacted]				
Pain – some	[redacted]				
Pain - a fair amount	[redacted]				
Pain - a moderate amount	[redacted]				
Pain - a considerable amount	[redacted]				
Pain - a lot	[redacted]				
Pain - an extreme amount	[redacted]				
Tired - very little	[redacted]				
Tired – some	[redacted]				
Tired - a fair amount	[redacted]				
Tired - a moderate amount	[redacted]				
Tired - a considerable amount	[redacted]				
Tired - a lot	[redacted]				
Tired - an extreme amount	[redacted]				
Wash and Dress - not at all	[redacted]				
Wash and Dress – slightly	[redacted]				
Wash and Dress - a fair amount	[redacted]				
Wash and Dress - a moderately	[redacted]				
Wash and Dress - a considerably	[redacted]				
Wash and Dress - a very much	[redacted]				
Wash and Dress - an extremely	[redacted]				
Leisure - not at all	[redacted]				
Leisure – slightly	[redacted]				
Leisure- a fair amount	[redacted]				
Leisure - a moderately	[redacted]				
Leisure - a considerably	[redacted]				
Leisure - a very much	[redacted]				
Leisure - an extremely	[redacted]				
Anxious - not at all	[redacted]				
Anxious – slightly	[redacted]				
Anxious- a fair bit	[redacted]				
Anxious - a moderately	[redacted]				
Anxious - a considerably	[redacted]				

Anxious - a very much	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxious – extremely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed - not at all	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed – slightly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed - a fair bit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed - a moderately	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed - a considerably	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed - a very much	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depressed – extremely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 57 in the Company Submission and Table 1 in the Lupin Vignette Utilities Report.[1, 59]
DCE = discrete choice experiment; INQoL = Individualized Neuromuscular Quality of Life Questionnaire

Using the vignette study results to value the INQoL data obtained from the trial leads to a substantial reduction in the utility gain associated with mexiletine compared to the utility gain that is observed using the DCE weights (shown in Table 5.13 below). The company stated that this could be due to the insignificance (resulting in zero coefficients for many of the levels) of the muscle locking and washing and dressing dimensions in the vignette study. They suspect this difference across studies was caused by the differing levels of information that was provided to patients about the symptoms across the studies.[59] In the DCE, descriptions of symptoms were provided to participants as shown below in Figure 5.4. However, in the vignette study, the only information provided was an explanation of how to complete the TTO exercise. Therefore, the information shown in the example vignette (Figure 5.3) was the only symptom information provided to participants in the vignette study. The company feel that a lack of symptom information, particularly for muscle locking, may have led members of the general population to underestimate its impact on HRQoL.

Figure 5.4: Descriptive information provided to participants in the DCE study



Source: Figure 1 in the Lupin Vignette Utilities Report[59]
DCE = discrete choice experiment

ERG comment: The ERG felt that there were also some issues in the design and results of the vignette study. Again, the included response options may cause some issues. In this case "very little", "a fair amount", "a considerable amount" and "an extreme amount" were included. The relative strength of preferences for a fair amount and a considerable amount may not be consistently strong as these labels are less concrete and less commonly used than terms such as "moderate" and "slight". It is difficult to

predict how different in severity participants will find the two intermediate levels in relation to each other and their neighbouring endpoint levels, which may affect their willingness to trade between levels. However, unlike "some" and "moderate", no issues with monotonicity would be expected for these levels, which is an improvement on the DCE study.

There were also several concerns surrounding the design of the study. No explanation of the elements of the health states was provided. The company suspect that this may have affected responses for terms such as muscle locking, which may not have been clearly understood by members of the general population. Additionally, the TTO task is quite cognitively demanding but no practice TTO exercises were given to give the respondents a chance to get used to the task and clarify the process before actual valuation tasks began.[24, 59] In more recent TTO valuation protocols, multiple example and practice exercises are given which cover the range of states and the TTO exercise variant for states valued worse than death.[60] This lack of practice exercises may be a particular problem when it comes to respondents valuing states worse than dead as this exercise is associated with a more complex task. This concern was raised by one of the experts consulted by the company to review the DCE and vignette studies.[55] Again the company reported that no quality control checks were undertaken on the TTO data. This is another key element of recent valuation protocol of the EQ-5D-5L.[60]

5.2.8.3 Utility values used in the model

Table 5.13 shows the utility values obtained for the different health states in the model using different methods proposed by the company as well as an average UK general population utility value for the EQ-5D-3L obtained from Ara and Brazier, calculated using the baseline age and gender mix of the MYOMEX trial.[1, 61] The three utility values for patients alive on treatment with mexiletine estimated based on the DCE study (with different bottom anchors) were very similar to the average utility value for the UK population.

Table 5.13: Comparison of utility values obtained from different valuation methods

Method (bottom anchor state)	Mexiletine (Alive on treatment)	BSC (Alive not on treatment)	Treatment effect	EQ-5D-3L UK average general population utility value (aged 44) [61]
DCE (33333)	[redacted]	[redacted]	[redacted]	0.8896
DCE (23223)	[redacted]	[redacted]	[redacted]	
DCE (23333)	[redacted]	[redacted]	[redacted]	
Vignettes	[redacted]	[redacted]	[redacted]	

Source: Economic model, updated from the response to the clarification letter.[24]
BSC = best supportive care; DCE = discrete choice experiment

ERG comment: The plausibility of the similarity between the utility values for patients alive on treatment generated from the DCE study and the UK age-matched general population utility value is concerning as patients and clinicians stated in the submission that treatment did not solve all issues associated with the condition. For example, one patient described "In late 30's, started medication which helped. Symptoms receded - 70% improvement [..] Took for 3 years, but there was inconsistent supply of mexiletine and periods where he couldn't gain access."[62] Given that this suggests that even on treatment, patients do not feel that 100% of issues are resolved, the ERG would expect that their HRQoL would be lower than the general population average. This expectation was mirrored in the comment of one clinical expert consulted by the company who stated that "patients may still have myotonia but it has improved."[38] Additionally, one clinician stated that they would expect utilities of approximately [redacted] in the mexiletine group, if the average in the general population was 0.9, while

another expert stated that we would expect utility values of [redacted] for patients on mexiletine and of approximately [redacted] in patients not receiving treatment.[38] Therefore overall, the vignette utility values appear more plausible. Using the utility values obtained from the vignette study also avoids issues with the DCE study, namely the widespread logical inconsistencies in the results and the anchoring issues.

The company did not incorporate any age-adjustment of utilities used in the model. It is standard practice to account for the fact that HRQoL and therefore utility, declines as patients age. This model has a long time horizon of 58 years with a baseline age of 44 and therefore it is important to account for the decline in utility due to ageing. Given the paucity of evidence surrounding the long-term HRQoL of patients with NDM, there is no evidence on how the utility of NDM patients declines as they age, and whether the rate of decline differs according to whether they are on or off treatment. Therefore, the ERG implemented the annual decline in utility based on the Ara and Brazier equation, which was based on UK general population data, adjusted using the baseline age and gender mix from the MYOMEX trial.[1, 61] This equation results in a steadily increasing annual decline in utility to account for the fact that as patients age they are increasingly more likely to experience additional comorbidities and health issues alongside their existing condition. The annual decline was applied equally to patients in the AOT state with mexiletine and to patients in the ANT state with BSC.

The method of age-adjustment applied by the ERG assumes that regardless of whether patients are on treatment, with a relatively high utility value, or off treatment, with a relatively low utility value, the impact of age on their utility is the same (an additive approach). However, in theory, this may not be entirely realistic. It is likely that the impact of ageing and experiencing increasing comorbidities and health issues will be felt more substantially in the group with a higher utility than in the group who already experience substantial limitations. This is because it has been seen that the impact of additional comorbidities on utility is not additive but is better reflected using a multiplicative approach. In this case the multiplicative approach would result in a steeper decline in utility due to ageing in patients who were on treatment than off treatment.[61] However, in their base-case, the ERG chose to use the more conservative approach in which age impacted both groups equally, as a lack of long-term data in this specific patient group leaves the relationship between treatment status and age unclear. A scenario exploring the multiplicative approach will be presented in Section 7.

5.2.9 Resources and costs

Unit costs are derived from NHS reference costs 2017-2018,[40] Personal Social Services Research Unit (PSSRU) 2018,[39] the British National Formulary 2019,[43] or as indicated otherwise.

5.2.9.1 Drug acquisition and monitoring

The economic analysis includes drug acquisition costs and monitoring costs for the mexiletine arm. Monitoring costs consist of the costs for cardiac monitoring upon initiation of treatment and during treatment follow-up. No acquisition costs or monitoring costs are included for the BSC group.

The acquisition costs for mexiletine, with and without PAS discount, are shown in Table 5.14.

Table 5.14: Mexiletine acquisition costs

Drug	Cost per pack	No. per pack	Cost per capsule/ tablet	Source
Mexiletine (list price)	£5,000	100	£50	BNF 2019[43]
Mexiletine (with PAS discount)	[redacted]	[redacted]	[redacted]	Lupin Healthcare (UK) Limited

Source: Table 59 in the CS.[1]
BNF = British National Formulary; CS = company submission; No. = number; PAS = patient access scheme; UK = United Kingdom.

The assumptions for monitoring costs in the first year are based on the summary of product characteristics (SmPC) of NaMuscla:[28] first, prior to mexiletine initiation, a cardiac evaluation is performed that consists of an electrocardiogram (ECG; test only), ECG monitoring for 24 – 48 hours, and an echocardiogram; subsequently, within 48 hours post-initiation of mexiletine, another ECG (test only) is performed. For the second year and onwards, it is assumed that an ECG (test only) is performed once in every two years. The frequencies of cardiac monitoring tests are shown in Table 5.15, and their unit costs and source in Table 5.16.

Table 5.15: Frequencies of cardiac monitoring tests

Test	Number of activities			
	Year One			From year 2 onwards (per year)
	Before initiation	<48 hrs after initiation	Total	
Electrocardiogram (test only)	1	1	2	0.5
Electrocardiogram monitoring for 24-48 hrs	1	0	1	0
Echocardiogram	1	0	1	0

Source: Table 60 in the CS.[1]
CS = company submission; hrs = hours.

Table 5.16: Unit costs and sources of cardiac monitoring tests

Test	Unit cost	Source
Electrocardiogram (test only)	£38	NHS Reference costs, 2017-2018[40]
Electrocardiogram monitoring for 24-48 hrs	£96	
Echocardiogram	£97	

Source: Table 67 in the CS.[1]
CS = company submission; NHS = National Health Service.

5.2.9.2 Health state costs

In the absence of any relevant trial data, previous literature or other sources of information, the company developed an original approach for including health state costs i.e. the costs of health care resource use other than for mexiletine acquisition and cardiac monitoring. The cost associated with the AOT health state (on mexiletine) was estimated based on the use of the following health care resources: physiotherapy, occupational therapy, speech therapy, day case attendance, and use of a wheelchair, walking stick and walking frame. Frequencies of health care resource use were estimated by clinical experts based on the frequency if patients in the mexiletine arm of the MYOMEX trial being in one of

three categories of disease severity (i.e. mild, moderate, or severe) for each dimension of the Clinical Myotonia rating Scale (CMS) disability scale. The CMS is an instrument that was newly developed for the MYOMEX study to assess the self-reported severity and disability of myotonia in patients. Patients from the MYOMEX trial were categorised as scoring either 'mild', 'moderate' or 'severe' on each dimension of the CMS disability scale: speech, handwriting, feeding, hygiene, walking, and ascending/descending stairs. Each dimension of disability is assumed to correspond to the use of a specific health care resource: physiotherapy for disabilities associated with handwriting, walking and ascending or descending stairs; occupational therapy for disabilities in feeding, hygiene and dressing; speech therapy for disabilities associated with speech; and mobility aids (i.e. a wheelchair, walking stick, and walking frame) for walking disabilities. Day case attendance was hypothesised to be associated with the categorisations of severity of disability in any of the dimensions of disability. For the frequencies and probabilities of use of the corresponding health care resource associations with the categorised severity scores are assumed. The categorisation of disease severity was informed by clinical experts, and the estimates of the frequencies and probabilities of health care resource use were informed by both clinical experts and patients, but no details were provided on how these categorisations and estimates were elicited. The CMS disability scale, scores, and the categorisation of disease severity are shown in Table 5.17. The proportions of patients in each level of disease severity on each of the CMS disability scale dimensions are shown in Figure 5.5 in the mexiletine arm, and in Figure 5.6 for the placebo arm. The assumed associations between CMS disability scales and resource use are shown in Table 5.18, the estimated expected frequencies of resource use in Table 5.19, and the unit costs in Table 5.20.

Table 5.17: The CMS disability scale, scores and severity categorisation

Dimension	Description	Score	Severity
Speech	Normal	0	Mild
	Slightly affected, no difficulty being understood	1	Mild
	Moderately affected, has to repeat oneself occasionally	2	Moderate
	Seriously affected, has to repeat oneself frequently	3	Severe
	Incomprehensible most of the time	4	Severe
Writing	Normal	0	Mild
	Slightly slower	1	Mild
	Visibly slower, all words are legible	2	Moderate
	Seriously affected, not all the words are legible	3	Severe
	Impossible to handle the pen OR most words are illegible	4	Severe
Eating and handling cutlery	Normal	0	Mild
	A bit slow and clumsy	1	Mild
	Able to feed oneself but needs help with preparation (cutting, opening yoghurt…)	2	Moderate
	Has to be fed	3	Severe
Hygiene (washing, etc.)	Normal	0	Mild
	A bit slow but does not require assistance	1	Mild
	Help required for a few gestures/movement	2	Moderate
	Help required with most gestures/movement	3	Severe
	Help required with all gestures/movements	4	Severe

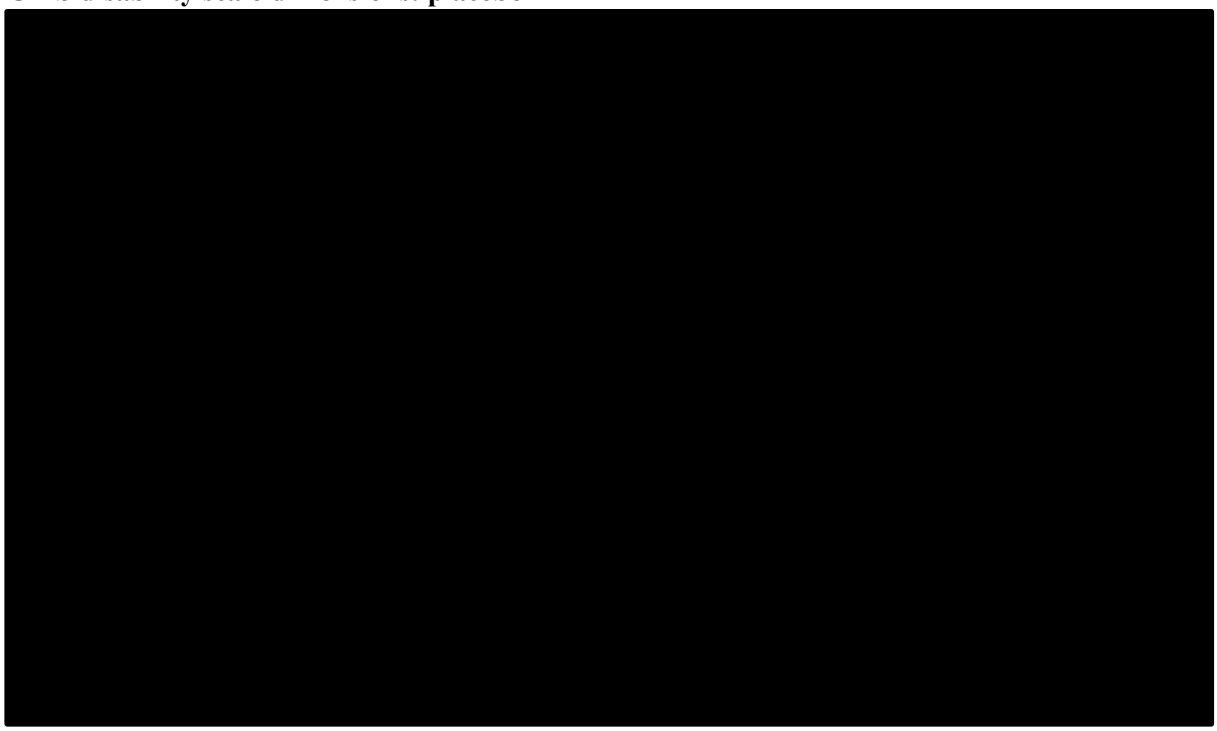
Dimension	Description	Score	Severity
Dressing	Normal	0	Mild
	A bit slow but does not require assistance	1	Mild
	Help required for a few gestures/movement	2	Moderate
	Help required with most gestures/movement	3	Severe
	Help required with all gestures/movements	4	Severe
Walking (tested on 3 to 5 metres)	Normal	0	Mild
	Discreet difficulties, hardly visible	1	Mild
	Moderate difficulties, asks for occasional help	2	Moderate
	Serious difficulties, needs walking aid (walking stick, third-party help)	3	Severe
	Totally unable to walk, uses a wheelchair	4	Severe
Ascending / descending stairs (tested on 5 stairs, or questions otherwise)	Normal	0	Mild
	Discreet difficulties, a bit more difficult but achievable	1	Mild
	Moderate difficulty, uses a ramp	2	Moderate
	Serious difficulty, ascends or descends step by step	3	Severe
	Impossible task	4	Severe

Source: Table 61 and 62 in the CS.[1]
CMS = clinical myotonia rating scale; CS = company submission; etc. = et cetera.

Figure 5.5: Proportions of MYOMEX patients in each level of disease severity on each of the CMS disability scale dimensions: mexiletine

Source: Figure 27 in the CS.[1]
CMS = clinical myotonia rating scale; CS = company submission.

Figure 5.6: Proportions of MYOMEX patients in each level of disease severity on each of the CMS disability scale dimensions: placebo



Source: Figure 28 in the CS.[1]
CMS = clinical myotonia rating scale; CS = company submission.

Table 5.18: Assumed relationships between CMS disability dimensions and health care resource use

CMS disability dimensions	Health care resource use
Handwriting	Physiotherapy sessions
Walking	
Stairs - ascending/ descending	
Eating	Occupational health sessions
Hygiene	
Dressing	
Speech	Speech therapy sessions
Walking	Mobility aids

Source: Table 66 in the CS.[1]
CMS = clinical myotonia rating scale; CS = company submission.

Table 5.19: Estimates for the expected frequencies of health care resource use per level of disease severity (probability of use * frequency of use)

Disease severity	Expected frequency estimate						
	Physio-therapy	Occupational therapist	Speech therapy	Day case attendance	Use of wheelchair	Use of walking stick	Use of walking frame
Mild	0.6	0.6	0.6	1	0	0	0
Moderate	3.6	3.6	3.6	1	0	0.2	0.1
Severe	4.8	4.8	4.8	2	0.05	0.3	0.4

Source: Table 63, 64, 65 in the CS.[1]
CMS = clinical myotonia rating scale; CS = company submission.

Table 5.20: Unit costs and sources of health care resources

Health care resource	Unit cost	Source
Physiotherapy session (1:1)	£54	PSSRU 2018[39]
Occupational therapy session (1:1)	£78	PSSRU 2018[39]
Speech therapy session (1:1)	£97	PSSRU 2018[39]
Day case attendance	£207	NHS Reference costs, 2017-2018[40]
Wheelchair	£257	PSSRU 2018;[39] average of 'self-or attendant propelled', 'active use', and 'powered' wheelchair types.
Walking stick	£17	NHS.uk website[42]
Walking frame	£150	NHS.uk website[42]

Source: Table 67 in the CS.[1]
CS = company submission; NHS = National Health Service.

The cost associated with the ANT health state (on BSC) was estimated in the same way as for patients in the AOT health state (on mexiletine), except that the health care resource use estimates that were based on the placebo arm of MYOMEX were multiplied by three. The company argued that this was done to account for the idea that the clinical experts whose estimate of resource use was sought may not see all health care use of patients over a year.

In the CS section 3.5.5,[1] additional unit costs are listed (Table 67 of the CS) for genetic testing, with no further explanation provided in that section. Based on p12 and p123 of the CS[1], it is clear that the company included the costs of genetic testing to be in line with the NICE final scope[14]. In the electronic model, these costs were applied to all patients in the first model cycle. The unit costs of genetic testing are shown in Table 5.21.

Table 5.21: Unit costs and sources of genetic testing

Health care resource	Unit cost	Source
Muscle Channelopathy Disorders 4 Gene Panel	£800	UK Genetic Testing Network 2017 cost[41], inflated using PSSRU 2018 HCHS index[39]
Muscle channel clinics	£167	NHS Reference costs, 2017-2018;[40] Neurology outpatient appointment
Total	£967	

Source: Table 67 in the CS.[1]
CS = company submission; HCHS = Hospital and Community Health Service; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; UK = United Kingdom.

5.2.9.3 Adverse event costs

For the treatment of adverse events (AEs), the company in the original CS[1] assumed one visit per year to the GP and the cost of treatment with omeprazole for dyspepsia, and (based on the electronic model, since no explanation is provided in the CS[1]) the costs of an A&E attendance and treatment of a fracture as a results of a fall. For dyspepsia treatment, the company assumed a cost of £0.03 per day for omeprazole (20 mg).[43] No further explanation is provided for this in the text of the CS[1], other than a summary table (Table 68 in the CS)[1] indicating that the average, total duration of dyspepsia treatment per patient is 358 days (51 weeks) per year. In the electronic model, the probability of patients experiencing a gastrointestinal (GI) AE was multiplied by the probability of receiving treatment for dyspepsia, which was multiplied by the costs of a visit to the GP plus the costs of treatment with omeprazole for dyspepsia.

For the costs of treatment of fractures, the electronic model multiplied the annual probability of falling with a resulting fracture (0.1 for the mexiletine arm, and 0.2 for the placebo arm; also see Section 5.2.7) with the cost of A&E attendance plus the cost of treatment of a fracture. The unit costs for the treatment of adverse events that were included in the original CS[1] are shown in Table 5.22.

In response to the ERG clarification questions,[24] the company provided an updated electronic model that included the costs for all relevant AEs based on data from the MYOMEX trial. The model showed that it was assumed that an AE would lead to a GP visit (only one visit per patient per year). Additionally, patients would be prescribed drug treatment for a limited time period, but no explanation was provided in the response to the clarification letter on what the choice of drug and the length of treatment was based. The estimated costs for the relevant AEs are shown in Table 5.23.

Table 5.22: Unit costs and sources for adverse events

Health care resource	Unit cost	Source
Omeprazole (20 mg, pack of 28)	£0.84	BNF 2019[43]
GP appointment	£34	PSSRU 2018[39]
A&E attendance	£130	NHS Reference costs, 2017-2018[40]
Treatment of a fracture	£733.00	NHS Reference costs, 2017-2018[40]

Source: Table 67 and 69 in the CS.[1]
A&E = accidents and emergencies; BNF = British National Formulary; CS = company submission; GP = general practitioner; mg = milligram; NHS = National Health Service; PSSRU = Personal Social Services Research Unit.

Table 5.23. Adverse events included in updated economic model

Adverse event category	Drug used for treatment (dosage)	Pack size	Cost per pack	Source for unit costs
Gastrointestinal disorders (Abdominal pain, Nausea, Abdominal pain upper)	Omeprazole (20 mg capsules)	28	£0.84	BNF 2020[63]
General disorders and administration site conditions (Fatigue, Chest pain, Asthenia, Chest discomfort, Malaise)	Diazepam (5 mg tablets)	28	£0.59	

Adverse event category	Drug used for treatment (dosage)	Pack size	Cost per pack	Source for unit costs
Nervous system disorders (Headache, Somnolence, Paraesthesia)	Diazepam (5 mg tablets)	28	£0.59	
Respiratory, Thoracic and Mediastinal disorders (Dyspnoea)	Azelastine hydrochloride (140 microgram per 1 actuation 22ml)	1	£10.50	
Cardiac disorders (Tachycardia)	Atorvastatin (as Atorvastatin calcium trihydrate; 20 mg)	28	£0.78	
Ear and Labyrinth disorders (vertigo)	Diazepam (5 mg tablets)	28	£0.59	
Musculoskeletal and connective tissue disorders (Pain in extremity)	Paracetamol (500 mg capsules)	100	£3.13	
Injury, Poisoning and Procedural complications	Paracetamol (500 mg capsules)	100	£3.13	
Skin and subcutaneous tissue disorders (Acne)	Cetirizine (10mg tablets)	30	£1.15	
Vascular disorders (Flushing, Hypotension)	Atorvastatin (as Atorvastatin calcium trihydrate; 20 mg)	28	£0.78	

Source: Economic model, updated from the response to the clarification letter.[24]
BNF = British National Formulary; mg = milligram; ml = millilitre.

ERG comment: According to the ERG, a substantial amount of uncertainty was introduced into the model that relates to the estimates of health care resource use other than drug acquisition, cardiac monitoring, and genetic testing. The estimates for resource use that includes physiotherapy, occupational therapy, speech therapy, and mobility aids were based on the CMS Disability scale. For this instrument, which was newly developed in the MYOMEX trial (a secondary objective of which was to assess the reliability and validity of the CMS, but the results of that assessment were not reported). An association between its scores and use of resources was hypothesised by the company and three clinical experts, who were, according to the company, knowledgeable about the CMS. Four other clinical experts, who were not involved in the estimation of the association, indicated not being familiar with the instrument. Each one of these four expressed their specific doubts about it (e.g. relating to the CMS not capturing all aspects of the condition, the descriptions being too extreme, expecting most patients with NDM to score between 0 and 1 (i.e. no to only little problems), and the difficulty in assigning probabilities of resource use to the various scores).[38] In light of these limitations that were noted by the clinical experts, the ERG considers the CMS Disability scale not fit for the purpose of health care resource use estimation. However, no relevant information is available from the literature and no (direct) data on health care resource use were gathered in the MYOMEX trial. In absence of any alternative relevant inputs for the model, the ERG has not changed the included estimates for health care resource use in their base-case.

On top of the hypothesised association between CMS Disability scores and health care resource use, the estimated total costs of health care resources used for the ANT health state i.e. on BSC were multiplied by three. This was not done for the AOT health state i.e. on mexiletine. The company justified this threefold multiplication of total health care resource use by noting that "The patient surveys [9, 64] highlighted a disparity in possible events such as fall & fractures experienced by patients compared to that perceived by clinical experts who typically may see patients once a year [38]". The ERG was not convinced by this argument to consider it a plausible assumption that all health care resource use on BSC arm is a multiple of the estimates that were based on the CMS Disability scale. Moreover, no justification at all was provided for choice of the value three for the multiplier and the ERG is not convinced that this is a plausible value if indeed a multiplier could be considered reasonable in the first place. In their base-case, the ERG has therefore removed this 'health care resource use multiplier' from the analysis. Hence, in the ERG base-case the estimated health care resource use directly follows from the hypothesised associations with the CMS Disability scores for both the AOT (on mexiletine) and the ANT (on BSC) health states.

Upon request of the ERG during the clarification phase, the company updated the economic analysis to include all relevant AEs (i.e. as listed in section B.3.3.6 of the CS[1]) in addition to only the gastrointestinal disturbances and risk of fractures following a fall that were included in the original CS.[1] For costs, the original CS[1] included those related to treatment of dyspepsia with omeprazole, GP appointments, A&E attendances, and treatment of a fracture. The updated model included the costs of various drugs that the company assumed were used for the treatment of all relevant AEs that were reported in the MYOMEX trial. Information on which drugs were assumed for each relevant AE was only available in the updated electronic model, and not further explained in text by the company (the values of the unit costs for each AE were provided in Table 19 of the response to the clarification letter,[24] without further justification of the underlying assumptions for these costs). This makes it difficult for the ERG to assess the validity of the estimated AE costs. However, since the AE costs are very low compared to other costs, their impact on the model results are negligible. The ERG has not changed the AE costs that were included in the updated electronic model by the company.

6. COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results

The discounted base-case results presented in Table 6.1 indicate that, with the PAS prices, mexiletine is expected to generate no incremental LYGs, but results in a gain of [redacted] QALYs at an additional lifetime cost of [redacted] compared to the BSC. Therefore, the estimated incremental cost effectiveness ratio (ICER) is [redacted] per QALY gained.

Table 6.1: Company base-case cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
Mexiletine	[redacted]	38.92	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	38.92	[redacted]	-	-	-	-

Source: Table 72 of the CS.[1]
BSC = Best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; QALYs = quality-adjusted life years.

The disaggregated discounted QALYs by health state are given in Table 6.2 and the disaggregated discounted costs by health state are given in Table 6.3.

Table 6.2: Summary of QALYs disaggregated by health state

Health state	QALYs intervention (Mexiletine)	QALY comparator (BSC)	Increment	Absolute increment	% absolute increment
AOT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ANT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Economic model submitted in the CS.[1]
ANT=alive no treatment; AOT= alive on treatment; BSC = Best supportive care (with no pharmacological treatment)

Table 6.3: Summary of costs disaggregated by health state

Health state	Costs intervention (Mexiletine)	Costs comparator (BSC)	Increment	Absolute increment	% absolute increment
AOT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ANT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Economic model submitted in the CS .[1]
ANT=alive no treatment; AOT= alive on treatment; BSC = Best supportive care (with no pharmacological treatment)

ERG comment: The total costs reported for the mexiletine group in the CS did not align with the total cost for this group in the model submitted with the CS. The values reported above are taken from the model. During the clarification process, some erroneous inputs were detected by the company regarding the patient level data within the model. These inputs have been corrected in the updated economic model

submitted in its response to the clarification letter, yielding a marginally higher ICER. The updated results of the company base case are provided in Section 7.

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

The company conducted a PSA based on 10,000 iterations. The input parameters included in the PSA, with their corresponding probability distributions, were reported in Table 70 of the company submission.[1]

An overview of the parameters that were sampled in the PSA and the corresponding distributions used are listed below:

- Time horizon (Gamma distribution)
- Treatment effectiveness clinical inputs such as compliance, discontinuation, health state utility, disease progression differential, likelihood of falls (Beta distribution)
- Mexiletine dose (Gamma distribution)
- Disease severity proxy, in terms of CMS disability score (Gamma distribution)
- Healthcare resource utilisation (percentages and units) such as ECG, physiotherapy, occupational therapist, speech therapy care package, mobility aids, etc. (Gamma distribution for units and Beta distribution for percentages)
- Unit costs for healthcare resource units as well as mexiletine drug costs (Gamma distribution)
- Adverse event probabilities (Beta distribution)

For all parameters, a standard error of 30% of the mean was assumed.

The discounted PSA results, with the PAS prices are shown in Table 6.4. The average incremental costs and incremental QALYs are [redacted] and [redacted] respectively, resulting in an ICER of [redacted] per QALY gained. The mean PSA results from the PSA are comparable to the deterministic analysis results.

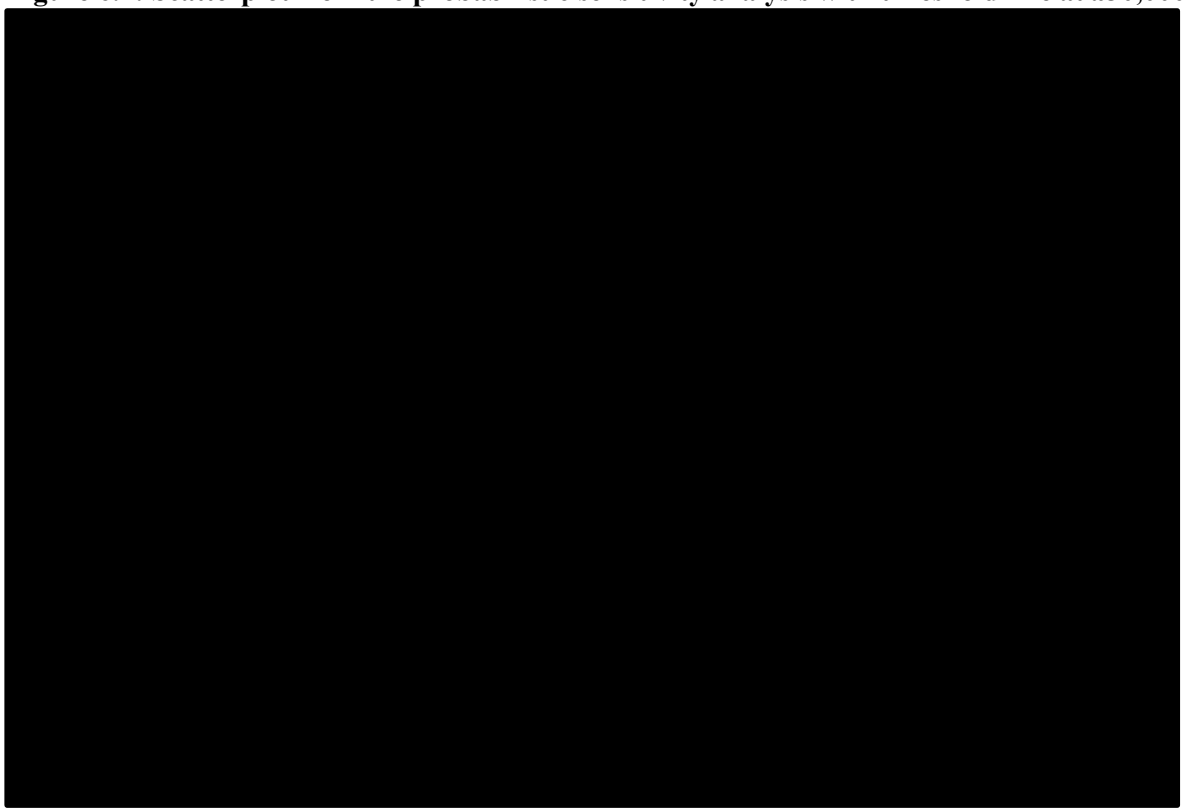
Table 6.4: Company base-case probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-

Source: Table 73 of the CS.[1]
BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life year/s gained; QALYs = quality-adjusted life years.

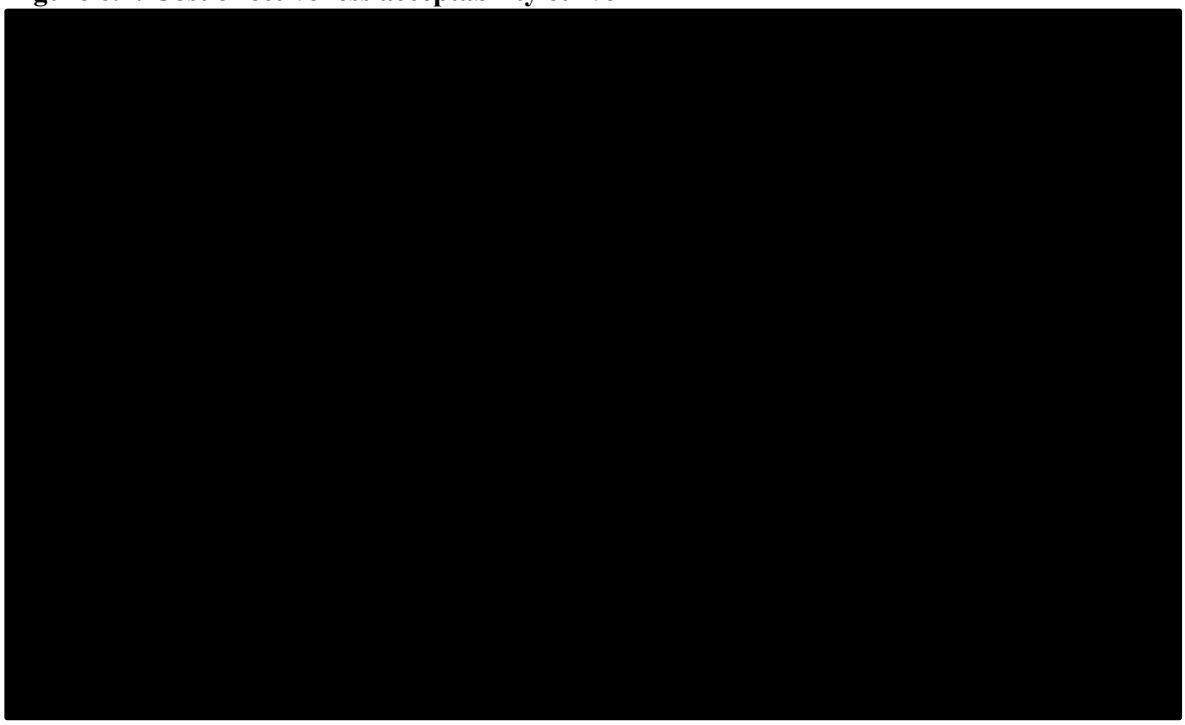
The PSA outcomes were plotted in the CE plane, and, subsequently, a CEAC was derived. These are shown in Figures 6.1 and 6.2, respectively. The majority of the PSA iterations provide results in the north-eastern quadrant of the CE plane, where mexiletine is more effective and more expensive than BSC alone. The CEAC shows that mexiletine has around [redacted]% probability of being cost effective at a threshold of £20,000 per QALY, and [redacted] at a threshold of £30,000.

Figure 6.1: Scatterplot from the probabilistic sensitivity analysis with threshold line at £30,000



Source: Figure 30 of the CS.[1]
CS = company submission; PSA = probabilistic sensitivity analysis; QALY= quality-adjusted life year.

Figure 6.2: Cost effectiveness acceptability curve



Based on Figure 31 of the CS.[1]
CS = company submission; PSA = probabilistic sensitivity analysis; QALY= quality-adjusted life year.

ERG comment: The ERG has doubts on whether parameter uncertainty was correctly reflected in the PSA of the company. Firstly, for almost all varied parameters, it was assumed that the standard error was 30% of the mean. Where possible, e.g. for the compliance rate and the discontinuation rate, these standard errors should have been obtained from the same sample from where the mean estimate was obtained. At the same time, the ERG recognises that with SEs of 30% of the mean a rather large uncertainty was assumed, providing most likely an overestimation of the true parameter uncertainty.

Additionally, the ERG noted that some parameters were included which are not subject to parameter uncertainty, i.e. the time horizon and capsule cost per mexiletine, thus creating unnecessary noise in the PSA.

The ERG expressed these concerns during the clarification process, however, the updated electronic model provided with the company's response had the same parameters and levels of uncertainty as the original model.[24]

6.2.2 Deterministic sensitivity analysis

The company also conducted a deterministic sensitivity analysis (DSA). The same parameters that were included in the PSA were also included in the DSA. In the DSA, the upper and lower bounds were assumed 130% and 70% of the mean value, as according to the company it was not possible to derive ranges from literature. The values used in the DSA were outlined in Table 70 from the CS.[1]

The tornado diagram in Figure 6.3 shows the impact on the ICER of the most influential parameters which cause the largest changes in the ICER. From this figure, it can be observed that changes in the mexiletine utility [redacted]), the mexiletine maintenance dose [redacted]) and the cost per capsule for mexiletine [redacted]) resulted in the largest changes in the ICER.

Figure 6.3: Tornado diagram – company's preferred assumptions

[redacted]

Source: Figure 34 of the CS.[1]

CMS= Clinical myotonia scale; ICER = Incremental cost effectiveness ratio.

ERG comment: Similar to the PSA, the ERG has doubts on how the deterministic analysis was conducted in the company submission. Due to the lack of data, in the deterministic analysis, the upper and lower bounds of each parameter were assumed to be 130% and 70% of the mean value. Appropriately, the upper and lower bounds of the parameters should have reflected the parameter uncertainty and they should have been calculated from the 95% confidence intervals from each parameter. Also, similar to the PSA in the CS, some of the parameters which were not subject to parameter uncertainty (time horizon and capsule cost per mexiletine) were included in the deterministic sensitivity analysis.

6.2.3 Scenario analyses

The company undertook a series of scenario analyses in order to test the impact of a number of assumptions on model results. The scenarios tested and results obtained are summarised in Table 6.5.

The scenarios which had the largest impact on results are:

- Changing the health outcome discount rate from 3.5% to 1.5% decreased the ICER by [redacted]
- Varying the disease progression differential (assumed to exist in NDM such that quality of life decreases over time in the absence of treatment for myotonic symptoms) between 0-25%. Changing the differential value from 15% to 0% would increase the ICER [redacted], whereas changing the differential value to 25% would lead to a reduction in ICER of [redacted].
- Changing the anchor for the DCE utility weighting, by assuming 23233 EQ5D as the worst state in INQoL (in the base case 33333 EQ5D state was assumed as the worst state), decreased the ICER [redacted]
- Changing the mexiletine daily dose from 400 mg to 429 mg (15 capsules per week) increased the ICER [redacted]
- Assuming no multiplier for the healthcare resource use under the BSC (in the base case a multiplier of three was applied) increased the ICER [redacted].

ERG comment: The majority of the scenarios had a minor impact on the incremental results. A new set of scenario analyses will be conducted on the ERG preferred base-case in Section 7.

6.3 Model validation and face validity check

The company mentioned in the CS that extensive internal and external technical validation efforts were conducted by programmers who were not involved in the development of the economic model. A brief overview of the quality checks of the finalised model were listed in the CS as followed:

- Basic validity checks; logical checks of the Markov trace and output in relation to inputs and intended functions
- Costs; checks of cost inputs for most recent sources and application
- Utilities and clinical; most applicable sources and application
- Model settings; standard model functionality and usability
- Sensitivity analysis; PSA, DSA and scenario analyses incorporation
- Macros/User Forms; VBA code functionality and efficiency

Additionally, the company claimed that external validation efforts for the model structure and functionality were conducted by two external consultancy companies, particularly on the functionality of the model inputs.

ERG comment: The company indicated that a review of the model, including functionality and calculation checks, were performed internally and externally by two leading health economics consultancies.[1, 24] However, the specific tests, and the documentation of the validation and verification efforts of the model, were not reported. Therefore, the degree of the validation of the model cannot be assessed by the ERG.

The ERG has performed extensive technical verification of the model and found issues with regards to the implementation of the half cycle corrections and the PSA, as earlier described. Given the extreme simplicity of the model structure, the face validity of the model results is directly reflected by the face validity of the model input. The ERGs comments on the validity of these inputs were described earlier in Section 5.

Table 6.5: Results of scenario analyses (PAS price)

Scenario	Mexiletine cost (£)	Mexiletine QALY	BSC costs	BSC QALY	Incr. cost	Incr. QALY	ICER	% change from base-case ICER
Base case results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Treatment disease progression differential 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment disease progression differential 5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment disease progression differential 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment disease progression differential 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment disease progression differential 25%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No multiplier for HC resource use in No Treatment health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier of 2 for HC resource use in BSC health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier of 4 for HC resource use in BSC health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events – MYOMEX[17]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events - Statland et al.[26]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events – Stunnenberg et al.[47]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daily dose 429 mg (15 capsules per week)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

23233 EQ-5D worst health state for INQoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No discount rate for health outcomes and costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcome discount rate 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate Statland et al.[26]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance rate Stunnenberg et al.[47]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 76 from CS.[1]
EQ-5D= EuroQol, 5 dimensions; HC = healthcare; ICER- incremental cost effectiveness ratio; INQoL = Individualized Neuromuscular Quality of Life Questionnaire; QALY = quality adjusted life years

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

Following the clarification questions from the ERG, the company made the following amendments to the originally submitted cost effectiveness model:

- Erroneous inputs in the 'Patient level analysis' sheet were corrected.
- The functionality to choose between additional data sources for utilities was added. In addition to the DCE study-based utility weights, vignette study-based utility weights were also included as an option in the economic model.
- An additional option was included in the economic model, which allows the inclusion of all AEs observed in the MYOMEX trial, instead of only including gastrointestinal disturbance in the original model.
- For DCE based utilities, additional bottom anchors were added for mapping to EQ5D (33233 and 23333 in addition to 33333 in the original model).
- An option to include the arithmetic average of the discontinuation rates from all mexiletine trials was added.

With these changes made in the model, the company re-ran the base-case and sensitivity analyses. The discounted base-case deterministic and probabilistic results are presented in Tables 7.1 and 7.2, respectively. The tornado diagram from the DSA, the CE-plane and CEAC from the PSA and the results of the scenario analyses are similar to those in the original submission and, therefore, not reported here. Further details can be found in the response to the clarification letter (economic appendix) submitted by the company with the responses to the clarification letter.[24]

Table 7.1: Company base-case cost effectiveness results after clarification (discounted with PAS)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 1 of the response to the clarification letter (economic appendix)[24]
BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality-adjusted life years

Table 7.2: Company base-case probabilistic cost effectiveness results after clarification (discounted with PAS)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 30 of the response to the clarification letter (economic appendix)[24]
BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality-adjusted life years

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[65]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

1. The half cycle correction was implemented incorrectly, this has been corrected
2. A utility decrement due to GI disturbance was included in the model, even though it was not described in the report. We assume there is no additional utility decrement due to GI disturbance, as those utilities might have been captured in the MYOMEX trial.

7.1.2.2 Fixing violations

3. Parameters that were not subject to parametric uncertainty (such as time horizon and mexiletine capsule price) were now excluded in the PSA and deterministic sensitivity analysis.

7.1.2.3 Matters of judgement

4. Assuming no disease progression differential for BSC
5. Using vignette-based utilities
6. Incorporating age-adjustment of utilities
7. Using treatment discontinuation rate from MYOMEX trial
8. Using AE rates from MYOMEX, including all AEs and not only GI
9. Assuming mexiletine dose in line with the MYOMEX trial (600 mg per day)
10. Assuming no additional multiplier for resource use.

The base-case assumptions of the company and the ERG are presented in Table 7.3, along with the ERG's justifications for changes to these assumptions.

Table 7.3: Company and ERG base-case preferred assumptions (ITT population)

Base-case preferred assumptions	Company	ERG	Justification for change
Utility values	HRQoL data from INQOL valued using the DCE study. The worst INQOL state was assumed equivalent to the worst EQ-5D-3L state when anchoring utility values.	HRQoL data from INQOL valued using the vignette/TTO study.	Use of utility values from the vignette/TTO study avoids issues with DCE study design and results and does not require assumptions regarding anchoring of states. (Section 5.2.8).

Base-case preferred assumptions	Company	ERG	Justification for change
Age-adjustment of utilities	No age-adjustment.	Equal decline in utilities due to ageing for patients alive on treatment on alive off treatment.	The adjustment of utilities due to ageing is standard practice (Section 5.2.8.3).
Treatment discontinuation	Treatment discontinuation calculated from Suetterlin et al. study.[29]	Treatment discontinuation calculated from MYOMEX trial.	Use of MYOMEX trial data more consistent with other data utilised (Section 5.2.6).
Adverse events	The only AEs included in the model were GI disturbances whilst on mexiletine (rates calculated from Suetterlin et al. study.[29]) and the treatment specific probability of fracture (rates based on UK Advisory Board[13])	Used adverse event rates from the MYOMEX trial. Included all adverse events and not only GI disturbances.	Use of MYOMEX trial data more consistent with other data utilised (Section 5.2.7).
Disease progression differential	An additional 15% reduction in HRQoL was applied to the patients under best supportive care or to the patients who discontinue mexiletine, on top of the difference in utilities between treatment groups observed in the MYOMEX trial.	15% differential removed.	The 15% disease progression differential was not evidence based (Section 5.2.6).
Mexiletine dose	400 mg daily dose of mexiletine assumed to reflect clinical practice.	600 mg daily dose of mexiletine to reflect the dosage in the MYOMEX trial.	Since the efficacy data from the MYOMEX trial is based on a dose of 600 mg it is inappropriate to only cost 400 mg (Section 5.2.4).
Resource use multiplier	A multiplier of 3 was applied to the resource use estimates of the BSC group.	The multiplier was removed.	Resource use was estimated separately for mexiletine and BSC based on hypothesized correlation between CMS Disability scores in the MYOMEX trial and

Base-case preferred assumptions	Company	ERG	Justification for change
			health care resource use. There is no evidence for an additional multiplier of 3 (on top of the difference calculated between treatment groups) (Section 5.2.9).
AEs = adverse events, BSC = best supportive care; DCE = discrete choice experiments; GI = gastrointestinal; HRQoL = health related quality of life; TTO = time trade off			

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted several additional scenario analyses in which the main sources of uncertainty identified by the ERG were explored. These were the uncertainties associated with the utility values used in the model, the comparators included in the model and the company's assumptions surrounding the disease progression differential and resource use.

7.1.3.1 Scenario set 1: utility values used in the model

The utility values for mexiletine and BSC are the drivers of results as treatment effect is solely based on HRQoL in this model, with the treatments having no impact on length of life. The fact that the company had to conduct their own conceptual mapping and valuation studies in order to obtain utility values for the model means that there are also important areas of uncertainties within the utility values obtained. These two issues translate into the two utility parameters being the most influential and fourth most influential in the DSA performed by the company. Therefore, the ERG felt it was appropriate to explore the different possible scenarios from the company's two valuation studies here. First the company base-case utility scenario, in which HRQoL is valued using the results of the DCE study, assuming a worst state equivalent to the worst EQ-5D-3L state (33333 = -0.594) will be examined. Then the impact on results of using alternative bottom anchors within the DCE study will be explored. The results obtained from these scenarios are compared to the ERG base-case which adopts the utility values obtained using the vignette/TTO study.

7.1.3.2 Scenario set 2: utility age-adjustment

The company did not incorporate any adjustment of utilities due to ageing, which is standard practice in modelling studies. In the ERG base-case, an annual decrement in utility due to ageing was estimated from the Ara and Brazier equation which estimates UK general population utilities by age.[61] This annual decrement was applied equally to the utilities of patients alive on treatment and alive off treatment. However, it is also possible that the addition of comorbidities developed as patients age will have less impact on the utility of patients with more substantial disease burden (those alive off treatment) than it will on those patients with lower disease burden who are alive on treatment, as comorbidities have been suggested to have a multiplicative effect on utility rather than an additive effect. Therefore, in this scenario, a multiplicative approach to the application of the decrement in utility due to ageing estimated from the Ara and Brazier equation will be examined.

7.1.3.3 Scenario set 3: lamotrigine as a comparator

Lamotrigine was listed as a comparator in the final scope but was not included as a comparator in the model. In this scenario, the ERG incorporated lamotrigine as a comparator by adding its cost and assuming the same discontinuation rates and AE costs as mexiletine. The cost of lamotrigine was

identified from the BNF. Different utility values for lamotrigine, ranging between a utility equal to BSC and a utility equal to mexiletine will be examined to explore the impact on the ICER.

7.1.3.4 Scenario set 4: disease progression differential

The ERG performed a scenario analysis in which a disease progression differential of 15% was assumed. This is in line with the company's base-case model and based on the company's assumption that HRQoL of patients in the ANT health state was overestimated following the notion that the severity of myotonia may increase over time. This scenario shows the impact of assuming an additional 15% reduction in the utility value of patients in the ANT health state.

7.1.3.5 Scenario set 5: health care resource use multiplier

The ERG performed a scenario analysis in which a 'health care resource use multiplier' of three, i.e., an additional threefold increase of health care resource use in the ANT health state, was assumed. This is in line with the company's base-case model, and based on the company's assumption that health care resource use in the ANT health state was underestimated following a discrepancy between the opinions of clinical experts (that initially informed the estimated relationships between the CMS Disability Scale scores and health care resource use of patients receiving placebo in the MYOMEX trial) and patients.

7.1.3.6 Scenario set 6: mexiletine dosage of 333 mg

The ERG performed a scenario analysis in which a (maintenance) dosage was assumed of 333 mg mexiletine daily (i.e. two capsules per day or equivalent to 400 mg mexiletine hydrochloride) instead of 500 mg mexiletine daily (i.e. three capsules per day or equivalent to 600 mg mexiletine hydrochloride). This is in line with the company's base-case model and based on the company's assumption that dosage in clinical practice would be lower than mexiletine dosage in the MYOMEX trial. Furthermore, no change in treatment effectiveness was assumed in relation to the alternative dosing assumption.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case

The results of the ERG preferred base-case are provided in Table 7.4. After the implementation of the ERG preferred assumptions, the ICER was [redacted]. Mexiletine was estimated to provide [redacted] additional QALYs, at an additional cost of [redacted]. Tables 7.5 and 7.6 show the disaggregated QALYs and costs per health state for each treatment group as well as the incrementals per health state.

Table 7.4: ERG base-case deterministic cost effectiveness results (discounted with PAS)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]				

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; QALY = quality-adjusted life year

Table 7.5: Summary of QALYs disaggregated by health state for ERG base-case

Health state	QALYs intervention (Mexiletine)	QALY comparator (BSC)	Increment	Absolute increment	% absolute increment
AOT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ANT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
ANT=alive no treatment; AOT= alive on treatment; BSC = Best supportive care (with no pharmacological treatment); QALY = quality-adjusted life year

Table 7.6: Summary of costs disaggregated by health state ERG base-case

Health state	Costs intervention (Mexiletine)	Costs comparator (BSC)	Increment	Absolute increment	% absolute increment
AOT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ANT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
ANT=alive no treatment; AOT= alive on treatment; BSC = Best supportive care (with no pharmacological treatment)

The ERG also conducted a PSA of their preferred base-case, with results displayed in Table 7.7. This yielded a probabilistic ICER of [redacted], which aligns closely with the deterministic results.

Table 7.7: ERG base-case probabilistic cost effectiveness results (discounted with PAS)

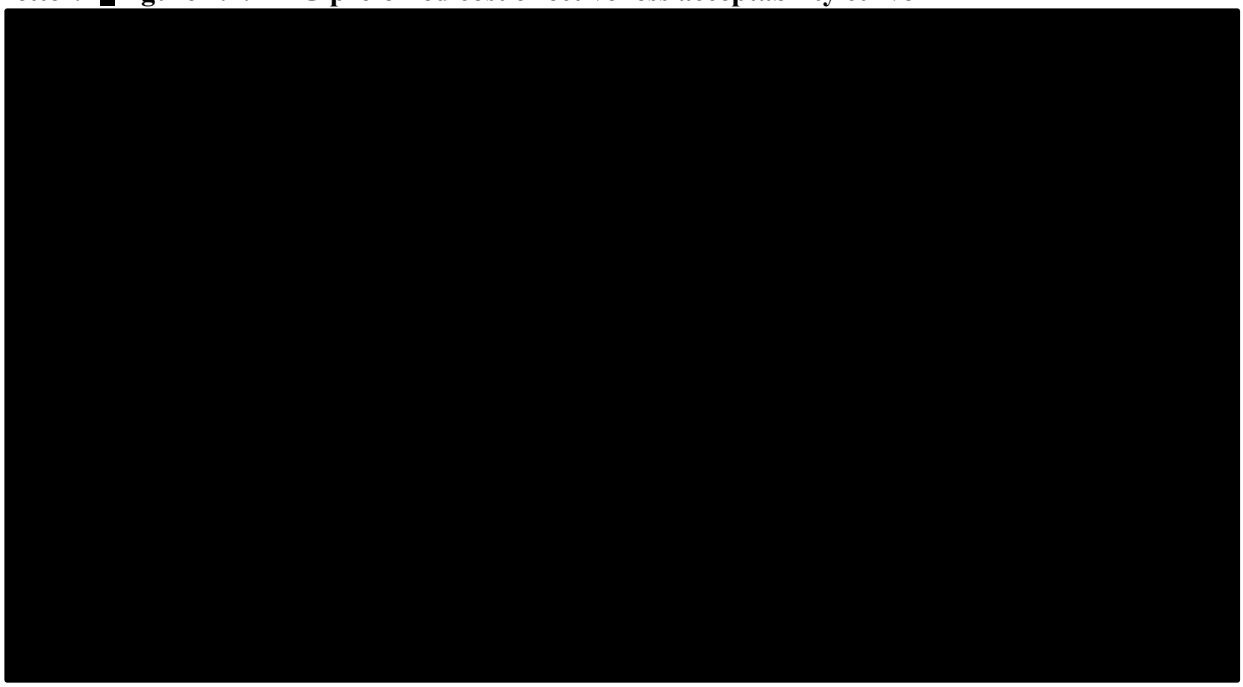
Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]			

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year

The ERG preferred cost effectiveness plane displayed in Figure 7.1 shows that all simulations resulted in additional cost. [redacted] of simulations fell in the north-west quadrant, where mexiletine is more costly and less effective, while the remaining [redacted] fell in the north-east quadrant where mexiletine is both more costly and more effective. The vast majority of simulations fell above the threshold of £30,000. The CEAC shows that at thresholds of £20,000, and £30,000, the probability that mexiletine is cost effective is [redacted] and [redacted] respectively. [redacted]

Figure 7.1: ERG preferred cost effectiveness plane

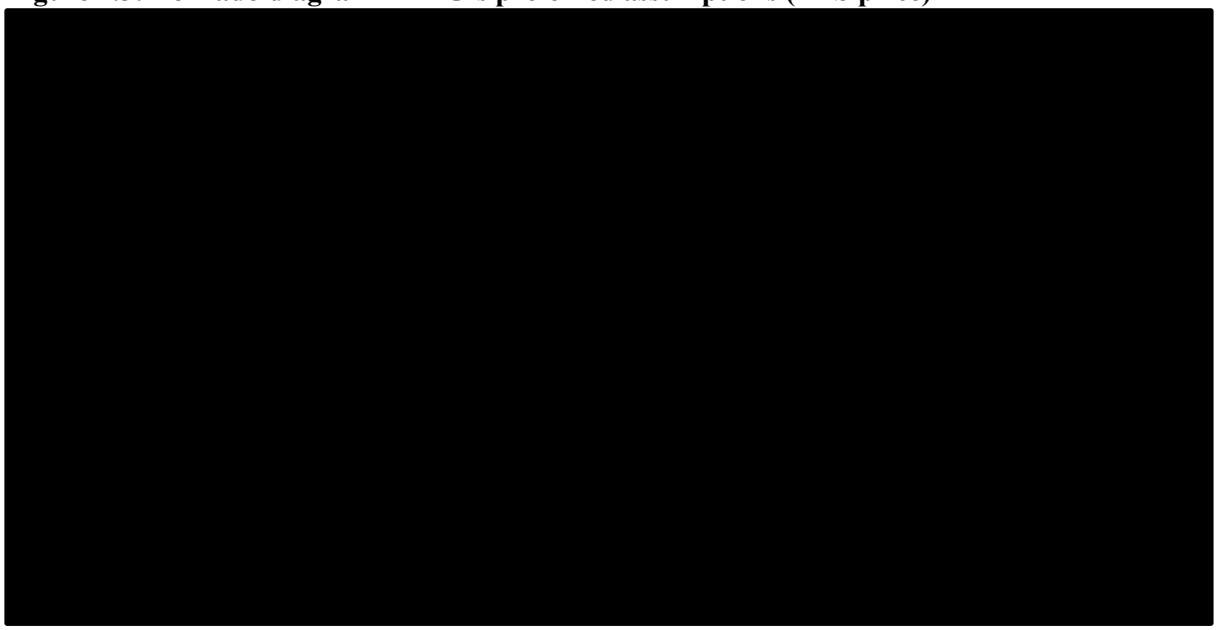
Source: Based on the economic model, updated from the response to the clarification letter.[24] Figure 7.2: ERG preferred cost effectiveness acceptability curve



Source: Based on the economic model, updated from the response to the clarification letter.[24]

The tornado diagram obtained from the ERG preferred base-case displayed in Figure 7.3 shows that the parameters which have the largest impact on model results in the DSA are the two utility values (mexiletine alive on treatment and BSC alive off treatment), followed by the mexiletine maintenance dose, compliance rate and the assumed disease progression differential.

Figure 7.3: Tornado diagram – ERG's preferred assumptions (PAS price)



Source: Based on the economic model, updated from the response to the clarification letter.[24]

7.2.2 Results of the ERG additional exploratory scenario analyses

7.2.2.1 Scenario set 1: utility values used in the model

The choice of which set of utility values to use in the model has a substantial impact on the model as shown in Table 7.8. The company base-case utility scenario, using the utilities obtained from the DCE study, assuming a bottom anchor equivalent to the worst state on the EQ-5D-3L (33333) results in the lowest ICER of . Varying the assumption of the bottom anchor state within the DCE study to 23333 increased the ICER by approximately and increasing the bottom anchor state to 23233 increased the ICER by a further to . Using the utility values obtained from the Vignette/TTO study increased the ICER to , approximately higher than the company base-case scenario.

Table 7.8: Results of scenario set 1: utility values used in the model

Utility values	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
DCE (bottom anchor 33333) (Company BC)							
DCE bottom anchor (bottom anchor 23233)							
DCE bottom anchor (23333)							
Vignettes (ERG BC)							

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BC = base-case; BSC = best supportive care; DCE = discrete choice experiment; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year

7.2.2.2 Scenario set 2: utility age-adjustment

The results for the age-adjustment scenarios are displayed in Table 7.9. The company and ERG base-case scenarios regarding the age-adjustment of utilities did not differ in terms of ICER, as the ERGs adjustment of utilities was applied equally in both treatment arms, so that the absolute decline in the utility values each year was the same in both groups. Assuming a multiplicative impact of comorbidities developed as patients age increased the ICER by approximately [redacted].

Table 7.9: Results of scenario set 2: utility age-adjustment

Utility age-adjustment	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
No age adjustment (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Equal adjustment both treatments (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier method	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality-adjusted life year

7.2.2.3 Scenario set 3: lamotrigine as a comparator

No direct head-to-head evidence assessing the effectiveness of mexiletine compared to lamotrigine was identified. The cost of lamotrigine was identified from the BNF. The same AEs were assumed for lamotrigine as for mexiletine. Given that the impact of treatment on HRQoL is the only unit of effectiveness in the model, this scenario investigates different utility values for lamotrigine, relative to those observed for BSC and mexiletine. This provides scenarios regarding the potential cost effectiveness of mexiletine compared to lamotrigine, dependent on the utility value assumed for lamotrigine, as shown in Table 7.10 and Figure 7.4. Assuming a utility value equal to that of best supportive care ([redacted]) resulted in an ICER of [redacted] for mexiletine compared to lamotrigine. It should be remarked here that in a full incremental comparison including BSC as well, lamotrigine would be dominated by BSC.

The ICER increases rapidly from this point to [redacted] at a lamotrigine utility of [redacted] and [redacted] at a utility of [redacted]. At a utility of [redacted] (equal to the utility of mexiletine) [redacted]

Table 7.10: Results of scenario set 3: lamotrigine as a comparator

Utility lamotrigine	Mexiletine		Lamotrigine		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility lamotrigine	Mexiletine		Lamotrigine		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; mex = mexiletine; QALY = quality-adjusted life year

Figure 7.4: The impact on the ICER of various assumed lamotrigine utility values

[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
ICER = incremental cost effectiveness ratio

7.2.2.4 Scenario set 4: disease progression differential

In line with the company's base-case model, an additional 15% reduction in the utility value of patients in the ANT health state was assumed in this scenario. The results of this scenario, displayed in Table 7.11, show that this assumption reduces the ICER in comparison to the ERG preferred base-case by [redacted], to [redacted] per QALY gained.

Table 7.11: Results of scenario set 4: disease progression differential

Disease progression differential	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
0% (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15% (Company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality-adjusted life years.

7.2.2.5 Scenario set 5: health care resource use multiplier

In line with the company's base-case model, a health care resource use multiplier of three was assumed. This scenario shows the impact of assuming an additional threefold increase of health care resource use in the ANT health state. The results of this scenario in Table 7.12 show that this assumption reduces the ICER in comparison to the ERG preferred base-case by [redacted], to [redacted] per QALY gained.

Table 7.12: Results of scenario set 5: health care resource use multiplier of three

Health care resource use multiplier	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
1 (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BC = base-case; BSC = best supportive care; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality-adjusted life years.

7.2.2.6 Scenario set 6: mexiletine dosage of 333 mg

In line with the company's base-case model, a (maintenance) dosage was assumed of 333 mg mexiletine daily (i.e. two capsules per day or equivalent to 400 mg mexiletine hydrochloride) instead of 500 mg mexiletine daily (i.e. three capsules per day or equivalent to 600 mg mexiletine hydrochloride in this scenario. The results of this scenario (Table 7.13) show that this assumption reduces the ICER in comparison to the ERG preferred base-case by 34%, to [redacted] per QALY gained.

Table 7.13: Results of scenario set 6: mexiletine dosage of 333 mg

Mexiletine dosage	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
500 mg (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mexiletine dosage	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
333 mg (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality-adjusted life years.

7.3 ERG's preferred assumptions

The ERG preferred changes to the updated company base-case were described in Section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.14 in 10 steps, where, in each step, all previous changes are also incorporated and the cumulative impact on the model results is shown. The assumption with the largest absolute impact on the ICER was adjustment of the mexiletine dosage from 400 mg to 600 mg, in line with the MYOMEX trial dosage, which increased the ICER by [redacted] (an increase of approximately [redacted]). The other change which had a substantial impact on results was using the utility values from the vignette/TTO study rather than the DCE study (assuming bottom anchor of 33333), which increased the ICER by [redacted] (an increase of approximately [redacted]). All the other changes made by the ERG had a smaller impact on the ICER (maximum of [redacted]). The base-case ICER in the company submission was [redacted]. The ICER based on the ERG preferred assumptions was [redacted].

Table 7.14: ERG's preferred model assumptions (PAS included)

Preferred assumption (combined with previous lines)	Section in ERG report	Mexiletine		BSC		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case (at submission)	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company updated base-case (after clarification)	7.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 1 – Corrected half-cycle correction	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 2 - Removed unmentioned disutility for GI AEs	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 3 – Removed parameters from PSA	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 4 – No disease progression differential	5.2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 5 – Vignette/TTO utility values	5.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 6 – Implementing age-adjusted utility decline from Ara and Brazier[61]	5.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 7 – Treatment discontinuation rates from MYOMEX trial	5.2.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 8 – AE rates from MYOMEX trial (including all AEs and not only GI)	5.2.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 9 – Mexiletine dose in line with MYOMEX trial	5.2.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 10 – No additional multiplier for resource use	5.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to the clarification letter.[24]

AE = adverse event; BSC = best supportive care; ERG = Evidence Review Group; GI = gastrointestinal; ICER = incremental cost effectiveness ratio; Inc = incremental; PSA = probabilistic sensitivity analysis; QALY = quality adjusted life year; TTO = time trade off

7.4 Conclusions of the cost effectiveness section

A single search was undertaken for cost effectiveness, costs and healthcare resource studies, and a separate search was conducted for HRQoL data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources and reference checking. Searches were well conducted and documented, making them transparent and reproducible.

The systematic literature review did not identify any relevant evidence and therefore the company developed a de-novo model comparing mexiletine to BSC in NDM patients. A lack of evidence on the natural history of the condition led the company to develop a simplistic three state Markov model, where patients could either be alive on treatment with mexiletine, alive with no treatment, where they receive only BSC, or dead. Therefore, patients in the comparator group begin the model in the alive no treatment state and remain there until death. Similarly, patients who discontinue from mexiletine remain in BSC until death, with no subsequent lines of pharmacotherapy considered. This treatment status focussed model is not able to describe the long-term disease state of patients and leads to a heterogeneous group of patients being assigned the same costs and quality of life. Instead, a more granulated disease model would be preferred, where each health state is fairly homogeneous with regards to costs and quality of life. However, given the lack of data available, the current model structure is difficult to improve on and is considered acceptable.

The baseline patient characteristics applied in the model were based on the patient characteristics from the MYOMEX trial. It is unclear to the ERG how representative the NDM patients included in the MYOMEX trial are of those patients eligible for mexiletine treatment in UK clinical practice. Evidence cited in the submission states that the age of onset of NDM symptoms is typically in infancy or childhood.[5] Therefore, the average baseline age of 44 from the MYOMEX trial might not reflect the average age of patients eligible for mexiletine in clinical practice. Additionally, the ERG is uncertain whether the eligibility criteria used in the MYOMEX trial would be reflective of the disease severity of NDM patients that would be eligible for mexiletine treatment in clinical practice.

Several issues arose regarding interventions and comparators. Firstly, the NICE scope listed lamotrigine as a comparator.[14] However, the company chose to use BSC as the sole comparator. The company excluded the use of lamotrigine as expert opinion elicitation and market research conducted by the company suggested that lamotrigine was not established in clinical practice (received by approximately 3% of patients with NDM). Additionally, lamotrigine is not licensed for this indication and there is a lack of long term efficacy and safety data or head-to-head evidence with mexiletine in NDM patients.[24, 38] Since it was listed in the final scope as a comparator, the ERG considers that lamotrigine should have been included in the economic model. Therefore, the ERG conducted several exploratory analyses in Section 7, comparing lamotrigine with mexiletine under various assumptions.

Secondly, the company assumed a different dosage for mexiletine in the model than the dosage used in the MYOMEX trial, on which the model efficacy and safety data was based. In the MYOMEX trial, the mexiletine dose was force titrated up to 600 mg daily, at which point efficacy was assessed. However in the company submission, the company assumed a daily dose of 400 mg, as the forced titration would not reflect clinical practice and the 400 mg daily dose was more in line with a UK real world retrospective study from Suetterlin et al., which reported that the mean clinically effective dose of mexiletine used was 416.7 mg daily.[29] However, experts consulted by the company suggested that 400 mg could be considered a minimum dose and given that the efficacy data in the economic model are based on the 600 mg dose, the ERG believe it is inappropriate to cost a lower dose.[38]

Given the assumed lack of impact of mexiletine on survival, the effectiveness of mexiletine in the model was driven by improvements in HRQoL and reductions in health care resource use estimated from the MYOMEX trial. Other clinical inputs implemented in the model were: treatment discontinuation, compliance, mortality and disease progression differential. In the company base-case treatment compliance was estimated from the MYOMEX trial, while discontinuation was estimated from a study by Suetterlin et al. study.[29] The ERG believe it is more appropriate to estimate discontinuation from the MYOMEX study to maintain consistency with other efficacy parameters.

In their base-case the company assumed a disease progression differential of 15%. This was implemented by reducing the HRQoL of patients receiving BSC by 15%, on top of the difference in HRQoL observed between mexiletine and BSC from the MYOMEX trial. This disease progression differential was applied based on the assumption by the company that quality of life in NDM patients decreases over time in the absence of treatment for myotonic symptoms, but that HRQoL would be maintained in patients receiving mexiletine as the treatment would not lose efficacy over time. However, clinical opinion on the long-term progression of NDM and the impact of this on HRQoL was mixed and there was no quantitative evidence for the assumed reduction in HRQoL of 15% in the BSC group on top of the difference in utility observed in MYOMEX and therefore the ERG removed this assumption in their base-case.

The company incorporated the costs associated with several AEs into the model. The AEs included were experiencing gastrointestinal disturbance whilst on mexiletine and being treated for dyspepsia associated with this gastrointestinal disturbance and treatment specific fracture probabilities. The probabilities of these events were obtained from Suetterlin et al. and a UK advisory board.[13, 29] However, the ERG requested that the AEs observed in the MYOMEX trial be incorporated into the model. The impact of AEs on HRQoL were assumed to be reflected in the HRQoL data collected in the MYOMEX trial.

The company measured health directly in patients in the MYOMEX trial using the condition-specific INQoL. The company argued that this was the most appropriate measure to use as it was able to best capture the impact of treatment on NDM. However, no psychometric evidence was provided showing that generic measures such as the EQ-5D were invalid or unreliable in this population. No mapping algorithm was available between he INQoL and EQ-5D and the INQoL is not preference based. Therefore, the company had to conduct a valuation study to be able to obtain utility values from the INQoL data collected.

To be amenable for valuation, the INQoL, which contains 45 items each with six to seven response options, needed to be substantially reduced. The company achieved this by selecting items and response levels which reflected the descriptive system of the EQ-5D, as well as additional items which were considered important to NDM. This reduced the 45 items down to eight items each with four response options included in the valuation exercise. The company presented two separate valuation studies; a DCE, used to value HRQoL in the company base-case, and a vignette study valued using TTO which was given to the ERG just before clarification. Issues were identified for each, as detailed in Section 5.2.8 of this report. However, the ERG believed that the issues in the DCE study were more widespread; including a lack of clear monotonicity in included response options, logical inconsistencies in results and issues with selecting an appropriate anchor for the DCE results. Therefore, the ERG chose to use the vignette/TTO study to value HRQoL in their base-case.

Regarding resource use and costs, the economic analysis includes drug acquisition costs and cardiac monitoring costs for the AOT health state (i.e. on mexiletine). These costs do not apply for the ANT health state (i.e. on BSC). Furthermore, the cost of genetic testing was included for all patients. To

inform further health care costs in the AOT and ANT health states, the company assumed hypothetical associations between levels of resource use and CMS disability scale scores that were categorized as 'mild', 'moderate', and 'severe' for each dimension of disability in patients in MYOMEX that received mexiletine and placebo, respectively. More specifically, patients that experienced problems in handwriting, walking, or ascending/descending stairs were hypothesised to make use of physiotherapy; patients that experienced problems in eating, hygiene, or dressing were hypothesised to make use of occupational health sessions; patients that experienced problems in speech were hypothesised to make use of speech therapy; and patients that experienced problems in walking were hypothesised to make use of mobility aids such as a wheelchair, walking stick and walking frame. Day case attendance was hypothesised to be associated with the categorisations of severity of disability in any of the dimensions of disability mentioned above. In the original CS, an additional 'health care resource use multiplier' of three was used for patients in the ANT health state (i.e. on BSC). This was justified based on a discrepancy between the opinions of patients and those of clinical experts who typically only see patients once a year. The ERG discarded this threefold multiplication of health care costs in the ANT health state for their preferred base-case. This is because the ERG was not convinced of the plausibility of ANT health care costs being a multiple of the initial estimates, whilst noting that the value of three lacked any foundation.

Although the model originally only included gastrointestinal disturbances as AEs, the model was updated upon request by the ERG during the clarification phase to include all relevant AEs that were observed in MYOMEX. This also included the costs for various drugs that were assumed by the company for the treatment of AEs.

The discounted results from the company base-case indicated that, compared with BSC, mexiletine generates an additional [redacted] QALYs at an additional cost of [redacted], resulting in an ICER of [redacted] per QALY gained. The company conducted a probabilistic and a one-way sensitivity analysis, and a number of additional scenario analyses. The probabilistic ICER was [redacted] per QALY gained. The majority of the 10,000 iterations fell in the north-east quadrant of the cost effectiveness plane, where mexiletine is more effective and more expensive than BSC alone. The CEAC shows that mexiletine has around [redacted]% probability of being cost effective at a threshold of £20,000 per QALY, and [redacted] at a threshold of £30,000. The results of the one-way deterministic sensitivity analysis indicated that the mexiletine utility, the mexiletine maintenance dose and the cost per capsule for mexiletine had the largest impact on results. The scenarios analyses conducted by the company which had the largest impact on results were varying: the disease progression differential, the anchor for the DCE utility calculation, the daily dose for mexiletine and the assumed healthcare resource use multiplier.

Following the clarification questions from the ERG, the company made several amendments to the original model. The list of amendments is provided in Section 7.1.1, but the effect of these changes on the base-case ICER was minor. Additionally, the ERG corrected several errors found in the model related to half-cycle correction and PSA parameters (with a minor impact on the results). The ERG also made the following changes to the company's base-case assumptions: 1) using utilities from the vignette/TTO study; 2) incorporating age-adjustment of utilities; 3) using treatment discontinuation rate from MYOMEX trial; 4) using AE rates from MYOMEX, including all AEs and not only GI; 5) assuming no disease progression differential for BSC; 6) assuming mexiletine dose in line with the MYOMEX trial (600 mg per day).; 7) assuming no additional multiplier for resource use.

The ERG preferred base-case analysis resulted in an ICER of [redacted], approximately [redacted] the size of the company base-case. The probabilistic ICER of [redacted] was slightly lower but in line with the deterministic ICER. The majority of simulations ([redacted]) fell in the north-east quadrant where

mexiletine is both more costly and more effective. The CEAC shows that at thresholds of £20,000, and £30,000, the probability that mexiletine is cost effective is [redacted] and [redacted] respectively. [redacted]. The parameters which had the largest impact on model results in the DSA were the utility values for mexiletine (AOT) and BSC (ANT), followed by the mexiletine maintenance dose, compliance rate and the assumed disease progression differential.

The ERG also conducted several additional scenario analyses in order to reflect the impact on results of the remaining areas of (mostly structural) uncertainty within the model. From the results of these analyses it can be concluded that the model is most sensitive to the exploratory scenario where lamotrigine is considered as the comparator to mexiletine. Due to a lack of direct head-to-head data considering the efficacy and safety of mexiletine compared to lamotrigine in this population, this exploratory scenario assumed the same AE profile, compliance and discontinuation for lamotrigine as mexiletine, while the cost of lamotrigine was identified from the BNF. Within the scenario various utility values for lamotrigine were examined, which varied between assuming that patients on lamotrigine would have the same utility as patients on BSC and the same utility as patients on mexiletine. Assuming the same utility as BSC for lamotrigine resulted in an ICER of [redacted] for mexiletine compared to lamotrigine, while assuming equivalent utilities between the treatment groups led to an equal amount of QALYs accumulated, but with lamotrigine being cheaper. The other scenarios which were found to have a substantial impact on the ICER were the valuation methods to derive the utility values used in the model and the assumed dosage of mexiletine.

In general, the key issue in the cost effectiveness analysis was the lack of robust long-term data on both the natural history of NDM and the efficacy and safety of mexiletine and other comparators. This lack of data prohibited the development of a model which could reflect the long-term efficacy of treatment and progression of disease, which could have provided a much clearer estimate of the cost effectiveness of mexiletine compared to relevant comparators. The lack of data also meant many assumptions were used in the submission which could not be substantiated by evidence. This means that important areas of uncertainty remain within the results which cannot be resolved using the current evidence base.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Thursday 30 April 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Clinical trial/ Study amends

Issue 1 MYOMEX unblinding and cross over effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11, 29, 30, 43, 59 In several places the ERG criticizes the MYOMEX clinical trial for what it suspects is unintentional unblinding of the participants and the consequences that brings as the ERG points out happened in the Statland trial.	The ERG should remove these references to the MYOMEX study.	Unevidenced claim. There is no evidence that the claim the ERG makes is true with regards the MYOMEX study. The trial followed standard blinding procedures. Quality of the trial was assessed by the "Revised Cochrane risk of bias tool for randomised trials (RoB 2.0) – Additional considerations for cross-over trials", and there was no risk of bias found for MYOMEX. Lupin would argue that the ERG stating that all the trials would have inadequate blinding is a very generalised statement to make and not based on any evidence specific to MYOMEX. Carry over effect and unintentional blinding were not evidenced as treatment sequence effect was non-significant in all domains.	Not a factual error.

Issue 2 Skewed data claim

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 50 MYOMEX performed an analysis of ranks as the change from baseline in stiffness was skewed and the results were reported as median and range Page 57 The statistical analysis methods were also different as MYOMEX performed a mixed effects linear regression model on ranks as the stiffness scores were not normally distributed and reported medians and ranges for change.	Clarity should be provided for the claims of skewed data or removed.	The ERG stated that ranks testing implied that data was not "normal". Although it is true "ranks" is used in non-parametric data. It can also be used in "parametric" or "normal" data. As a result, ranks test is appropriate whether the data was "normal" or not "normal" (skewed) and therefore statements on whether or not the data is skewed based solely on this assumption are not justified.	Not a factual error. The ERG agrees that an analysis of ranks can be used for both normally and non-normally distributed data but note that the stiffness results in Table 11-8 of the MYOMEX CSR indicate that the change from baseline results for the placebo group were not normally distributed.

Issue 3 Long term efficacy and safety of mexiletine

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14, 73, 122 In several places the ERG states that there is a lack of robust long-term data for the efficacy and safety of mexiletine.	The ERG should clarify why they believe the evidence provided is not robust and long-term or remove the statements	For a newly licensed medicine in an orphan disease, it is quite rare to have such significant post-marketing safety data (Page 54/ 55 ERG report), and significant long-term safety and efficacy data (Suetterlin et al (2015) & MYOMEX follow up data)	Not a factual error.

Comparator

Issue 4 Lamotrigine as a comparator

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 71 A list is provided by the ERG of the reasons why the company excludes Lamotrigine as a comparator	The list is incomplete and should be updated to incorporate the full list previously provided.	A list of reasons was provided by the company in its answer to B1a of the ERGs clarification questions which is not fully incorporated into the report.	Not a factual error. The full list is available to the committee in the response to clarification.

Economic Assumptions

Issue 5 Use of MYOMEX data in the company and ERG base case models

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12, 71, 74, 108, 119, 120 In many places the ERG makes changes to the company's base case model to include outputs of the MYOMEX trial. These changes include the average daily dosing of the medicine, safety (adverse events), and discontinuation rates. The changes being based on expert opinion that "400mg could be considered a minimum", and to maintain a consistency since the efficacy and safety inputs to the	The statements should be amended/removed to reflect that there is not a consistency of the company base case being based on MYOMEX and therefore adjusting dosing for example as a consistency argument is not true.	Lupin utilises several sources of data within the company base case as outlined in our submission, including available longer-term data sources, and real wold evidence. There is not the consistency of the inputs that the ERG suggests, and it is incorrect to state that safety (adverse events) in the base case model is from MYOMEX.	Reference to consistency with safety data has been removed on p71, p108 and p119. The rest of Issue 5 is not a factual error. In most instances it is clear that the ERG is seeking consistency, which in the introduction, page 13, has been clarified further.

model were obtained from the MYOMEX trial.			

Issue 6 ERG model changes

Description of problem	Description of proposed amendment		Justification for amendment	ERG Response
ERG economic model 'Markov'!O7:O63 includes implementation of age-related disutilites, but this is only active when the AllAE switch is set to 'Yes' (ERG change 8)	The formula has been amended as so: =IF(A7="","",IF(AllAE="Yes",D7*(((p_QALY_Mexiletine-N7)*L7)-perc_R_MX_Gastro*disutility_AE_GI*prob_GI)*(1-p_disease_differential_mexiletine),D7*(p_QALY_Mexiletine**-N7**)***L7***(1-p_disease_differential_mexiletine))) This does not impact the company or ERG-preferred deterministic base case ICER, but does impact the results presented in Table 7.14 between ERG change 6 and ERG change 7 (see below ICERs).		Model correction.	The ERG thank the company for noticing and fixing this and agree with the change. The relevant table in the ERG report has been updated.
	ERG change 6	[redacted]		

	ERG change 7	[redacted]		

Issue 7 Dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25 The ERG writes “NDM patients in UK practice receive a maintenance dose which is in accordance with the intensity of a patient’s symptoms and clinical response (usually somewhere between 400 and 600 mg/day)”	Change: “NDM patients in UK practice receive a maintenance dose which is in accordance with the intensity of a patient’s symptoms and clinical response (usually somewhere between 400 and 600 mg/day)” To: “NDM patients in UK practice receive a maintenance dose which is in accordance with the intensity of a patient’s symptoms and clinical response”	There is no evidence for the dose being “usually somewhere between 400 and 600 mg/day” and therefore should be removed. The Namuscla SmPC allows for anything between 1 and 3 doses a day (ERG report page 70).	According to the company submission (CS, page 15): “Patients are dose titrated up, according to clinical response, after at least 1 week of treatment, to a daily dose of 333 mg mexiletine daily (i.e. two capsules per day or equivalent to 400 mg mexiletine hydrochloride). After at least 1 further week of treatment, the dose can be further increased to 500 mg daily (three capsules per day or equivalent to 600 mg mexiletine hydrochloride) based on clinical response.” Our understanding of this is that all patients receive a daily dose of at least 400mg. This corresponds with our statement.

Issue 8 CMS use in estimating resource use

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 96 The ERG writes of the CMS: “An association between its scores and use of resources was hypothesised by the company. This association was based on the opinion of clinical experts who indicated not being familiar with the instrument, and who each expressed their specific doubts about it (e.g. relating to the CMS not capturing all aspects of the condition, the descriptions being too extreme, expecting most patients with NDM to score between 0 and 1 (i.e. no to only little problems), and the difficulty in assigning probabilities of resource use to the various scores).“	Change: “An association between its scores and use of resources was hypothesised by the company. This association was based on the opinion of clinical experts who indicated not being familiar with the instrument, and who each expressed their specific doubts about it (e.g. relating to the CMS not capturing all aspects of the condition, the descriptions being too extreme, expecting most patients with NDM to score between 0 and 1 (i.e. no to only little problems), and the difficulty in assigning probabilities of resource use to the various scores).” To: “An association between its scores and use of resources was hypothesised by the company and clinical experts. This association was based on the opinion of clinical experts who were knowledgeable of the CMS. Other clinicians, not involved at all in this exercise indicated not being familiar with the instrument, and who each expressed their specific doubts about it (e.g. relating to the CMS not capturing all aspects of the condition, the descriptions being too extreme, expecting most patients with NDM to score between 0 and 1 (i.e. no to only little problems), and the difficulty in assigning probabilities of resource use to the various scores)”	The ERG has misunderstood which clinical experts were consulted for the CMS disease severity proxy for healthcare resource use. For this exercise, three experts were consulted in May to June 2019. These experts understood the CMS well. The process is described in B.3.5.5 of the company submission and addressed in the ERG clarification questions B5 & B20.	The ERG is grateful for the company pointing this out, and has changed the text as follows: “An association between its scores and use of resources was hypothesised by the company and three clinical experts, who were, according to the company, knowledgeable about the CMS. Four other clinical experts, who were not involved in the estimation of the association, indicated not being familiar with the instrument. Each one of these four expressed their specific doubts about it (e.g. relating to the CMS not capturing all aspects of the condition, the descriptions being too extreme, expecting most patients with NDM to score between 0 and 1 (i.e. no to only little problems), and the difficulty in assigning probabilities of resource use to the various scores)”

DCE, Vignettes & Conceptual mapping

Issue 9 Conceptual mapping of INQoL to EQ5D

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 77 The wording of "Finally, it was observed in the literature that fatigue had an important impact on NDM patients' assessment of their HRQoL.[5, 7, 26, 51, 52] Experts agreed, and fatigue was also included in the conceptual mapping" could be misinterpreted.	Change: "Finally, it was observed in the literature that fatigue had an important impact on NDM patients' assessment of their HRQoL.[5, 7, 26, 51, 52] Experts agreed, and fatigue was also included in the conceptual mapping" To: "Finally, it was observed in the literature that fatigue had an important impact on NDM patients' assessment of their HRQoL.[5, 7, 26, 51, 52]. Fatigue is among the most frequent complaints reported by patients with chronic illnesses. For this reason, and as validated by the experts, fatigue was included for conceptual mapping"	Fatigue was included not because of its impact to NDM patients but because "fatigue is among the most frequent complaints reported by patients with chronic illnesses" (see company submission page 131).	This has been amended to "Finally, it was observed in the literature that fatigue had an important impact on NDM patients' assessment of their HRQoL and that fatigue is among the most frequent complaints reported by patients with chronic illnesses.[5, 7, 26, 51, 52] Experts agreed, and fatigue was also included in the conceptual mapping."

Issue 10 ERG's description of the rationale for mapping studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 78 The ERG criticises the mapping exercise because for some INQoL items there is not a complete conceptual overlap	Include additional text at the end of paragraph one of ERG comment: "However, it is a characteristic of mapping studies that there is unlikely to be complete conceptual overlap and does not reflect the use of incorrect methodology."	Additional text should be included that acknowledges that Mapping studies between two measures generally don't assume a 100% conceptual overlap between the	Not a factual error. Mapping works best when there is high conceptual overlap. Therefore, limited overlap is a limitation for

between the INQoL items and the EQ-5D-5L items.		two measures. This is not an enforced error.	mapping studies in general as well as in this specific case.

Issue 11 INQoL content validity

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 78 The ERG suggest content validity of the INQoL is not retained because not all of the items in the scale are included, however also state the INQoL needed to be substantially reduced to be amenable for valuation. The content validity of the retained items is unaffected by removing some other items. This is commonly done in this type of work.	Change: “The content validity of the INQoL also no longer be fully argued as the substantially reduced INQoL for valuation misses several domains from the full INQoL entirely, with other domains greatly reduced.” To: “The content validity of the retained INQoL items can still be claimed.”	Content validity of the retained items is not affected by the fact that some have been removed.	Not a factual error. COSMIN methodology for assessing the content validity of PROMs states: Three aspects of content validity are: (1) relevance (all items in a PROM should be relevant for the construct of interest within a specific population and context of use), (2) comprehensiveness (no key aspects of the construct should be missing), and (3) comprehensibility (the items should be understood by patients as intended). By removing items and domains from the original measure, the comprehensiveness (and therefore content validity) of

			the reduced measure can no longer be fully argued.

Issue 12 ERG DCE methodology advice

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 82 The ERG recommend some work which explored tweaks to the DCE methodology to avoid logical inconsistencies. This work was published in March 2019 and was not available to the study team when they initiated their work in early 2019.	The following sentence on page 82 should be removed: "Recent methods to improve the study designs of DCEs which contain many domains have recommended including overlap within the choice pairs, so that some attributes stay constant within the choice pair, while overs vary.[58] This overlap allows participants to focus on those attributes which vary within the choice set, reducing the chances that participants make heuristic shortcuts, by ignoring some attributes in the face of a complex choice with many variables. This technique has been shown to be effective in reducing task complexity which reduces dropout rates and increases choice consistency.[58] This type of design requires a larger sample or more choice tasks but can help to improve the data quality obtained and may have improved the quality of the data and results in this study."	It is unreasonable to expect projects undertaken to support the NICE submission to reflect recommendations from studies that have only just been published. This should be deleted.	Not a factual error. The method of overlap within choice tasks was not invented in the paper cited in the ERG report. This paper discussed this method and tested its impact on task complexity, drop out and choice consistency. The paper cited in the ERG report cites papers which discuss and adopt attribute level overlap long before the conduct of the company's DCE e.g. Kessels et al. (2012), Norman et al. (2016) and Jonker et al. (2018) Many other examples of the use of attribute overlap are available in the literature.

Issue 13 DCE Lower anchor clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 82-83 The ERG criticise the work and suggest that the DCE method is inappropriate because the lower anchor of worst health cannot be justified.	Proposed additional wording: "We do note, however, for example that the worst level on the pain/discomfort dimension equates to extreme pain and extreme tiredness fatigue which is worse than extreme pain or discomfort. The worst level on anxiety/ depression item equates to extreme depression and extreme anxiety which is worse than extreme anxiety or depression."	From Table 5.11 the Worst & Best health state defined by INQoL is criticised because the mobility items do not align with the EQ-5D. However, as an example, the worst health state for mobility would be someone with extreme muscle weakness and extreme muscle locking which in scenarios we have equated to *Some problems walking about.* Or for example, it doesn't seem to be recognised that our worst health state includes an extreme amount of pain and extreme amount of tiredness or fatigue which equates to Extreme pain or discomfort in EQ-5D. Also, the worst health state includes extreme depression and extreme anxiety compared with the EQ-5D where the worst level is extreme anxiety or depression. For both of these dimensions the INQoL worst health state is logically worse.	Not a factual error. These are additional examples of differences between the measures which may impact the appropriateness of the anchors. The ERG commented on those that they felt were of most concern. Adding additional examples of differences between the measures does not change the argument.

Issue 14 Response labels

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 87 The ERG make claims about response labels. These are not supported by evidence and in our view are not true. This is a completely speculative suggestion.	The following wording on page 87 should be removed: “The relative strength of preferences for a fair amount and a considerable amount may not be consistently strong as these labels are less concrete and less commonly used than terms such as “moderate” and “slight”. It is difficult to predict how different in severity participants will find the two intermediate levels in relation to each other and their neighbouring endpoint levels, which may affect their willingness to trade between levels.”	This claim has no evidence to support it and are based purely on speculation.	Not a factual error. This is not based purely on speculation, but on knowledge of the importance of response label wording and response scaling. An important stage of a preference study should be testing that the response levels selected behave appropriately, using response scaling exercises. Response levels should be clearly monotonic and be evenly spread across the underlying scale of that item. As an example from the literature, response scaling exercises were undertaken when deciding the response labels for the EQ-5D-5L (Herdman et al., 2011). This showed that Moderate performed best as a central point on the response scale and was the most consistently valued label out of the mid-range options tested, as it had the lowest inter-quartile range across respondents. Extreme

			had the lowest IQR out of top end options and Slight and Minor had the lowest IQRs for lower end response options. Other labels included in the study included: a few, some, many and a lot, which were all less consistently understood than Slight, Moderate and Extreme. The EQ-5D-5L team removed labels which used additional modifiers such as 'very' or 'quite' during piloting as well as any labels that were considered excessively colloquial. Fair and Considerable are very colloquial quantifiers. Given the results of the labels tested in the EQ-5D study, many of which are more easy to precisely quantify than "a fair amount" and a "considerable amount", as well as the ERGs broader expertise in the area of PROM development and validation, the ERG believe it is reasonable to hypothesise that there would be more variability in the valuations of a fair amount and a considerable amount and that it is difficult to predict how these labels would be interpreted by respondents.

			However the ERG would like to note that a response scaling exercise should have been performed by the company prior to both studies in order to ensure that the levels selected performed well. This would have given the ERG more confidence in results and would have ruled out issues with response labels as the cause of issues in results.

Issue 15 Monotonicity and logical inconsistencies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 78-86 The ERG in several places place a lot of emphasis on the lack of monotonicity in the coefficient weights that emerge from the DCE. We acknowledge this is a study limitation. But the ERG do not acknowledge that.	The following should be removed from page 82: “Therefore this lack of clear monotonicity could have had a widespread impact on results.” And: “Perhaps more concerning are the three logical inconsistencies in which the coefficients for “no problems” and either “slight” or “moderate” problems are mis ordered. These level comparisons are clearly monotonic and therefore suggest deeper issues with participant understanding of the task or attention to the task or DCE design.”	None of the logical inconsistencies listed at the top of page 80 were statistically significant. They represent measurement error, but may also relate to the response labels (moderate & some) which are open to misinterpretation. No misordered coefficient weights were included in the cost effectiveness analysis. So misordered items should not bias the results in favour of the treatment. Our independent experts did not express any concerns regarding the	Not a factual error. Even though adjustments were made so that there was no misordering in the final model, the coefficients of this model are still based on the results of the DCE study where widespread misordering was seen and therefore these issues are having an impact in the final model. The experts and the ERG did not express concern about the company’s handling of the misordering as there is little

		manner in which the misordered coefficients were handled in the scoring algorithm.	more you can do with problematic results at that stage. However, it does not mean that this misordering does not signal issues in the underlying study which will have influenced results.

Issue 16 INQoL being disease specific

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 78 The ERG criticise the inclusion of two items to reflect mobility (muscle weakness and muscle locking) because they are “very disease specific”. This is common when you use disease specific measures like the INQoL. No other mobility items were available in the INQoL measure.	Change: “The INQoL items chosen to reflect the mobility are very disease specific, focusing on muscle weakness and muscle locking rather than issues in walking about as on the EQ-5D.” To: “The INQoL items chosen to reflect the mobility focussed on muscle weakness and muscle locking.”	Mapping from disease specific PRO measures (to EQ-5D) inevitably means that disease specific items are included. This is not a valid basis for criticising our approach. There are no questions in the INQoL regarding ‘walking about’.	Not a factual error. This is a weakness of the mapping approach in general.

Administrative/ Minor errors

Issue 17 Wrong trial duration

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10, section 1.2. MYOMEX described as having a "duration of four weeks" Statland trial described as having a "duration of 18 days"	MYOMEX trial has a duration of 18 days Statland trial has a duration of 4 weeks	Accuracy, the trial durations are the incorrect way around.	This has been corrected.

Issue 18 Difference between Mexiletine and Mexiletine Hydrochloride dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 10, 12, 13, 25, 30, 51, 56, 58, 59, 70, 71, 72, 102, 107, 108, 117, 119 The incorrect description of dose is given for mexiletine, when what is meant is mexiletine hydrochloride.	Amend throughout where mexiletine is meant, and where mexiletine hydrochloride is meant	Accuracy, and avoidance of confusion as the dosing of mexiletine is expressed differently to the dosing of mexiletine hydrochloride.	Not a factual error. As the company state, this is a minor error and the committee understand what is meant.

Issue 19 Omission of critical real-world evidence dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 10, 30, 59 Suetterlin retrospective review stated treatment “up to 600 mg/day”	A mean dose in the Suetterlin retrospective review can be calculated to be 416.7 mg mexiletine hydrochloride and should be stated	Omission of known real world evidence which is crucial to understanding the patient dosing in a lifetime economic model and with a significant impact on the resulting ICER.	The mean dose of 416.7 mg daily is reported on page 12 of the ERG report.

Issue 20 Pros and Cons of short duration trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 11, 59 The ERG states that “a major limitation of all included trials is that the treatment duration was very short (between 18 days and four weeks).”	This statement needs clarification as there are both pros and cons of the short duration of the trial, rather than describing simply as a “major limitation”.	There are specific advantages of a short trial in a rare disease, such as Non-Dystrophic Myotonia, trialling an acknowledged therapy such as mexiletine, where the treatment effect is seen in a short space of time. These include meeting the challenges of recruiting sufficient patients to enrol in the trial, and meeting patient ethical considerations (see section B.2.13.2 of the company submission). Whilst Lupin agrees with the ERG’s position in terms of extrapolating the data over a lifetime horizon,	Not a factual error.

		fortunately long-term data exists from the Suetterlin et al study and the MYOMEX follow up data to help mitigate some of the associated uncertainty.	

Issue 21 Disease Accuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 17 The wording of the below is not quite correct. “Patients with MC are described as having rapid, voluntary movements following a period of rest.”	Change: “Patients with MC are described as having rapid, voluntary movements following a period of rest.” To: “Patients with MC are most symptomatic during rapid voluntary movements following a period of rest.”	Accuracy	This has been corrected.

Issue 22 Equity & Equality

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23 “Special considerations including issues related to equity or equality” described as: “Not addressed by the CS”	The ERG should include additional text in their comments to reflect accuracy of the submission being in line with the NICE Scope	Accuracy. This was addressed in section B.1.4 of the company submission.	This issue was not addressed in the Table. On page 26 of the ERG report there is a reference to CS, Section B.1.4, page 32.

Issue 23 NDM comparators from NICE scope

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 68-69 The ERG writes: "It was also stated that the most common medicines used to treat NDM in second-line were phenytoin, flecainide and acetazolamide, which were not licensed for NDM, and therefore not part of the BSC, according to the company.[44] " This can be interpreted as a decision solely by the company, which is untrue.	Change: "It was also stated that the most common medicines used to treat NDM in second-line were phenytoin, flecainide and acetazolamide, which were not licensed for NDM, and therefore not part of the BSC, according to the company.[44]" To: "It was also stated that the most common medicines used to treat NDM in second-line were phenytoin, flecainide and acetazolamide, which were not licensed for NDM, and therefore not part of the BSC, in line with the original scope. "	Accuracy. The NICE scope states that these medicines do not form part of standard care, rather than the company and the sentence should be amended. The reference (44) to Janet Stone should be removed as it is not clear why it would be appropriate here.	This has been amended

Issue 24 Adverse Event costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 95 The ERG writes "For dyspepsia treatment, the company assumed a cost of £0.03 per day for omeprazole (20 mg).[43] No further explanation is provided for this in the CS[1], other than a summary table (Table 68	Amend the criticisms in this section to be accurate or remove. Should the cost of the AEs for the placebo arm run through the model, now the ERG have asked for the MYOMEX AE data to be in the model?	Accuracy. The Assumptions are provided in the model (in year 1 that treatment for side effects are initiated a week after initiating treatment, hence, only 51 weeks of treatment required in the economic model),	Not a factual error. Assumptions for drug costs need justification in text, which was not provided. Drug costs for all AEs were only provided

in the CS)[1] indicating that the average, total duration of dyspepsia treatment per patient is 358 days (51 weeks) per year." And: "but no explanation was provided in the response to the clarification letter on what the choice of drug and the length of treatment was based. "		and a full response to the ERG was given to why continuous PPI treatment was considered to be reflective of the treatments for all types of gastrointestinal disturbances. We don't believe the ERG asked for a clarification on the choice of drug or the length that the treatment is based, but for the record in our response to the ERG clarification question B4a we wrote that in the Suetterlin et al (2015) study, on which our base case is based for AEs, " the most common adverse event reported was dyspepsia, and this was the only gastrointestinal disturbance recorded. Sixteen of the 23 patients (69.6%) who reported dyspepsia required dyspeptic therapy. As none were reported as serious it could be expected they were treated with a PPI" Omeprazole 20mg is the most used PPI in the UK (IMS Midas Q4 2019).	during clarification (again without justification in text). The ERG has changed the text to: "For dyspepsia treatment, the company assumed a cost of £0.03 per day for omeprazole (20 mg).[43] No further explanation is provided for this in the text of the CS[1], other than a summary table (Table 68 in the CS)[1] indicating that the average, total duration of dyspepsia treatment per patient is 358 days (51 weeks) per year."

Issue 25 Number of individuals in the MYOMEX trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 10, Table 4.3 of page 30	Change:		Not a factual error.

Error in the number of participants in MYOMEX trial.	"MYOMEX: A double blind, cross-over randomised controlled trial (RCT) (N=26), comparing mexiletine 600 mg/day with placebo, with a duration of four weeks, performed in 2011 to 2014 in France;" To: "MYOMEX: A double blind, cross-over randomised controlled trial (RCT) (N=25), comparing mexiletine 600 mg/day with placebo, with a duration of four weeks, performed in 2011 to 2014 in France;"	The MYOMEX trial had 26 patients, but before starting the trial, one of them withdrew. This value can create lot of confusion in the tables reported in the report.	26 patients were randomised and the Intention-to-treat population included 26 patients (CS, Table 4, page 34).
	Change: "Double blind, cross-over RCT (N=26)" To: "Double blind, cross-over RCT (N=25)"		

Issue 26 Distributions in PSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
PSA Page 99 Paragraph 6.2.1	Change: "Healthcare resource utilisation (percentages and units) such as ECG, physiotherapy, occupational therapist, speech therapy care package, mobility aids, etc. (Gamma distribution)" To:	The percentages of healthcare resource utilisation were associated to the Beta distribution, while the units of healthcare resource utilisation were associated to Gamma distribution.	This has been amended.

	“Healthcare resource utilisation (percentages and units) such as ECG, physiotherapy, occupational therapist, speech therapy care package, mobility aids, etc. (Gamma distribution for units and Beta distribution for percentage)”		

References

Herdman, M., Gudex, C., Lloyd, A. *et al.* (2011) Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* **20,** 1727–1736. https://doi.org/10.1007/s11136-011-9903-x

Jonker, M. F., Donkers, B., De Bekker-Grob, E. W., & Stolk, E. A. (2018). Effect of level overlap and color coding on attribute non-attendance in discrete choice experiments. Value in Health, 21(7), 767–771.

Kessels, R., Jones, B., & Goos, P. (2012). A comparison of partial profile designs for discrete choice experiments with an application in software development

Norman, R., Viney, R., Aaronson, N. K., Brazier, J. E., Cella, D., Costa, D. S. J., … Rowen, D. (2016). Using a discrete choice experiment to value the QLU-C10D: Feasibility and sensitivity to presentation format. Quality of Life Research, 25(3), 637–649. https://doi.org/10.1007/s11136-015-1115-3

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: August 2020

1. Topic background

1.1 Disease background

- Non-dystrophic myotonias (NDM) are a group of rare, genetic diseases caused by mutations in skeletal muscle chloride or sodium ion channels which do not have the systemic features and dystrophic weakness of dystrophic myotonia.

- The common features of the diseases are delayed muscle relaxation following muscle contraction or following mechanical stimulation such as percussion. There are differences in sub-categories and gene-coding mutations such as severity and location.

- The primary symptom is skeletal muscle stiffness, but other symptoms include pain, muscle weakness and fatigue. Muscle locking (myotonic episode) describes the inability to relax a muscle and can last from seconds to minutes. This can cause the inability to relax a tight grip or to stand and/or sit with ease, inability to walk fast and potential to fall. People with myotonia try to avoid triggers such as cold weather, stressful situations or the need to use stairs. These symptoms have a significant impact on daily living and emotional health related quality of life.

1.2 Treatment pathway

- There are no current NICE guidelines or other international guidelines for NDM due to the rarity of the diseases.

- Non-pharmacological management involves training to avoid triggers and muscle warming routines but may also require specialist physiotherapy or speech or occupational therapy, depending on the individual patient symptoms.

- For more than 10 years, pharmacological management of the disease has involved using mexiletine off-license and mexiletine has recently become

the first licensed treatment for the disease. Other sodium channel blockers are also used off-label including antiarrhythmics (flecainide, procainamide and tocainide) and antiepileptics (phenytoin and carbamazepine). Lamotrigine also has some evidence for efficacy, although the company do not consider this to be an appropriate comparator (see Issue 3).

1.3 The technology

UK approved name and brand name	Mexiletine (NaMuscla) – Lupin Healthcare
Mechanism of action	Mexiletine blocks channels in muscle cells which allow sodium ions (electrically charged particles) to pass in and out of the cell. These sodium channels play a role in the contraction and relaxation of muscles and are hyperactive in patients with myotonic disorders. It improves myotonic symptoms by decreasing muscle stiffness through reduction of the delay of muscle relaxation i.e. it reduces the rate of contractions and hence the associated stiffness.
Marketing authorisation	Mexiletine has a marketing authorisation for the 'symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders' (granted December 2018) Restrictions include: • Cardiac evaluation and monitoring • Caution with mild or moderate hepatic impairment • Not recommended for severe renal impairment
Dosage in the summary of product characteristics	Daily oral administration between 167-500mg (1 to 3 capsules) • Starting dose of 167mg (equal to 200mg of mexiletine hydrochloride). • After at least 1 week of treatment, according to clinical response, the dose can be titrated up to 333mg (equal to 400mg of mexiletine hyrdrochloride)

	• After at least 1 week of further treatment, the dose can be further increased to 500mg (equal to 600mg of mexiletine hydrochloride)
Price	List price: £5,000 for a pack of 100 capsules A simple discount Patient Access Scheme (PAS) has been submitted to PASLU and NHS England.

1.4 Clinical evidence

- The key clinical evidence comes from:
    - **MYOMEX –** A randomized, double-blind, placebo-controlled, crossover trial of 26 adults with genetically confirmed NDM. The primary outcome was muscle stiffness as measured on a visual analogue scale (VAS) and quality of life was also measured on a disease specific instrument, the Individualized Neuromuscular Quality of Life Questionnaire (INQoL) after 18 days.
    - **Statland et al. –** A randomised, double-blind, placebo-controlled crossover study of 59 patients with symptoms of NDM or genetically confirmed NDM. The primary outcome was stiffness measured by interactive voice response measured at 4 weeks.
    - **Stunnenberg et al. –** A series of aggregated, double-blind, randomized, placebo-controlled N-of-1-trials, performed in a single academic referral centre for 30 patients with genetically confirmed NDM. The primary outcome was stiffness as measured by interactive voice response every 3-4 weeks up to 44 weeks.
    - **Suetterlin et al. –** A retrospective review of 63 patients in the UK with genetically confirmed NDM prescribed mexiletine with a minimum of 6 months follow up.

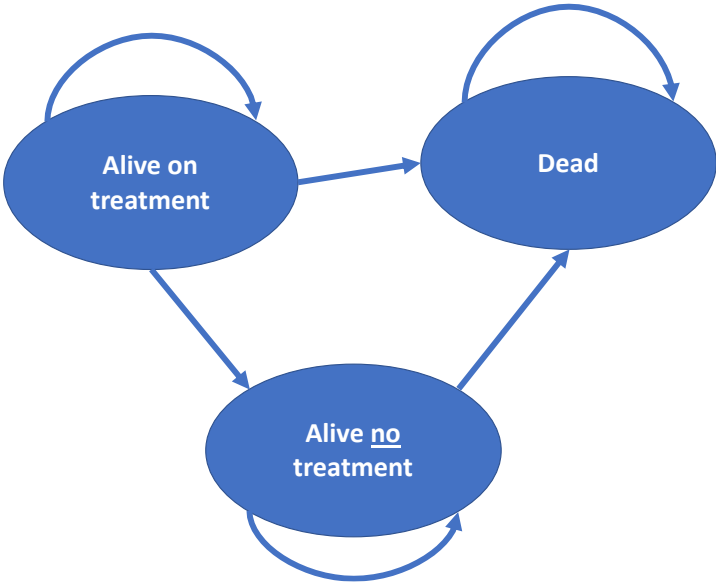
1.5 Key trial results

- INQoL measurements were the outcome measure used in the economic model and are presented in Figures 1 and 2 below:

- Figure 1: Scores for INQoL symptom subdomains before study initiation and in treatment and no treatment arms of study (Figure 21 in company submission)

- Figure 2: Scores for INQoL impact of daily living domains before study initiation and in treatment and no treatment arms of study (Figure 22 in company submission)

1.6 Model structure



- Markov cohort model structure with 3 states, based on treatment status or death. The only events modelled are discontinuation of mexiletine and death. There is no modelled treatment effect on mortality so all benefit is captured through health-related quality of life in each health state.

1.7 Key model assumptions

Area	Assumption	Company justification
Time horizon	Lifetime – starting age in the model is 44 years with 56-year time horizon	As in NICE reference case, starting age is the mean age of the MYOMEX study
Cycle length	1 year with half cycle correction	Considered appropriate to capture changes in treatment benefit and costs
Treatment discontinuation	Annual rate calculated from Suetterlin et al. retrospective study	Study has the longest follow-up and is therefore most appropriate for calculating treatment discontinuation
Dose	333mg (400mg mexiletine hydrochloride equivalent)	Clinical expert judgement and closest dose to Suetterlin et al. mean dose
Disease progression	Assumed additional 15% decrease in utility for people without treatment to account for disease progression	UK patient survey suggests worsening of symptoms since diagnosis, MYOMEX long-term data for maintenance of treatment benefit (i.e. no progression)
Adverse events	Gastric event incidence from Suetterlin et al. Fall incidence from UK advisory board	Forced titration of the dose in the interventional trials makes the results difficult to interpret for gastric events. No other information about fall incidence.
Health-related quality of life (HRQoL)	INQoL questionnaire from the MYOMEX study valued using company valuation studies (discrete choice experiment and vignettes)	Patient level data available. Primary data used in the economic model, valuation required to map onto EQ-5D utility values.
Resource use	Estimated using clinical opinion and clinical myotonia severity scale, assumed 3x multiplier for patients with no treatment options	No resource use data were collected in the trial, so these have been assumed using the clinical myotonia scale. Patient surveys suggest more events such as fractures may occur compared to perception by clinician experts.

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 The marketing authorisation for mexiletine is wider than the evidence from the MYOMEX trial and it is unclear whether this is generalisable to the entire UK clinical practice

Issue 2 The dose and dosing schedule of mexiletine in MYOMEX is not in line with the marketing authorisation or expected clinical use

Issue 3 The company have not included any comparator treatments but some unlicensed treatments are still used in clinical practice

Issue 4 The natural history of the disease is not well known so the company assumption that disease worsens over time only for patients not receiving treatment is speculative

Issue 5 The valuation of health using the INQoL health-related quality of life measurement using a discrete choice experiment and vignette study is highly uncertain

Issue 6 Modelling assumptions such as treatment discontinuation data, adverse event incidence, resource use estimation and lack of age-adjustment for utility values increase uncertainty

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The MYOMEX clinical trial evidence is based on small patient numbers (n=25).
- NDM refers to a number of related diseases, for the purpose of the appraisal these have been considered to be equivalent
- Some patients in the trials had received mexiletine prior to initiation of the study and therefore may not be effectively blinded, this could affect the patient-reported outcomes if the participants knew which treatment they were receiving.

2.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for mexiletine.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of [redacted] gained compared with best supportive care (see Table 1), although considering other comparators would likely increase this ICER considerably.

2.5 The technology is unlikely to be considered innovative because it has been standard of care for more than 10 years (see Table 3).

2.6 An equality issue was identified that people with NDM may have difficulty travelling to the regional neurology centres that specialise in neuromuscular issues due to disability. (see Table 3)

3. Key issues for consideration

Issue 1 – Generalisability of the trial

Questions for engagement	1. Are the inclusion criteria of the MYOMEX trial generalisable to NHS clinical practice? 2. Which patients would require symptomatic treatment of myotonia?
Background/description of issue	The MYOMEX trial inclusion criteria included participants between ages 18 and 65 with genetically confirmed NDM and with myotonic symptoms severe enough to justify treatment. The severity of symptoms was evaluated by whether it affected more than one segment of the body and if it impacted on 3 or more daily activities. Mexiletine is indicated for the symptomatic treatment of myotonia in adult patients with non-dystrophic myotonic disorders. **The company** consider that "there is no reason to believe that the results seen in [MYOMEX] would not be broadly generalisable in England and Wales." **The ERG** noted that no results for mexiletine are presented for patients over 68 years and the number of patients over the age of 65 in the UK is not known. Additionally, the ERG noted the EMA assessment which states "only patients with severe enough myotonia were included in the MYOMEX study", but this "does not necessarily mean these patients suffered from "severe myotonia"; rather, they have clinical symptoms of myotonia that are severe enough to justify treatment with mexiletine." According to the company, there is no generally recognised and agreed upon definition of myotonia severity. **The technical team** is concerned that the severity of myotonia in participants of MYOMEX may not be representative of patients in clinical practice. The technical team are aware that an interim deal with NHS England is available for mexiletine with access managed by Blueteq criteria. Assuming the patients covered in the interim access deal are representative of NHS clinical practice, these criteria could be compared with the inclusion criteria of the MYOMEX trial for better understanding of myotonia severity and generalisability. The technical team also noted that participants of MYOMEX could previously have received mexiletine before participating in the trial, this could affect generalisability of results because these patients are known to respond to and tolerate treatment.

Why this issue is important	The marketing authorisation for mexiletine is broader than the trial population, it is unclear when symptomatic treatment would be needed for people with non-dystrophic myotonia.
Technical team preliminary judgement and rationale	The natural history of patients with NDM has not been prospectively studied and the characteristics of patients in NHS clinical practice are not available, therefore the generalisability of MYOMEX to NHS clinical practice is uncertain. We request that severity inclusion criteria in MYOMEX should be compared with Blueteq criteria to understand which patients require symptomatic treatment for NDM.

Issue 2 – Dose and dosing schedule

Questions for engagement	3 What is the appropriate dose to be used in the economic model? 4 Will off-label dosing of mexiletine hydrochloride be used to support dose titration?
Background/description of issue	The dose and schedule in the SmPC is a starting dose of 167mg mexiletine per day, titrated after at least one week of treatment to 333mg mexiletine per day and after a further week of treatment increased to 500mg (equivalent to 200mg/400mg and 600mg of mexiletine hydrochloride). The decision to increase dose is based on clinical response and intensity of patient symptoms. In the MYOMEX trial, the scheduled titration happens after 3 days and all patients were force titrated to the highest dose, at which point efficacy was assessed. **The company** consider that the 400mg mexiletine hydrochloride dose is more in line with UK clinical practice from the Suetterlin et al. study which reports a mean clinically effective dose of 416.7mg and apply the costs of the 400mg equivalent dose in the model. **The ERG** consider it is inappropriate to cost a lower dose when the efficacy and safety data used in the economic model are based on the 600mg equivalent dose. **The NHS commissioning expert** considers that it is 'critical to titrate from a low dose to an optimal dose' and that unlicensed 50mg and 100mg equivalent mexiletine hydrochloride may be necessary to support dose titration. This is to avoid gastric disturbances which are common adverse events and the main reason for treatment discontinuation. This is also supported in the Suetterlin et al. article that states "An adequate treatment trial of mexiletine requires slow-dose titration and dyspeptic therapy where indicated. Clinicians should be particularly mindful of this in patients with missense mutations in CLCN1 as they required significantly higher mexiletine doses."
Why this issue is important	The choice of dose has a large effect on the ICER, increasing the company base case from [redacted] to [redacted]
Technical team preliminary judgement and rationale	**The technical team** consider that it is not appropriate to separate the costs and the benefits of treatment and therefore it is appropriate to use the cost of the 600mg equivalent dose in the economic model, although this is a conservative assumption. It is unclear how important the dosing schedule and rate of titration is to safety, discontinuation rates and the potential need for off-label mexiletine for titration.

Issue 3 – Comparator treatments

Questions for engagement	5 Should lamotrigine be considered as a comparator for this appraisal? 6 How should other comparator treatments be considered in this appraisal?
Background/description of issue	The final scope listed the comparator as "Established clinical management without mexiletine, including but not limited to: Lamotrigine, best supportive care". These comparators were chosen because there was limited information about what treatments are used in clinical practice, clinicians suggested mexiletine has already been the standard of care for over 10 years but there are other antiarrhythmics and anti-epileptics that could be used. At the scoping workshop, it was noted that lamotrigine is increasingly used as an alternative to mexiletine. Standard care for all people with NDM is limited to non-pharmacological management include physiotherapy, lifestyle adaptations, mobility aids and occupational assistance. **The company** does not consider lamotrigine to be established clinical practice, citing market research that shows current use across 8 neurological centres as of Oct-Nov 2019 (see Table 3 of the company submission): • 115/373 use mexiletine (31%) • 94/373 use other off-label treatments such as phenytoin, acetazolamide and flecainide (25%) • 3/373 use lamotrigine (1%) • 161/373 are currently untreated (43%) The company therefore provided only a comparison with best supportive care in its economic model using placebo data from the MYOMEX trial. **The technical team** note that: • Established clinical management without mexiletine would include off-label treatments as reported in the market research (also carbamazepine). The large proportion of people taking these off-label treatments indicates that, although they are not part of standard care, they have a major impact on management of NDM and may sometimes be preferred to mexiletine. Use of these comparator treatments were listed as exclusion criteria in MYOMEX, so were not used concurrently with mexiletine or placebo. The technical team

	recognise the difficulty of including efficacy estimates for off-label comparator treatments but consider that the costs and benefits of these treatments have not been captured in the economic model. • Lamotrigine appears to have low uptake in the market research data. Almost all patients that ever received lamotrigine, were reported to receive it as second-line treatment from one respondent centre. However, the market research data also quotes clinicians that "if mexiletine continues to become harder to prescribe, clinicians may be forced to prescribe lamotrigine which they are less familiar with" and that lamotrigine is "More likely to use in patients with cardiac arrythmia history than mexiletine and flecainide" and there is a "preference to use lamotrigine over phenytoin in woman because it is less teratogenic". • The decision problem is unusual because the intervention is already established in clinical practice for 31% of the population in the market research data. In order to establish the true counterfactual scenario of clinical practice without mexiletine, the decision problem would need to consider what treatments these 31% of patients would receive without mexiletine. Anti-arrhythmics and anti-epileptic medicines have some efficacy, shown by widespread current use in patients and the market research indicates lamotrigine may be the second-choice treatment. Therefore, it is reasonable to infer that these 31% of patients would receive one of these off-label treatments rather than best supportive care. Therefore, the one comparator treatment chosen by the company does not represent established clinical practice without mexiletine. **The ERG** considered that lamotrigine should be included in the economic model because it was in the final scope as a comparator. Efficacy data was available for lamotrigine from a study (Andersen et al., 2017) comparing lamotrigine to placebo for patients with NDM. The primary outcome was measured on the myotonia behaviour scale (MBS), whereas mexiletine studies all used visual analogue scales to measure stiffness. However, the conclusion states "the standardized effect size of lamotrigine was 1.5 (CI: 1.2–1.8) and of mexiletine 1.4 (CI: 0.6–2.2) and 3.0 (CI: 0.1–3.1). Thus, the standardized effect size was in the range of the other treatment's CI, indicating a similar treatment effect of mexiletine and lamotrigine". The measurements of stiffness may not be comparable so the results should be considered with considerable caution. The ERG concluded that an indirect treatment comparison was not appropriate and instead provided scenarios that varied

<table>
<tr><td></td><td>utility between no effect of lamotrigine (i.e. best supportive care) and equal effect of lamotrigine and mexiletine to show the effect on the ICER of lamotrigine treatment.</td></tr>
<tr><td>Why this issue is important</td><td>The inclusion of lamotrigine as a comparator likely increases the ICER considerably, assuming it has an effect greater than best supportive care, as shown in the table below for the effect on the ERG base case (ERG report, Table 7.10)
<table>
<tr><th rowspan="2">Utility lamotrigine</th><th colspan="2">Mexiletine</th><th colspan="2">Lamotrigine</th><th rowspan="2">Incr. Costs (£)</th><th rowspan="2">Incr. QALYs</th><th rowspan="2">ICER (£)</th></tr>
<tr><th>Costs (£)</th><th>QALYs</th><th>Costs (£)</th><th>QALYs</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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</table></td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>Best supportive care as modelled in the company base case does not represent established clinical management without mexiletine. Analysis performed by the ERG shows that if lamotrigine has an effect greater than best supportive care, the ICER increases significantly. The relatively low cost of other off-label treatments compared with mexiletine means that this analysis is likely to be indicative of the effect of other comparator treatments on the ICER.

This issue remains a major uncertainty, with a considerable bias in favour of mexiletine. The technical team appreciate it is not possible to do an indirect treatment comparison with any of the off-label treatments, but other techniques such as clinical expert elicitation or observational data should be employed to understand the effect of comparator treatments.</td></tr>
</table>

Issue 4 – Disease progression

Questions for engagement	7 What is the natural history of NDM, does the disease severity worsen over time?
Background/description of issue	The detailed natural history and determinants of morbidity have yet to be prospectively studied in NDM, this makes characterising the disease in an economic model difficult. Therefore**, the company** assumes a simple model with the 3 states; 'alive on treatment', 'alive with no treatment' and 'death'. The company also assumes a differential effect exists in NDM such that quality of life decreases over time in the absence of treatment for myotonic symptoms based on the concept that disease severity worsens over time only for those not on treatment. This assumption is based on patient surveys that showed worsening of symptoms since diagnosis and clinical opinion (see section B.3.3.3 in the company submission). This is applied in the model as a 15% reduction in quality of life for patients in the 'alive with no treatment' state. **The ERG** considers that the model is adequate given the current level of data available but could have been improved by including more than one line of treatment to better reflect clinical practice (including other treatment options, see Issue 3). The ERG considers the disease progression differential was arbitrary and not implemented appropriately in the model as it does not match the reason stated by the company which would show utility decreasing over time. The ERG base case takes a conservative approach that does not include a disease progression differential because of the lack of data and uncertainty in both long-term data on treatment effectiveness and the natural course of the disease. The ERG note uncertainty of disease progression is captured by clinical expert and patient opinions with a lack of consensus in the company submission (Appendix M). Patients may learn to live with their condition and practice avoidance of triggers (i.e. an increase in the efficacy of non-pharmacological management over time). The **technical team** also consider that the evidence for a long-term sustained effect of mexiletine is minimal and has not been fully explored. It is unknown how the disease would progress for patients in the 'alive on treatment' state.
Why this issue is important	Removing the disease progression differential from the economic model increases the company base case from [redacted] to [redacted].

Technical team preliminary judgement and rationale	The reasoning behind the disease progression differential does not match how it is implemented in the model. The magnitude of the effect has not been justified appropriately and is not based in evidence. It is highly uncertain how disease severity worsens over time and what the effect of treatment would have on disease progression. Therefore, the technical team considers that the disease progression differential should not be applied in the model.

Issue 5 – Health-related quality of life valuation

Questions for engagement	8 What is the appropriate method for valuing health related quality of life?
Background/description of issue	The MYOMEX trial measured health related quality of life using the condition-specific Individualized Neuromuscular Quality of Life Questionnaire (INQoL) measurement tool. No mapping algorithm was available between the INQoL and EQ-5D and therefore a valuation study had to be conducted to be able to obtain utility values from the INQoL data. Two general population valuation studies were conducted: a discrete choice experiment (DCE) and a vignette study with time trade off valuation. A potential issue with the DCE valuation method is that the worst state in INQoL is equivalent to the worst state in the EQ-5D for each dimension. For example, for the mobility domain – 'Extreme amount of muscle weakness in the muscles affected by your condition and extreme amount of muscle locking at the moment' in INQoL is equivalent to 'confined to bed' in the EQ-5D. **The company** considered the states to be equivalent in the base case but also provided a scenario that varied the bottom anchor state for the mobility and usual activities domains. The utility values for each scenario are shown below (adapted from ERG report table 5.13)

Method (bottom anchor state)	Mexiletine (Alive on treatment)	BSC (Alive not on treatment)	Treatment effect	EQ-5D-3L UK average general population utility value (aged 44)
DCE (33333)	[redacted]	[redacted]	[redacted]	0.8896
DCE (23233)	[redacted]	[redacted]	[redacted]	
DCE (23333)	[redacted]	[redacted]	[redacted]	
Vignettes	[redacted]	[redacted]	[redacted]	

<table>
<tr><td></td><td>The ERG considered there to be a number of issues with the design and implementation of the DCE valuation exercise (see section 5.2.8 of the ERG report):
Conceptual mapping for mobility and usual activities
Response levels not including a “no problems” option which could alter the top anchor
Monotonic ordering of response options –ordering of “some” and “moderate” may be confusing for some respondents
A number of logical inconsistencies were present which could suggest lack of participant understanding or attention
No quality control on participant understanding other than completion of the task
Eight attributes varying simultaneously within each choice task may be too complex
Inconsistencies between reporting and the documentation provided
The ERG also considered the vignette study with time trade-off to have some design issues such as the relative strength of response options, the lack of explanation of health states, no practice questionnaires and lack of quality control. However, the ERG considered that the vignette study utility values appeared more plausible and avoid some of the logical inconsistencies and anchoring issues of the DCE.
The technical team noted that health-related quality of life derived from the trial could have been biased by some participants having received mexiletine previously.</td></tr>
<tr><td>Why this issue is important</td><td>The ICER is very sensitive to choice of utility values from the valuation exercises. The effect of each valuation method with corresponding effect on the company base case ICER are shown below.<table><tr><th>Method of valuation (bottom anchor state)</th><th>ICER</th></tr><tr><td>Company base case - DCE (33333)</td><td>[redacted]</td></tr><tr><td>DCE (23233)</td><td>[redacted]</td></tr><tr><td>DCE (23333)</td><td>[redacted]</td></tr><tr><td>ERG base case – Vignettes</td><td>[redacted]</td></tr></table></td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>The utility values as calculated through the valuation studies are inconsistent and highly uncertain. A generic measure of health-related quality of life should have been included in the clinical evidence to</td></tr>
</table>

	mitigate this uncertainty. However, the technical team agree with the ERG that the vignette study appears to be more plausible as a valuation method. Additionally, in the absence of robust evidence, the most conservative assumption should be considered, although it is also unclear if the results of the vignette study are conservative. The technical team request that the utility values derived from INQoL measurements in the MYOMEX trial should be further validated against mapped SF-36 changes as measured in the Statland et al. publication because this is generic measure of health-related quality of life.

Issue 6 – Other modelling assumptions

Questions for engagement	9 What should the source of treatment discontinuation rates be in the economic model? 10 What should the source of adverse event rates be in the economic model? 11 Do patients with no treatment use more NHS resource?
Background/description of issue	The economic model includes a number of assumptions that have minimal to moderate impact on the ICER. **The company** included the following assumptions in their economic model for their base case: • Treatment discontinuation – The probability of transitioning from 'alive on treatment' to 'alive with no treatment' was estimated using the annual discontinuation rate from Suetterlin et al. with an annual discontinuation of 5.15%. • Adverse event rate – The rates of adverse events were applied in the model per cycle and the rates were calculated using adverse event data from Suetterlin et al. data for gastrointestinal disturbances and UK advisory board estimates for probability of fractures. • Resource use – The costs of health care resource use within each state were estimated by asking clinicians to estimate frequency of use within a category of disease severity (mild, moderate, severe) of the clinical myotonia rating scale (CMS). People in the 'alive with no treatment' health state were assumed to require 3 times the amount of health care resource. • Age-adjusted utility values – Utility values were not assumed to change over the lifetime horizon of 56 years.

	The ERG considered alternative assumptions in its base case: • Treatment discontinuation – An alternative is to use the discontinuation rate in the MYOMEX trial of 8%. The ERG considers this to be more consistent with other model inputs although this is at the cost of shorter treatment duration to calculate the annual discontinuation rate. The technical team also note that the Suetterlin et al. study used a different dose and smaller increments in the dosing schedule (see Issue 2), so this may account for the reduced treatment discontinuation in comparison to the MYOMEX trial. However, the technical team also note that mexiletine had no effect on 12 of the 15 patients that discontinued in the retrospective study, so it is not appropriate to model these as discontinuation events in an annualised calculation because mexiletine would be discontinued due to lack of efficacy sooner in clinical practice. Additionally, participants in MYOMEX could have received mexiletine previously and have a known response which would affect discontinuation. • Adverse event rates – The ERG also considers that the MYOMEX trial data should be used for incidence of adverse events for consistency with other model inputs. The technical team note that the adverse event rate is lower in MYOMEX than in Suetterlin et al. study despite a higher dose and faster dosing schedule. The technical team consider that the Stunnenberg et al. study may provide the most appropriate adverse event data for the dosing schedule used in the MYOMEX trial although this uncertainty is linked to Issue 2. • Resource use – The CMS was newly developed for the MYOMEX trial so the reliability and validity of using it to estimate healthcare resource use is uncertain and the ERG consider that it is not fit for purpose (see section 5.2.9 of the ERG report). However, no other source of resource use data is available, so the ERG do not change the assumptions in their base case. The ERG consider the multiplier of resource use to be inappropriate as a concept and there is no justification for the number 3, so removed this in their base case. • Age-adjusted utility values – The ERG consider it standard practice to adjust utility values for utility decline as patients age. The ERG base case considers an equal decline in utility based on general population data and baseline characteristics of the trial. However, they also suggest a scenario that uses a multiplicative approach to account for the concept that additional comorbidities on utility are not additive.
Why this issue is important	These modelling changes by the ERG have minimal effect on the ICER, individually changing the company base case from [redacted] to:

	• [redacted] for changing the data source of treatment discontinuation to MYOMEX • [redacted] for changing the data source of adverse events to MYOMEX • [redacted] for removing the 3x resource use multiplier • [redacted] for applying age-adjustment to utility values However, each issue may interact with other modelling assumptions or contribute to overall uncertainty in the economic model.
Technical team preliminary judgement and rationale	These modelling assumptions have minimal impact on the ICER but have a moderate cumulative effect and greatly increase the uncertainty of the decision. It is uncertain whether treatment discontinuation and adverse event rates should be estimated from MYOMEX for consistency with other model inputs due to the dosing schedule (see Issue 2). Further justification for a resource use multiplier is necessary because this is not based on evidence, a conservative assumption is equal resource use between health states. Age-adjusted utility values are appropriate for a more accurate estimate of benefit over the entire model horizon.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER	Change from base case
Company base case	–	[redacted]	
1. ERG correction of minor errors	Technical team agreed with the ERG's amendments (see section 7.1.2.1 of the ERG report)	[redacted]	[redacted]

Alteration	Technical team rationale	ICER	Change from base case
2. Applying the dose used in the MYOMEX trial	See Issue 2	[redacted]	[redacted]
3. Removal of the disease progression differential assumption	See Issue 4	[redacted]	[redacted]
4. Using utility data derived from the vignette study	See Issue 5	[redacted]	[redacted]
5. Changing other modelling assumptions	See Issue 6	[redacted]	[redacted]
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	[redacted]	[redacted]

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Small patient numbers	The MYOMEX trial only included 25 patients in its modified intention to treat analysis. This introduces substantial uncertainty in the results.	Unknown
Non-dystrophic myotonia is a group of disorders	NDM refers to a group of conditions with varying severity and location, therefore varying the effect on quality of life. For the purposes of the appraisal, the company considers these to be an equivalent condition.	Unknown
All the intervention-based trials may not have been effectively blinded for all participants	The ERG notes in section 4.1.4 of the ERG report that a number of patients in all trials had received mexiletine before the initiation of the study and may therefore have known	Could lead to overestimation of the effectiveness of the treatment for some

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	which treatment they were on by the side effects.	patients as the main outcomes were patient-reported.

Table 3: Other issues for information

Issue	Comments
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model. Additionally, mexiletine has been used in clinical practice for more than 10 years although in a different formulation.
Equality considerations	An equality issue was identified by the lead team regarding the protected characteristic of disability. People with NDM have a disability that could make travel to regional neurology centres for treatment more difficult. The committee will consider how the decision will impact people with NDM with regards to geographic access to treatment.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Mexiletine for treating myotonia in adults with non-dystrophic myotonic disorders [ID1488]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm on 3 September 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Lupin Healthcare (UK) Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

New data and base case analysis	
Given the unprecedented COVID environment, Lupin is exceptional grateful to the clinicians, patients and their carers who continue to provide valuable insights for NDM and the treatment with Namuscla. We are also indebted to the NICE technical team who have allowed us the opportunity to share these insights within our submission process 1. UK Advisory board 2. Delphi panel 3. Janet Stone letter 4. An audit of mexiletine use from Queen Square 5. A clinicans statement from Queen Square 6. Patient/ Care Giver Surveys 7. New PAS price accepted 8. Updated company base case cost-effectiveness results	In such a rare disease as Non Dystrophic Myotonia (NDM), we acknowledge that data gaps will inevitably exist, but believe that the significant patient and clinician elicitation has and continues to provide NICE value in resolving the issues raised**.** **1. UK Advisory board (Appendix A)** Eight Neuromuscular experts attended a meeting on 17th July. Objectives included improving the company's understanding of treatment pathways, guidelines the clinical implications of Myomex data[1] and improving patient outcomes. Includes supplementary data comparison for treatment usage. **2. Delphi Panel (Appendix B)** Nine Neuromuscular experts entered the Delphi panel. The objective was to provide qualitative context and quantitative estimates to address current data gaps and areas of uncertainty including healthcare resource use (HRU), the natural history of NDM including disease progression, dosing, Quality of Life (QoL) mapping, and caregiver QoL. **3. Janet Stone letter (Appendix C)** A letter has been sent to Lupin and is requested to be forwarded to the NICE committee, from Janet stone from The Myotonia Project, giving a patient perspective on the use of Lamotrigine. **4. An Audit of Mexiletine use at different doses (Appendix D)** An audit from the Centre of Neuromuscular disease, Queen Square of mexiletine NDM patient use at different doses, Timed get up and go (TUG), and Timed-stands test (TST), received 2nd September 2020.

5. A clinicians statement from the National Hospital for Neurology and Neurosurgery, Queen Square. (Appendix E)

A letter has been sent to Lupin from the most senior clinicians at Queen Square outlining the use of mexiletine and Lamotrigine at the main centre.

6. Patient & Care Giver Surveys

These surveys are likely to be complete in Late September/ October 2020, and therefore will not be available before the committee meeting, which we do not wish to be delayed.

7. New PAS price

A new discounted price per pack of [redacted] has been accepted for the submission, replacing the original price of [redacted], and is included in the new base case analysis

8. Updated company base case cost-effectiveness results

The impact of each change on the original company base case (with previous and updated PAS) is shown in the corresponding issue responses, with the cumulative impact of these changes shown in **Error! Reference source not found.**.

Table 1: Updated company base case cost-effectiveness results

	Incremental cost-effectiveness ratios (£/QALY)	
	Original submitted PAS	Updated PAS
Original company base case	[redacted]	[redacted]
+ Issue 2 – An average of 15 capsules per week for maintenance dosing	[redacted]	[redacted]
+ Issue 4 – Updated disease progression and QoL decrease	[redacted]	[redacted]
+ Issue 5 – Consideration of carer disutility	[redacted]	[redacted]
+ Issue 6 – MYOMEX treatment discontinuation	[redacted]	[redacted]

	+ Issue 6 – MYOMEX AE rate, including all AEs	[redacted]	[redacted]
	+ Issue 6 – Delphi panel resource use estimates	[redacted]	[redacted]
	+ Issue 6 – age-adjusted utility values	[redacted]	[redacted]
	Updated company base case	[redacted]	[redacted]
	Scenario using DCE and 23233 for lower utility anchor and vignette for upper utility anchor	[redacted]	[redacted]
Issue 1: Generalisability of the trial			
1. Are the inclusion criteria of the MYOMEX trial generalisable to NHS clinical practice?	Lupin understands from the technical engagement call that the Blueteq criteria will not provide additional insight into the characteristics of patients in current clinical practice. However, Lupin note from our recent advisory board that the inclusion criteria of the MYOMEX[1] study is very similar to that of NHS clinical practise as: • [redacted] of patients treated are under 65. For the small number of patients over 65, clinical opinion from the recent UK advisory board is that they would not be treated differently[2]. • Clinicians noted that the severity inclusion criteria of MYOMEX[1] is not as relevant to assessing patients as that of the impact on Activities of Daily Living (ADLs), but they did confirm that the vast majority of NDM patients being treated with mexiletine have been affected by more than one body part, and are affected by three or more activities/ functions[2] During the advisory board clinicians also agreed that the age range and mean age in the MYOMEX[1] trial (18-65 years range and 43 years mean) is representative of their expectations of an average patient age of 43 years[2].		
2. Which patients would require symptomatic treatment of myotonia?	There was consensus amongst clinical experts from the Delphi panel that they would consider adult patients with NDM for treatment with mexiletine if they have[3]: • Genetically confirmed NDM • Symptoms severe enough to impact their daily lives • A normal cardiac exam as performed by a cardiologist, including electrocardiogram (EKG) and cardiac ultrasound. The most important factor for starting or increasing treatment is patient desire, stemming from the impact that the condition has on patient activity[2].		

Issue 2: Dose and dosing schedule	
3. What is the appropriate dose to be used in the economic model?	Lupin believe the appropriate dose for the economic model is a titration of capsules in line with the SmPC, with a maintenance dose on average of two capsules per day (400mg mexiletine hydrochloride): • MYOMEX long-term data for eight patients has been collected for up to 94 months follow-up after the completion of the study, showing at least maintained response to treatment at a mean dose of two capsules per day[4]. • A consensus of clinical opinion from the Delphi panel of an average daily dose of 400mg mexiletine hydrochloride is most appropriate over the lifetime of a patient[3]. • The 63 patients from the Suetterlin observational study (range 6 months - 17.8 years)[5], (the study was conducted at Queen Square, Highly Specialised Service (HSS)) where doses were titrated "until symptoms resolved" and had an average dose of 416.7 mg. Although some patients will have been on higher doses of 600mg, this suggests that many patients on lower doses will receive the same clinical benefit. The mean dose of 416.7mg of mexiletine hydrochloride reflects the optimal possible outcome for these patients, as those on the lower doses did not have any symptoms, and received the maximum benefit that mexiletine can provide in resolving symptoms. The Suetterlin et al study describe the patient dosing in the study as the "Mean Effective Dose". • A letter (Appendix E) has been received from the clinicians from Queen Square (HSS), which highlights that the average dosing for patient in their clinical practise is approximately 300-400mg per day and this is "usually sufficient to improve quality of life to normal". • The therapeutic range of exposure of mexiletine hydrochloride is between 0.5-2ug/mL supports efficacy potential from dosing lower than 600mg[6]. The EMA noted that some patients had already significant reduction of stiffness score on day four (200 mg once a day) in the MYOMEX study and that the posology in section 4.2 of the SmPC (200mg to 600mg range) "reflects that different dose levels could be effective and allows a treating physician to make a choice." • This may go some way to explain related supporting data which comes from 2 randomised trials for mexiletine for the treatment of myotonia in DM1 patients[7]. The initial trial compared a lower dose of 150 mg of mexiletine hydrochloride 3 times daily to placebo, and the second trial compared a higher dose of 200 mg of mexiletine hydrochloride 3 times daily to placebo. The percentage improvement in the primary outcomes of hand grip response time was not

significantly greater in the 200 mg TID trial than in the lower 150 mg TID trial dosing.

- An audit of NDM patient outcomes has been received from Queen Square (HSS). Please see appendix D, where available, the Timed get up and go (TUG) and Timed-stands test (TST) outcome measures, are recorded for patients on variable doses of mexiletine or patients who are untreated. No patient baseline characteristics are provided for the NDM patients, so a comparison between the patient groups must be viewed with caution. The author does note the outcomes for the lower doses (200mg to 400mg) are significant, whist "Higher doses are usually only needed for the more severe patients".

In such a very rare condition it is unusual to have long-term studies. The evidence summarised above identifies an optimal average dose between 400mg and 416.7mg of mexiletine hydrochloride in clinical practice that provides optimal patient outcomes. Lupin acknowledge that the average dose of the Suetterlin data is between 14 and 15 capsules per week, and therefore have updated our base case to align with a scenario of 429mg mexiletine hydrochloride (15 capsules per week), which is very conservative given the main centre, Queen Square provides approximate usage between 300mg to 400mg per day. These updated results are presented in Table, considering the company's updated PAS and the ERG correction of minor errors, labelled as change 1 in Table 1 of the technical engagement report.

Table 2: Updated cost-effectiveness analyses – dosing

	Incremental cost-effectiveness ratios (£/QALY)	
	Original submitted PAS	Updated PAS
Original company base case (14 capsules per week maintenance dose)	[redacted]	[redacted]
Updated company approach (15 capsules per week maintenance dose)	[redacted]	[redacted]

4. Will off-label dosing of mexiletine hydrochloride be used to support dose titration?	In assessing the SmPC titration, the EMA considered that the optimal dose regimen of NaMuscla in NDM has been established[6]. and the new data provided by the MYOMEX[1] trial, suggests that dose titration reflected in the NaMuscla's SmPC is effective and safe, and Lupin recommends

	prescribing to the SmPC. Additionally, the supply of imported medicines, such as special imported mexiletine is uncertain[8-11]. • Lupin understands that the majority of clinicians now titrate using NaMuscla[2]. • Lupin does also understand that some clinicians, notably from the main centre at Queen Square (HSS) may choose to titrate using special import mexiletine hydrochloride[2,5.] • Lupin has modelled the rate of titration from the SmPC and the dosing costs using the costs of NaMuscla, which will capture the costs conservatively[2,12]. • There is no evidence that there might be any difference in the quality of life benefits over the life time of the patient when using the SmPC titration to that highlighted in the Suetterlin et al study, where patients taking less than 600mg mexiletine hydrochloride were titrated until symptoms resolved.
Issue 3: Comparator treatments	
5. Should lamotrigine be considered as a comparator for this appraisal?	Lupin does not believe lamotrigine should be considered as an appropriate comparator as its use is not established practice in the NHS[13,14,15]. Lamotrigine is not licensed to treat NDM patients and no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients. • Lupin have tried to engage directly with the clinicians who treat NDM patients at Queen Square (HSS) since the start of the NICE process, including a freedom of information request for Lamotrigine use. Only recently in July 2020 onwards have Lupin been successful in engaging directly with the clinicians. Lupin has received a clinicians statement from Queen Square (HSS), Appendix E, that describes Lamotrigine use as only “in specific circumstances” and “not fully established” at the main centre in the UK. • Market research conducted in November 2019 involving eight neurology centres in the England and Wales (including the largest centre, Queens Square (HSS)) shows that lamotrigine is not established in practice with less than 1% of patients currently treated with lamotrigine[14]. • This data was further supported by an NDM patient survey where of the 37 responses provided by patients to the questions “Please indicate any medications you have taken for myotonia”, only one patient indicated they had ever taken lamotrigine[15]. • More recently at a UK advisory board in July 2020, the clinical experts identified that [redacted] of patients who were treated with a pharmacological medication were treated with mexiletine[2] ([redacted] of total NDM patients).

	• The patient numbers from the advisory board in July 2020 are different to the findings of the market research in November 2019, driven by the largest centre declaring only patients seen by the centre in the last two years under active management. For further information please see the supplementary data comparison for treatment usage (Appendix A). Notwithstanding the above, the comparison analysis undertaken by the ERG assumes the same AE profile, compliance, discontinuation and utility range as those for NaMuscla. This analysis seems inappropriate to inform decision making, given no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients. In its licensed indications, lamotrigine has a very common (≥1/10) undesirable effect of skin rash[16]. For Patients who develop a lamotrigine related rash, treatment should be withdrawn immediately[16]. Serious rashes requiring hospitalisation have also been reported, including life-threatening rashes such as Stevens–Johnson syndrome (SJS). The medicine has significant clearance issues associated with hormonal contraceptives, and other common (≥1/100 to <1/10) undesirable effects include insomnia and behavioral change/ psychiatric disorders[16]. A very unfavourable use of Lamotrigine from a patient perspective is found in Appendix C. Further we have received a clinicians statement from Queen Square (HSS), Appendix E, who state that they have found that titrating lamotrigine to a sufficient dose takes significantly longer than with mexiletine" and, due to the association with severe complications or death, "more cautious in its use."
6. How should other comparator treatments be considered in this appraisal?	Lupin believe the comparison presented vs BSC captures the alternative options for NDM patients. • The NICE final scope states "Other antiarrhythmic and antiepileptic medicines have been used off-label to manage the symptoms of myotonic disorders. However, this does not form part of standard care." Therefore, Lupin do not believe these medicines are intended as comparators. • The market research[14] has identified other alternatives. These are unlicensed medicines, their efficacy is unproven and unsubstantiated through clinical trials with no data supporting their use, and their long-term safety profile unfavourable[6]. • NDM patient treatment was a discussion point of the recent UK advisory board[2]. Lupin understands that there was a historical usage of alternative medicines which were used if there were side effects, or lack of supply of the imported mexiletine, but that they lacked efficacy. Some patients may still remain on these medicines if they have less symptoms

	(but it is unknown), or are now lost to follow up. However, experts at the advisory board did agree that they "very rarely use off license medicines currently". • From the market research[14], 55% (216/393) of NDM patients have ever been treated with any other medicine than mexietine. However the recent UK advisory board suggests that only [redacted]% of total NDM patients are currently treated with any other medicine than Mexiletine[2]. • Would patients who have already tried and failed these other medicines, which lack efficacy want to try them again? Five of the seven clinicians who provided answers for the recent advisory board pre work questionnaire agreed that patients who fail a first line therapy may no longer be treated, as "Patients who fail can be reluctant to try another agent" and "patients raise questions about placebo effects"[1] . The placebo effect is increasingly well understood, especially for conditions which include pain and fatigue[17], and therefore in the absence of any substantial efficacy evidence, a sensible conclusion is that these medicines should have no additional benefit to placebo, as reflected in the economic model, and that it is uncertain that patients would be treated.
Issue 4: Disease progression	
7. What is the natural history of NDM, does the disease severity worsen over time?	• Several studies suggest that QoL worsens over time in the absence of treatment. In a Dutch cross-sectional study, Trip et al.[17] found that 58% (n=36) of the patients reported that the severity of their myotonia had increased since the onset of their symptoms. Similarly, findings from a patient survey[15] amongst UK patients with NDM showed that 87.3% and 70.8% of the patients experienced a worsening of their stiffness and weakness since diagnosis, respectively. Feedback from clinical experts and patient interviews conducted by Lupin[13,19] also suggested that QoL decreases over time without treatment • In the recent Delphi panel there was a consensus of opinion that, on average, the proportion of patients who experience a QoL increase over their lifetime will be higher for those who are treated with NaMuscla compared with patients on BSC. The panellists also provided estimates for the mean annual rate at which QoL decreases, and that for patients receiving BSC would experience QoL decreases [redacted] faster than patients treated with mexiletine. • Lupin acknowledge that the disease progression assumption in the original model did not match the stated rationale of a decreasing QoL over time. Using the new inputs described above, we have amended this functionality in the model. Within the limitations of the

existing model structure, and in the absence of data on the rate of decrease of quality of life in NDM patients, for the placebo arm, we have assumed that patients start in an 'on treatment' state, reflective of early disease where QoL has not yet decreased. We then use the mexiletine treatment discontinuation rate as a proxy for QoL decrease/progression, applying the increase of [redacted] from the Delphi panel findings for the placebo arm. Upon 'progression', placebo and mexiletine patients then experience a 15% decrease in QoL as modelled previously. The switch for this model change can be found in C90 of the Inputs tab of the updated cost-effectiveness model, which additional calculations in the Clinical inputs tab and amends to the Markov tab. As there is no available quantitative evidence on the QoL change for progressed patients, we have presented a range of scenarios for this model input (Table).

Table 3 Updated cost-effectiveness results – disease progression

	Incremental cost-effectiveness ratios (£/QALY)	
	Original submitted PAS	Updated PAS
Original company base case (15% QoL decrease for placebo patients only)	[redacted]	[redacted]
0% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing 3.7% quicker than mexiletine patients	[redacted]	[redacted]
5% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing 3.7% quicker than mexiletine patients	[redacted]	[redacted]
10% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing 3.7% quicker than mexiletine patients	[redacted]	[redacted]
Updated company approach (15% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing 3.7% quicker than mexiletine patients)	[redacted]	[redacted]

Issue 5: Health-related quality of life valuation

8. What is the appropriate method for valuing health related quality of life?	In the absence of any available EQ-5D data, when planning an alternative approach to utility estimations we considered the NICE Methods Guide and TSD11 which discusses alternatives to the use of EQ-5D. The INQoL measure is the most appropriate and only validated measure of HRQoL in NDM patients. It refers specifically to the presence and impact of myotonic symptoms[20,21]. Therefore, it is the appropriate measure to capture changes in HRQoL from the MYOMEX study, that captured patient level INQoL data. Our first study (the DCE) was designed to determine the importance of a subset of INQoL items (from the general public perspective) and then to rescale these importance weights against EQ-5D. (A more standard mapping approach is not possible because no appropriate dataset is available). We accept there were some limitations, however attempted to be conservative in how they were managed. The second study estimated a utility based scoring algorithm for the INQoL from TTO interviews. TSD11 outlines the methods in this approach which we followed where possible. The INQoL items cover similar content to EQ-5D and were valued using very similar methods to EQ-5D. As recommended on page 16 we selected INQoL items that were representative of the measure; but the psychometric approaches were not possible because there was insufficient data. We note page 19 of TSD 11 where it states: *"CSPBMs {*condition-specific preference based Measures} *meet the NICE Methods Guidance for alternatives to EQ-5D provided they are based on validated measures of HRQL using valuation methods comparable to those used for the UK EQ-5D value set."* Lastly as presented in the table for the ERG clarification question A8. There were no differences between the naïve and non-naïve subjects, either in placebo or in the mexiletine groups for the stiffness VAS scores. Therefore any previous treatment with mexiletine did not influence the expectations of the patients with respect to treatment effects. • The valuation methodologies were independently reviewed by three experts. None of the experts suggested that the valuation exercises were highly uncertain. Indeed one commented a "confidence in the general validity and supportiveness for both approaches"[22], and another for the TTO that "The overall approach is sound"[23]. A conservative approach was taken to any logical inconsistencies (page 141, Document B of the company submission) and therefore the result not bias in favour of the treatment. • The experts did note that the differences in result are most likely to be due to the anchoring of the DCE to the Dolan et al[24] scale, but also noted that the impact of the

muscle coefficients are lower in the TTO model, The Delphi panel has identified that muscle locking is the most impactful to NDM patients QoL[3].

- Further analysis shows that by applying the upper and lower anchors of the vignette study to the DCE estimates, the incremental utility is [redacted], which is extremely similar to the Vignettes result (incremental utility of [redacted]), which only adds confidence and credence to the two datasets, reflected in the comments of the expert reviewers. This has been applied to the Economic Model for illustrative purposes.
- In the clinical elicitation process (Appendix M of the CS submission)[13], clinicians confirmed a greater than 0.3 utility gain, supportive of the significantly positive impact mexiletine can have on an NDM patients life. This is further supported by patient feedback. One patient describing mexiletine as “a wonder drug” and another saying “I wouldn’t have a proper life without it” , as described in the Muscular Dystrophy UK (MDUK) Technical Engagement paper, and by another patient who is able to play rugby in the winter[2]. Additionally in a clinicians statement from Queen Square in Appendix E (HSS), patient quality of life when treated with mexiletine is described as improved to “normal”.

Lupin believe the most likely incremental utility gains are between the two valuation approaches, whereby the Vignette study has not picked up the quality of life impact of the muscle condition, as highlighted above by the expert reviewer. Lupin proposes to address the lower bound uncertainties using the DCE 23233 as an alternative conservative scenario:

INQoL worst health state	**EQ5D worst health state**
Both Extreme amount of muscle weakness in the muscles **and** Extreme amount of muscle locking	Some problems in walking about
Extremely affects ability to do daily activities e.g. washing, dressing & housework	Unable to wash or dress
Extremely affects ability to do leisure	Some problems with usual activities
Both Extreme amount of pain **and** an Extreme amount of tiredness or fatigue	Extreme pain **or** discomfort

Both Extremely anxious **and** Extremely depressed	Extremely anxious **or** depressed

Lupin acknowledge that there may be some upper bound anchoring uncertainties with the DCE approach and therefore propose applying the vignette upper bound to the DCE 23233 results, providing an incremental utility gain of [redacted]. This has been added to the model as part of the switch in C31 of the Inputs sheet, with results presented in Table .

Table 4: Updated cost-effectiveness analyses – utility data calculations

	Incremental cost-effectiveness ratios (£/QALY)	
	Original submitted PAS	Updated PAS
Original company base case (utilities using DCE with 33333 as the worst health state for the lower bound anchor and 1 as the upper bound anchor)	[redacted]	[redacted]
Utilities using DCE with 23233 as the worst health state for the lower bound anchor, and the upper bound anchor informed by the vignette results)	[redacted]	[redacted]

Lupin also believe that there is a strong case for applying a carer disutility within the model based on feedback from the Advisory board in November 2018[25], the MDUK response in the Technical Engagement papers, and the Delphi panel, where there is a clear expectation that caregivers of patients receiving NaMuscla are not expected to have a significant negative impact on their QoL[3].

The significant impact and disease burden of NDM on patients' lives is documented in section B.1.3.5 of the company submission, from the baseline characteristics of the patients from the MYOMEX trial[1], patient surveys[15,26] and patient studies[27] . Lupin does note that the clinicians in the advisory board in July 2020 were unaware of the impact on carers, but we also note that [redacted]% of their patients who are treated are now on mexiletine.

Based on this evidence, Lupin believe this should be captured in the economic modelling, and as such have updated the base case analysis. As discussed in the technical engagement call,

	precedent from previous appraisals in disease areas such as Duchenne (recommended to Lupin by the technical team) and MS (recommended to Lupin by MDUK) has been followed[28]. In the absence of NDM-specific carer utilities, we have assumed that for a severe NDM patient who is not on mexiletine treatment, a carer disutility would be 0.11[29], comparable to that of a non-ambulatory Duchenne patient, and within the carer disutility range for MS patients (between 0 and 0.18 dependent on severity)[30]. It is assumed that only one carer is required per severe NDM patient not on mexiletine, and that no carers are required for a patient on mexiletine. These assumptions broadly aligning with the findings from the Advisory board in November 2018[25] In a Dutch cross-sectional study of 62 untreated patients with genetically confirmed NDM, Myotonia was described as severe (score ≥5 on a numerical rating scale of 1 to 10) in 70% patients[27]. However we have used a conservative 20% as the input for this proportion, but show sensitivity analysis around this proportion and the carer disutility. The updated cost-effectiveness results are shown in Table .

Table 5 Updated cost-effectiveness results – carer utilities

	Incremental cost-effectiveness ratios (£/QALY)	
	Original submitted PAS	Updated PAS
Original company base case (no carer disutilities applied)	[redacted]	[redacted]
Carer disutility of 0.05 applied to 10% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]
Carer disutility of 0.05 applied to 20% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]
Carer disutility of 0.11 applied to 10% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]
Updated company approach (Carer disutility of 0.11 applied to 20% of NDM placebo patients and patients off mexiletine)	[redacted]	[redacted]
Carer disutility of 0.18 applied to 10% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]
Carer disutility of 0.18 applied to 20% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]

Lupin do not believe SF-36 is an appropriate tool to assess HRQoL for NDM patients, and it is not supported by the literature.[20,21,31,32,33] . We have previously described the limitations of the SF 36 in sections B.1.3.5. & B.3.4.1 of the company submission, and our response to the ERG question B6.

- NDM is a disease of the locking of the muscles. It is unsurprising that in the Delphi panel the experts identified that the muscle locking domain is the most impactful to NDM patients QoL[3.], which is supported by the literature[20,33].

  Sansone and colleagues 2012 note:
  "…myotonia should be the treatment target for patients…and improvement of myotonia should be the primary outcome measure …" [20]

  Further Sansone and colleagues 2010 note:

	"The domain Locking, in INQoL, does not correlate with any of the physical domains of SF-36. This is a very specific muscle symptom confined to a restricted number of patients with muscle diseases which cannot find a comparable health concept/scale in SF-36."[32] • SF-36 fails to address clinically important aspects of the disease impact of specific disorders[31]. INQoL has the advantage of recording specific disease symptom impacts omitted by the SF-36 questionnaire such as locking, independence and body image[21,32] • The Trivedi paper included the experts from Queen Square, HSS (Hanna, Matthews & Rayan being among the authors on both the Statland (2012) and the Trivedi studies 2013), described INQoL as *"a more relevant instrument for determining symptom impact on quality of life in non-dystrophic myotonia compared with the generic SF-36"* [33]. • Clinical experts consulted by Lupin unanimously agreed that INQoL more relevant and appropriate to capture the impact on the quality of life of NDM patients compared to SF-36 (Appendix M of the company submission)[13].
Issue 6: Other modelling assumptions	
9. What should the source of treatment discontinuation rates be in the economic model?	Lupin believe that the most appropriate long-term discontinuation rates for the economic model should be those derived from the Suetterlin et al study. The Suetterlin study is long term data reflecting real world longer term discontinuation of patients. However, as the discontinuation rate between the MYOMEX study and that of the Suetterlin et al study are relatively similar, Lupin are happy to include the more conservative MYOMEX assumption in the manufacturer base case (**Error! Reference source not found.**).
10. What should the source of adverse event rates be in the economic model?	Lupin believe that the most appropriate long-term adverse rates for the economic model should be those derived from the long term real world Suetterlin et al study. However, as the adverse events between the MYOMEX study and that of the Suetterlin et al study are relatively similar, and AEs are not a large driver of cost-effectiveness results, Lupin are happy to align will the Technical teams assumption of the MYOMEX AE input in the manufacturer base case (**Error! Reference source not found.**).
11. Do patients with no treatment use more NHS resource?	Within the manufacturers submission, Lupin submitted information pertaining to resource use from a UK advisory board in November 2018[25]. Lupin acknowledge some of the concerns raised by the technical team regarding the applicability of resource use dependent on the CMS.

Lupin have since conducted a Delphi panel to understand better resource use in the UK for NDM patients[2]. This provided Lupin with updated resource use inputs (proportion of patients requiring resource and the frequency of resource use required) with a majority of respondents agreeing that resource use is less for patients treated with mexiletine. Lupin have updated the company base case accordingly with these new inputs (

Table).

The switch added to C47 of the Inputs tab allows the user to switch between frequencies and proportions taken from the November 2018 advisory board (dependent on CMS) and frequencies and proportions taken from the Delphi panel findings. The Delphi panel option uses the mexiletine inputs from the Delphi panel findings, with the multiplier required to estimate those for BSC patients. The Delphi panel found that on average, respondents predicted there to be [redacted] times more resource use visits required for patients on BSC, and for [redacted] times more patients than those on mexiletine. This would suggest that on average [redacted] (=[redacted]) times as much resource use is required for BSC patients than mexiletine patients. This provides validation of the multiplier of 3 used in the original company base case. As such, when using the new Delphi panel option, a multiplier of 3 is still applied, which may be conservative.

Table 6: Updated cost-effectiveness results – resource use

	Incremental cost-effectiveness ratios (£/QALY)	
	Original submitted PAS	Updated PAS
Original company base case (Nov 2018 advisory board inputs with 3x multiplier for BSC patients)	[redacted]	[redacted]
Updated company approach (August 2020 Delphi panel inputs for 3x multiplier for BSC patients)	[redacted]	[redacted]
August 2020 Delphi panel inputs for [redacted] multiplier for BSC patients	[redacted]	[redacted]

	In addition, although not considered in the cost-effectiveness model, Delphi panel findings suggested that there could be additional support needed for NDM patients in the form of mental health visits to a psychologist or general practitioner[3]. As with other resource use, this was predicted to be more of a burden for BSC patients, and as such, the cost-effectiveness model may be conservative in the difference of resource use costs between arms.
12. Age-adjusted utility values	The company agree with the ERG and the NICE technical team and are happy to consider age-adjusted utility values in their updated base case (**Error! Reference source not found.**).

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Deadline for comments **5pm on 3 September 2020**

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Muscular Dystrophy UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Muscular Dystrophy UK has received/receives no past or current, direct or indirect links to, or funding from, the tobacco industry**

Questions for engagement

Issue 1: Generalisability of the trial	
1. Are the inclusion criteria of the MYOMEX trial generalisable to NHS clinical practice?	Muscular Dystrophy UK cannot comment on this issue.
2. Which patients would require symptomatic treatment of myotonia?	Muscular Dystrophy UK cannot comment on this issue.
Issue 2: Dose and dosing schedule	
3. What is the appropriate dose to be used in the economic model?	Muscular Dystrophy UK cannot comment on this issue.
4. Will off-label dosing of mexiletine hydrochloride be used to support dose titration?	Muscular Dystrophy UK cannot comment on this issue.
Issue 3: Comparator treatments	
5. Should lamotrigine be considered as a comparator for this appraisal?	We are not convinced that lamotrigine should be considered as a comparator for this appraisal. Our understanding from one neuromuscular service is that lamotrigine is primarily used only in cases where mexiletine cannot be used. Further to this, we have recently had correspondence

	from a patient forum group – The Myotonia Project – which although based in the USA, has many UK participants. The forum leader, Janet Stone says: *"I moderate a large international forum for people with non-dystrophic myotonias (NDMs) including patients from the UK, and I wanted to give some input regarding the comparison of lamotrigine versus mexiletine as a treatment for these conditions.* *I have interacted with patients and caregivers for over 30 years (I'm a patient myself), and know the personal stories which may not always be relayed to the healthcare providers in the short time allotted for appointments.* *Anti-seizure medications have been used to treat myotonia for decades. One of the earliest was phenytoin, first used to treat seizures in 1936, then later carbamazepine which was first marketed in 1963. While these offered variable relief of myotonia symptoms, they also had the potential for some serious psychiatric side effects and have been abandoned as treatments in most countries. When lamotrigine was introduced in the UK in 1991, it was a bit different from the other anti-epileptics in that it could address seizure activity by inhibiting the action of voltage-gated sodium ion channels, but it also was discovered to be effective at treating bipolar disorder. There is very little mention of lamotrigine as an anti-myotonic drug until 2017 when a clinical trial was conducted in Denmark. While some of our members had been prescribed lamotrigine earlier than that, it was coincidental to myotonia and was primarily used for depression.* *By contrast, mexiletine was being discussed as an anti-myotonic as far back as 1983 in medical journals. It is the oral form of the anaesthetic lidocaine which is a sodium channel blocker that was useful in treating heart arrhythmias, but it also reduced the action potential in skeletal muscle allowing more normal relaxation and alleviated myotonia. It was used off-label for several decades but has recently been approved in both the US and Europe as a preferred treatment for NDMs.* *In very rare instances some of our members have taken lamotrigine, mainly as a combination treatment for those with both bipolar disorder and myotonia. While they felt it was effective in relieving stiffness, there were several concerns as well. The first had to do with Stevens-Johnson Syndrome (SJS). One of our members developed a life-threatening reaction five weeks into her therapy...this is from her post:*

	*"*I don't know about that "0.1%" statistic. That's what my doctors told me too. Three of them, to be exact, as I wanted to make absolutely certain before starting the medication. They all told me I would be fine and that SJS was extremely rare. Well I developed SJS, and while in the hospital there was another woman there at the same time who also developed SJS on Lamictal. I find it to be too big of a coincidence that two of us were in the same hospital at the same time with the same near fatal reaction to the same drug." *Another concern expressed was psychiatric side effects. While the anti-depressant effect may be beneficial for a very small number of people with NDM and actually reduce the need for two different medications, for others it was not tolerable. Insomnia was also reported. This is from one of our members:* *"*It absolutely worked within minutes on my muscles. It scared me what it did to my mind though. I felt like I could not think straight and there was a wall between my thoughts and emotions and I could not feel emotions like I should*."* *We have a large number of members on mexiletine, and while there are definitely reported side effects, almost all were related to digestive upset and none were life-threatening. In many cases the patient had not been given proper instructions about taking with a meal or antacid as noted by the manufacturers. I have not seen complaints about psychiatric side effects, rashes or SJS. Lamotrigine can also cause hemophagocytic lymphohistiocytosis (HLH) and aseptic meningitis which are not associated with mexiletine use.* *Another consideration is the effect of contraceptives on lamotrigine. This is from Epilepsy Action UK:* *"*The Pill, patch and vaginal ring may reduce the amount of lamotrigine in your bloodstream. This would make you more at risk of having seizures. So your doctor may need to increase the amount of lamotrigine you take*."* *My last concern is related to the required titration. While both medications are started at a lower dose than the intended target, mexiletine is eliminated from the system quickly and there are no withdrawal symptoms if it is stopped suddenly. Lamotrigine can cause mild to severe withdrawal syndrome and needs to be reduced gradually. As we have seen with this pandemic, when a*

	supply chain is suddenly interrupted, it's far better to be on a medication that does not require tapering. *In summary, I have interacted with thousands of NDM patients, and mexiletine will always be my first recommendation because of my observed lack of psychiatric side effects (especially important in patients under 25 years of age) and the very high response rate. Lamotrigine is rarely used to treat myotonia because of the safety profile and the requirement for more intensive monitoring. If mexiletine is not available to NDM patients in the UK, I don't see a suitable replacement for our members at this time".*
6. How should other comparator treatments be considered in this appraisal?	Muscular Dystrophy UK cannot comment on this issue.
Issue 4: Disease progression	
7. What is the natural history of NDM, does the disease severity worsen over time?	Muscular Dystrophy UK cannot comment on the details of the natural history of NDM. Nevertheless, mexiletine currently forms part of the standard of care for the treatment of patients with nondystrophic myotonia and has done for over 10 years. Randomised clinical trials support the efficacy of Mexiletine for the treatment of nondystrophic myotonia with patients reporting a reduction in the average daily reported muscle stiffness (Stunnenberg et al 2018) and improved patient-reported stiffness (Statland et al 2012). However, we know from patients who have been on mexiletine treatment that their symptoms improved (particularly if they addressed the gastrological side-effects) and this improved their quality of life. We know that every day counts for people with neuromuscular conditions because without treatment conditions progressively worsen. Having access to treatments that alleviate symptoms and slow progression is vital to improved, and even maintained, quality of life. Patients who have received mexiletine state that the treatment "controls my aches and pains on a daily basis", "can get up out of a chair" and that they "wouldn't have a proper life without it". It is important that these patients – and patients like them – are able to

	maintain their quality of life. Mexiletine has been the standard of care at the national referral service for muscle channelopathies for over 10 years and there is a significant group of patients already receiving this medicine long-term (over 100 patients). Any future impaired access to the drug would have a significant impact on this group who are already receiving treatment.
Issue 5: Health-related quality of life valuation	
8. What is the appropriate method for valuing health related quality of life?	We believe strongly that any quality of life measure for a neuromuscular condition should include instruments that measure the impact of key muscle disease symptoms (i.e. weakness, myotonia, pain, and fatigue). For example, The Individualized Neuromuscular Quality of Life questionnaire (INQoL) is one such instrument.
Issue 6: Other modelling assumptions	
9. What should the source of treatment discontinuation rates be in the economic model?	Muscular Dystrophy UK cannot comment on this issue.
10. What should the source of adverse event rates be in the economic model?	Muscular Dystrophy UK cannot comment on this issue.
11. Do patients with no treatment use more NHS resource?	Muscular Dystrophy UK cannot comment on this issue.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Representative on scientific advisory board for Lupin Healthcare (UK) in 2020.**

Questions for engagement

Issue 1: Generalisability of the trial	
1. Are the inclusion criteria of the MYOMEX trial generalisable to NHS clinical practice?	Overall the inclusion criteria appears to be generalisable to NHS practice. Patients are treated based on clinical severity and if their myotonia impacts on their activities of daily living. The criteria used in the MYOMEX study for severity of myotonia (2 body segments and impact on 3 daily activities) is not a published criteria used in clinical practice and therefore it is not possible to fully evaluate it. It does seem reasonable that patients with myotonia that impacts on at least 3 activities would be severe enough to warrant treatment in line with current practice and may under estimate the patients that we may try treatment on. In current NHS practice we would estimate approximately 13% of non-dystrophic myotonia patients under a neurologist are over 65 years and the majority are on treatment (>92%).
2. Which patients would require symptomatic treatment of myotonia?	In NHS practice we would treat any patient with myotonia severe enough to impact on their daily function. This is typically measured through patient discussion but more objectively via assessment of prolonged hand grip or eye closure opening, timed up and go and sit to stand tests.
Issue 2: Dose and dosing schedule	
3. What is the appropriate dose to be used in the economic model?	The most commonly used dose is 400mg mexiletine/ day. In very severe cases we will use 600-800mg/ day
4. Will off-label dosing of mexiletine hydrochloride be used to support dose titration?	On initiation of treatment it is common practice to use 100mg tablets of mexiletine to slowly uptitrate mexiletine to minimise the side effects and reduce the risk of discontinuation due to gastric symptoms as described in Suetterlin et al. When 100mg tablets are not available then

	200mg tablets are used instead. Patients who are not naïve to mexiletine will often tolerate faster titration using 200mg tablets.
Issue 3: Comparator treatments	
5. Should lamotrigine be considered as a comparator for this appraisal?	Lamotrigine is not established practice and as only recent evidence has been published regarding its efficacy in the treatment of non-dystrophic myotonia its place in treatment is uncertain. It is currently used in patients who do not tolerate mexiletine, who have cardiac arrhythmias or in women trying to conceive. It does not give the immediate improvement in symptoms seen in mexiletine. It has been noted to have some efficacy at high doses in this group of patients but takes significantly longer to titrate up and has the potential life-threatening side effects limiting its use compared to mexiletine.
6. How should other comparator treatments be considered in this appraisal?	There are no other treatments in current clinical practice that have comparable efficacy. Carbamazepine, flecainide, acetazolamide and phenytoin have significantly poorer efficacy and a more significant side effect profile to make their use rare in clinical practice.
Issue 4: Disease progression	
7. What is the natural history of NDM, does the disease severity worsen over time?	In our clinical experience the natural history of NDM is to show some worsening in older years and is likely the reason why a large proportion of older patients under a neurologist are on treatment.
Issue 5: Health-related quality of life valuation	
8. What is the appropriate method for valuing health related quality of life?	We have found INQoL to be a validated method of quantifying quality of life in neuromuscular diseases. In clinical practice it appears to correlate with clinical severity in myotonia. We also commonly use SF-36 although in NDM it seems to have a less clear correlation than in other more systemic conditions.

Issue 6: Other modelling assumptions	
9. What should the source of treatment discontinuation rates be in the economic model?	We find that the Suetterlin et al data correlates closest to long term clinical practice as it sampled a large number of NDM patients with a minimum 6 month treatment period.
10. What should the source of adverse event rates be in the economic model?	The adverse events rate should be based on a combination of the Suetterlin, Stunnenberg et al and MYOMEX data. The Suetterlin et al data is based on having availability of lower doses of off-label mexiletine which are not always readily available and may not be available going forward. That study is also not blinded or placebo-controlled and therefore may not be sufficient in isolation to give accurate estimates of the adverse events rate.
11. Do patients with no treatment use more NHS resource?	Yes. Patients on no treatment who have significant myotonia use significantly more NHS resource. They have frequent falls and may fracture bones or cause long term injuries when not on treatment leading to the need for NHS care and treatment. They are also more likely to attend their primary care physician with symptoms of pain and fatigue. They are also more likely to have low mood and therefore need NHS treatment for mental health issues. In severe cases they may develop swallowing difficulties or laryngospasm which may require more NHS care.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Mexiletine for symptomatic myotonia in adults with non-dystrophic myotonic disorders

ADDENDUM: Critique of the company's response to Technical Engagement

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 23/09/2020

1. Company's response to technical engagement

The purpose of this addendum is to provide a critique of the new evidence submitted by the company as part of their response to the technical engagement report.[1]

In their response to the technical report, the company submitted responses to the key issues raised in the Technical Report written by the NICE technical team, some additional evidence relevant to these issues, as well as a new PAS and an updated company base-case.[1, 2] The company response to the technical engagement issues and the new evidence presented in relation to these issues will be discussed in Section 1 of this addendum. Section 2 will outline the company's updated base-case and cost-effectiveness results and Section 3 will provide the ERG's updated base-case and scenario analyses, in response to the company changes. A conclusion will be given in Section 4.

Issue 1: Generalisability of the trial

Questions 1 and 2

The ERG is encouraged that findings from the advisory board appear to support the generalisability of the trial. The ERG defers to the opinion of clinical experts within the committee meeting for further comment on the generalisability of the trial.

Issue 2: Dose and dose schedule

Questions 3 and 4

The main reason for the ERG to initially deviate from the company's dosing assumptions is that the 600 mg dose would be in line with the efficacy and safety data from MYOMEX. However, in this study that dosage was per protocol and force titrated. In clinical practice dose titration occurs up to the dose at which symptoms are resolved. The ERG agrees that the data provided by the study of Suetterlin et al., 2015[3] is better reflective of this clinical practice. Furthermore, the study by Suetterlin et al., 2015[3] seems to indicate that the required dose is determined by whether the NDM is caused by a mutation in the gene for sodium channels (in that case the lower dose is more likely) or for chloride channels (in which case the higher dose is more likely) in skeletal muscle cells (i.e. see Figure 2 in Suetterlin et al. 2015).[3] In the Suetterlin study 40 patients had a chloride channel mutation (requiring a mean dose of 550 mg), 21 patients had a sodium channel mutation (requiring a mean dose of 333 mg), and 2 had both mutations. In the Statland et al. 2012 / MYOMEX study 34 patients had a chloride channel mutation, 21 had a sodium channel mutation, and 4 had no mutation identified. Using the dosages from the Suetterlin study this would imply a weighted average of 467mg.

In summary, the ERG agrees that a base case using a dosage assumption of 429mg mexiletine hydrochloride (i.e. 15 capsules per week) is the one that would best represent dosing in clinical practice and appears likely to lead to similar efficacy as observed in MYOMEX. However, given the remaining uncertainty about the latter statement an additional scenario using a dosage of 600 mg serves a useful purpose in exploring the sensitivity of the results to the conservative assumption of needing this maximum dosage for all patients in order to achieve the efficacy as observed in MYOMEX..

Issue 3: Comparator treatments

Questions 5 and 6

The ERG would like to point out that it is not surprising that there is little use of lamotrigine currently in the UK given that mexiletine has been available, and also for much of the time at a lower price than in this appraisal. The question that needs to be considered with regards to lamotrigine is 'What would patients receive if mexiletine were no longer available i.e. not given a positive recommendation.' As stated in the ERG report, since lamotrigine was listed in the final scope as a comparator, the ERG considers that lamotrigine should have been included in the economic model.

The company cite the clinician statement from Queen Square (HSS) in Appendix E, quoting that they have found that titrating lamotrigine to a sufficient dose takes significantly longer than with mexiletine" and, due to the association with severe complications or death, "more cautious in its use." However, this clinician statement also says "in specific circumstances where mexiletine cannot be used we use other agents including lamotrigine but we consider it our second line treatment as its precise place in the management of NDM is not fully established. Anecdotally we have found lamotrigine can be effective and there is now published RCT evidence supporting its use. ... We currently use lamotrigine when patients have failed mexiletine, cannot try it due to cardiac arrhythmias, or in women who are trying to conceive." This statement suggests that there is place for lamotrigine in clinical practice and there is available evidence of its effectiveness.

Finally, the ERG acknowledges the limitations to their comparison between mexiletine and lamotrigine. This was only intended to be an explorative scenario, in the absence of lamotrigine having been included in the model with its own efficacy and safety evidence.

Issue 4: Disease progression

Question 7

The ERG acknowledges that the company have attempted to improve their previous modelling of disease progression and associated decline in QoL. However, the implementation is still sub-optimal and surrounded by many uncertainties.

It appears that the [redacted] is not in fact the annual decrease in utility but is instead used to increase the probability that BSC patients "progress" earlier, i.e. experiencing the 15% decrease in QoL earlier, than in the mexiletine group. The ERG question how well this single decrease in QoL reflects the natural history of the condition, as they consider it more likely that patients experience a steady decline in QoL. Modelling a steady decline in QoL would have better reflected the stated aim of representing a decrease in QoL over time.

The appropriateness of the 15% decline in QoL upon "progression" or moving from on to off treatment in the mexiletine arm, on top of the differences in utility between patients receiving mexiletine and patients receiving BSC which have already been observed, is also questionable. No evidence has been provided that the utilities from patients in the trial represent only patients in the early stage of NDM and therefore the ERG do not agree with arbitrarily further increasing the observed difference in utility between individuals receiving mexiletine and BSC or the arbitrary reduction in the utility of patients remaining on BSC.

It is difficult for the ERG to assess the plausibility of the new disease progression assumptions given the lack of data in this area. It is unclear whether the estimate from the Delphi panel of QoL declining [redacted]

quicker in patients receiving only BSC is reflective of the relative rate of decline in QoL in this patient group in reality. It is also not clear how reflective of reality the modelling of an early disease state for patients receiving BSC only, followed by a sudden progression of 15%, would be. Therefore, the ERG prefers to continue to use their base-case assumption in their updated base-case presented in this addendum.

The company ran a series of scenario analyses around the assumed percentage decline in QoL following "progression", which was always applied equally across arms, as shown in Table 3 of their Response to TE. The difference in ICER between the company's updated disease progression differential assumption and ERG's base-case assumption (where no disease progression differential is assumed) is very small ([redacted]) and therefore the ERG note the uncertainties in relation to the updated modelling are not a major issue in terms of results, but still prefer to maintain their assumed modelling due to substantial uncertainties around the company's updated approach.

Issue 5: Health related quality of life valuation

Question 8

Valuation method

With regards to the DCE study, the ERG stands by its concerns regarding the design and the likely impact on the results of this study as outlined extensively in the ERG report. The company's attempts to handle data with serious potential limitations conservatively does not fix these limitations or necessarily remove their impact from the results. The experts consulted by the company did raise various limitations in the design and analysis of the DCE and TTO studies, which should be mentioned as well as their general support for the approach. The fact that the different approaches produce very different results in terms of treatment effect indicates that there is substantial uncertainty regarding the true utility values and treatment effect. No additional evidence has been presented which alleviates the ERGs fundamental concerns.

The company argued that there being no difference between naïve and non-naïve subjects, either in placebo or in the mexiletine groups for the stiffness VAS scores means that any previous treatment with mexiletine did not influence the expectations of the patients with respect to treatment effects. However, this result for VAS stiffness does not necessarily extend to HRQoL.

The ERG has several points to note in response to the company's argument that CSPBMs meet the NICE Methods Guidance for alternatives to EQ-5D provided they are based on validated measures of HRQL using valuation methods comparable to those used for the UK EQ-5D value set:

- The stipulation of the use of valuation methods comparable to those used for the UK EQ-5D value set provides another argument in support of using the TTO valuation approach as NICE does not currently recommend the UK EQ-5D-5L value set (which was developed using DCE/TTO methods) and therefore recommends the UK EQ-5D-3L value set which was valued using TTO.
- The INQoL may be validated, but not as a preference based measure. By greatly reducing the number of items used in the valuation, the validity of the measure may have been affected.

In response to the company's argument that quotes from clinicians and patients support a utility gain of at least 0.3 the ERG has several things to note:

- The support for the company's expected size of the utility gain depends on the quotes selected from the CS. The ERG report includes statements from patients such as: "In late 30's, started medication which helped. Symptoms receded - 70% improvement" [4] and comments from clinical experts such

as "patients may still have myotonia but it has improved" and another who stated that they would expect utilities of approximately [redacted] in the mexiletine group, if the average in the general population was 0.9, which does not support the argument that patients are restored to normal utility on mexiletine.[5]

The ERG would also like to note in response to the further analysis conducted by the company showing that when the upper and lower anchors of the vignette study are applied to the DCE estimates, the incremental utility is [redacted] which is very similar to the Vignettes result (incremental utility of [redacted]), which they argue adds confidence and credence to the two datasets. It would be expected that if you restrict the range of values from the DCE study to be equal to the TTO study, the values would be much more similar. However, this does not change the issue that the two approaches, when applied according to their separate utility ranges as in the company and ERG base-cases produce very different utility values and treatment effects.

Lupin state that they believe the most likely incremental utility gains are between the two valuation approaches. Therefore, the company acknowledge that the DCE results used in their base-case are likely overoptimistic. The additional scenarios conducted by the company investigating using the DCE with lower anchor 23233 and using the lower bound of 23233 in combination with the upper bound from the vignette study provide additional scenarios, but no change was made to the company's base-case approach.

None of the arguments made by the company do anything to alleviate the ERGs fundamental concerns about the design and results of the DCE study. The ERG therefore chooses to continue to use the utility values produced by the vignette/TTO study in their base-case.

Validation of utility values by mapping published SF-36 values

The ERG would like to signpost readers to their comments from the ERG report on the company's judgement of the SF-36 as inappropriate in NDM patients. The ERG would like to note here that disease specific measures are, by their nature as specific to the disease, always going to be considered more relevant to the condition than generic measures. However, this does not constitute evidence that the generic measure is inappropriate or incapable of measuring HRQoL in that condition.

Additionally, the ERG would like to add, as stated in TSD11, that HRQoL measures should measure the impact of health issues on quality of life and not solely measure symptoms themselves.[6] Therefore, arguments that the SF-36 does not measure muscle locking are limited, as the SF-36 may sufficiently capture the impact of muscle locking on HRQoL in terms of limitations in physical functioning, physical role and other relevant areas. The argued failure of the SF-36 to capture other clinically important elements of NDM, such as independence and body image was also not solved by the company's chosen HRQoL approaches as these items were removed from the reduced INQoL used in the valuation studies and therefore were not captured in the model.

Again, the ERG reiterates that without psychometric evidence of the inappropriateness of the SF-36 in NDM, it cannot be concluded to be inappropriate. The ERG believe that the requested validation of utility values in the model by mapping the published SF-36 values to EQ-5D-3L values would have been very helpful in determining which set of values from the alternative valuation studies in this submission were most appropriate and that this should have been conducted by the company.

The ERG conducted its own mapping of the published SF-36 data from Statland et al. 2012 to EQ-5D-3L UK utility values using the mapping algorithm developed and published by Rowen et al. 2009 at the request of the NICE technical team.[7, 8] In this trial, patients received either mexiletine (n=28 provided HRQoL data) or placebo (n=29) for 4 weeks in period 1 and then switched to receive the other treatment in period 2.

Statland et al. report mean dimension scores across patients, for the two trial periods combined for some dimensions and separately for the two periods for others, as shown in Table 1.1.[7] Per period data was mapped to EQ-5D utility values using the random effects GLS algorithm, which included dimension scores, squared dimension scores and interactions (model 3 in the publication). [8] This algorithm was recommended by Rowen et al. as the most accurate of the five algorithms developed and tested. First the SF-36 dimension scores shown in Table 1.1 were rescaled to be between 0 and 1, as stipulated by the Rowen et al. algorithm. Then the published coefficients for the random effects GLS model were applied to the rescaled data. This provided mapped EQ-5D-3L utility values for period 1 and period 2, where for the domains for which only overall scores were presented, scores were assumed to be the same across periods. Average utility values across the period were also estimated as the average between the period 1 and period 2 utility values. Resulting utility values are shown in Table 1.2. The impact on results of assuming these utility values instead of those calculated by the company can be seen in Section 3.1.2.

Table 1.1: SF-36 domain scores from Statland et al. 2012

	Mean mexiletine score		**Mean placebo score**	
SF-36 domain	**Period 1**	**Period 2**	**Period 1**	**Period 2**
Physical functioning	42.8		37.8	
Physical role	46.5		39.2	
Bodily pain	49.8		42.0	
General health	45.5		44.5	
Vitality	45.5	51.9	43.7	40.0
Social functioning	47.1		41.9	
Emotional role	46.2	49.9	45.5	39.1
Mental health	47.3	53.3	47.3	44.4
Source: Statland et al. 2012 [7]				

Table 1.2: Mapped utility values (SF-36 to EQ-5D-3L)

Mapped utilities	**Mexiletine**	**BSC**	**Incremental**
Period 1	0.67	0.54	0.13
Period 2	0.61	0.53	0.08
Averaged periods	0.64	0.54	0.10
BSC = best supportive care			

The ERG acknowledges many limitations associated with this mapping analysis relating to: limitations in the trial, in the data presented and in the mapping algorithm used. These limitations include the following:

- Trial limitations
    - Small patient numbers
    - Short term trial (only 4 weeks per treatment)
    - Cross-over design could introduce bias in second period scores
    - Some patients had previous experience of the treatment which could introduce bias into scores

- Statland data presented
    - Per-period SF-36 scores were not available for some domains. Therefore, the ERG had to assume that the average across the two periods applied to both periods.
    - There was no individual patient data with which to map and therefore only the mean score could be mapped. Given that mapping algorithms perform differently at different points on the utility scale this could introduce bias.

- Limitations with the mapping algorithm
    - The mapping algorithm was estimated in a different patient population (inpatients and outpatients at Cardiff and Vale NHS Hospitals Trust). The relationship between the measures may not be exactly the same as for an NDM population.
    - The algorithm has been shown to overpredict the utility of more severe health states. This may reduce the overserved treatment effect if patient in the placebo group are in a more severe state, but their utility is overpredicted, while this overprediction is smaller or non-existent in mexiletine patients in a better health state.

Given all of these limitations, the ERG does not believe that these utilities should necessarily replace the company analyses. The intention was simply to estimate, even crudely, a set of utilities with which to validate the company analyses and help inform which of the company utilities may be the best to use in the base-case. Given that the incremental utility estimated between mexiletine and BSC using the mapped Statland data is substantially lower than the values calculated in either of the company's approaches, the ERG believe this reinforces the argument that the vignette/TTO approach, which resulted in a lower treatment effect in terms of utility than the DCE approach, should be used in the base-case.

Carer disutilities

The ERG does not disagree that carer disutility may be relevant in this condition. However, the ERG is uncertain as to whether the assumption that 20% of patients will be severe and require the equivalent care of non-ambulatory Duchenne patients is reflective of the real-world situation. The ERG note that it can be determined from Tables 61 and 62 and Figures 27 and 28 of the CS that no participants in the MYOMEX trial required a wheelchair or walking aid, but that approximately 44% in the placebo group did have moderate difficulties in walking, asking for occasional assistance.[9] This suggests that, while the disutility applied may be slightly too high to represent the ambulatory ability of patients in MYOMEX, the proportion who still need some assistance (associated with a smaller disutility for carers) may be higher than 20%. There is also the possibility over the long-term that the ambulatory status of patients on BSC will decline, making the assumption that 20% of BSC patients are severe more reflective in the long-term. Given the

uncertainties in this area the ERG did not change the company base-case but did conduct scenarios around the assumed disutility and proportion of patients deemed severe.

Issue 6: Other modelling assumptions

Question 9: Discontinuation rates

The company believe that the most appropriate long-term discontinuation rates for the economic model should be those derived from the Suetterlin et al. study as this study provides long term data reflecting real world longer-term discontinuation of patients.[1, 3] However as the discontinuation rates in MYOMEX and Suetterlin et al. are relatively similar, the company were happy to include the more conservative MYOMEX assumption in their updated company base-case.

Question 10: Adverse event rates

Similarly, the company believe that the most appropriate long-term AE rates for the economic model should be those derived from the long term real world Suetterlin et al. study.[1, 3] However as the AEs rates in MYOMEX and Suetterlin et al. are relatively similar, and AEs are not a large driver of cost-effectiveness results, the company were happy to use the MYOMEX AEs in their updated company base-case.

Question 11: Resource use

The ERG agrees with the company that the estimates for proportions of patients requiring health care resource use, and the frequencies for health care visits from the Delphi panel are a better source to inform the model than the previous estimates that were based on the CMS.

However, within Round 1 of the Delphi process, the experts were asked to estimate the frequency of resource use for adult NDM patients receiving BSC or receiving treatment with NaMuscla, defined as the mean number of annual visits per patient per identified resource. This formulation suggests, or could suggest, that this already reflects the expected number of visits over all patients, rather than the number of visits conditional on the fact that the patient uses the resource in the first place. This is further reinforced by the fact that for several types of resource the range of answers starts at zero, which cannot happen when it is clear that the number of visits should be given, conditional on using that resource. Thus, the ERG considers the multiplier of [redacted] found through this question the most reliable estimate of the resource use multiplier.

Question 12: Age-adjustment of utility values

The company agreed with the ERG and the NICE technical team and included the age-adjustment of utility values in their updated base case.

The ERG can confirm that their preferred base-case assumptions for discontinuation rates, AE rates and the age-adjustment of utility values have been included in the company's updated base-case. As summarised in section 1.6.3 the company and ERG still disagree about the size of the resource use multiplier applied in the model. The ERG updated base-case will use a multiplier of [redacted] instead of the company's preferred 3.

2. Company's updated cost effectiveness results

A new discounted price per pack of [redacted] has been accepted for the submission, replacing the original price of [redacted], and is included in the new base-case analysis.[1]

Based on the issues raised at technical engagement the company made the following changes to their original base-case:

- Mexiletine maintenance dose amended from 14 to 15 capsules per week (from 400mg to 416.7 mg of mexiletine hydrochloride)
- Amended the disease progression and associated QoL decrease as described in Section 1.4
- Included a carer disutility of 0.11 for 20% of patients off-mexiletine who were assumed to be severe
- Assumed treatment discontinuation rates from the MYOMEX trial
- Assumed AE rates from the MYOMEX trial, including all AEs
- Re-estimated resource use based on the Delphi Panel
- Adjusted utilities for age

2.1 Company's cost effectiveness results

The company's updated base-case cost effectiveness results are shown in Table 2.1. These results indicate that mexiletine was both more costly and more effective than BSC. The incremental costs and QALYs were [redacted] and [redacted], respectively. This resulted in an ICER of [redacted] per QALY gained. All results were based on the new PAS price of mexiletine.

Table 2.1: Company updated base-case cost effectiveness results (New PAS price, discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]	-	-	-	-

Based on company model submitted alongside their Response to Technical Engagement.[1]
BSC = best supportive care; CS = company submission; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years.

2.2 Company's sensitivity analyses

2.2.1 Probabilistic sensitivity analysis

The probabilistic results from the company's updated analysis align closely with the deterministic results, as shown in Table 2.2 below. The cost effectiveness plane in Figure 2.1 shows that the vast majority of simulations fell into the north-east quadrant, with a few in the south-east quadrant. The cost effectiveness acceptability curve (CEAC) in Figure 2.2 shows that at thresholds of £20,000 and £30,000, mexiletine has a [redacted] and [redacted] probability of being cost-effective, respectively.

Table 2.2: Company's updated base-case probabilistic results (New PAS price, discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]	-	-	-	-

Based on the company model submitted alongside their Response to Technical Engagement.[1]
BSC = Best supportive care; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years.

Figure 2.1: Company's updated cost effectiveness plane

Based on company model submitted alongside their Response to Technical Engagement. [1]
PSA = probabilistic sensitivity analysis; QALYs quality-adjusted life years, WTP = willingness to pay.

Figure 2.2: Company's updated CEAC

Based on company model submitted alongside their Response to Technical Engagement.[1]
CEAC = cost effectiveness acceptability curve.

2.2.2 Deterministic sensitivity analysis

Figure 2.3 shows the tornado diagram of the 10 most influential parameters. The parameters with the largest impact on the ICER were the assumed maintenance dose of mexiletine, the compliance rate, the assumed utility values for each treatment and the assumed disease progression differential in each arm. These parameters closely reflect the key issues at technical engagement and reinforce the importance of these issues within the modelling.

Figure 2.3: Tornado diagram: impact on ICER

Based on company model submitted alongside their Response to Technical Engagement.[1]
ICER = incremental cost effectiveness ratio.

2.2.3 Scenario analyses

The results of the scenario analyses defined by the company in their response to technical engagement are shown in Table 2.3. These scenarios were rerun by the ERG as in their technical engagement response the company conducted scenarios on their original base-case rather than their updated base-case. Therefore, the impact of the updated assumptions was not reflected in the results. The scenario which had the largest impact on the ICER was the one that was based on the DCE utility approach with bottom anchor 23233 and top anchor equal to the vignette upper utility. This was the only scenario that resulted in an ICER above [redacted] per QALY gained.

Table 2.3: Results of the company's scenario analyses

Scenario	Mexiletine		BSC		ICER £/QALY
	Costs	QALYs	Costs	QALYs	
Updated Company BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dosing					
14 capsules per week maintenance dose (original company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 capsules per week maintenance dose (updated company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Mexiletine		BSC		ICER £/QALY
	Costs	QALYs	Costs	QALYs	
Updated Company BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease progression					
Original company BC (15% QoL decrease for placebo patients only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing [redacted]% quicker than mexiletine patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing [redacted]% quicker than mexiletine patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing [redacted]% quicker than mexiletine patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company approach (15% QoL decrease for 'progressed' placebo and mexiletine patients, with placebo patients progressing [redacted]% quicker than mexiletine patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient utilities					
DCE (bottom anchor 33333, top anchor 1) (original and updated company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DCE (bottom anchor 23233, top anchor vignette upper utility)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutilities					
Original company base case (no carer disutilities applied)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.05 applied to 10% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.05 applied to 20% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Mexiletine		BSC		ICER £/QALY
	Costs	QALYs	Costs	QALYs	
Updated Company BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.11 applied to 10% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company approach (Carer disutility of 0.11 applied to 20% of NDM placebo patients and patients off mexiletine)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.18 applied to 10% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.18 applied to 20% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use					
Original company base case (Nov 2018 advisory board inputs with 3x multiplier for BSC patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company approach (August 2020 Delphi panel inputs for 3x multiplier for BSC patients)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
August 2020 Delphi panel inputs for [redacted] multiplier for BSC patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on the company's response to technical engagement and the accompanying model.[1]
BC = base-case; BSC = best supportive care; DCE = discrete choice experiment; NDM = non-dystrophic myotonia; QoL = quality of life.

3. Exploratory and scenario analyses undertaken by the ERG

As explained in Section 1, the company made a series of changes to their original base-case, some of which the ERG agreed with and some of which the ERG did not. Additionally, there were elements of the ERG base-case which were not reflected in the company's updated base-case.

Therefore, the ERG made the following changes to the updated company base-case:

- The vignette/TTO HRQoL valuation approach was used instead of the company's preferred DCE approach
- The disease progression assumption was removed as per the ERG's original base-case
- The ERGs preferred resource use multiplier of [redacted] was used to replace the company's preferred multiplier of 3.

These elements were implemented in an updated ERG base-case, the results of which are shown in Table 3.1. After the implementation of the ERG's preferred assumptions, the ICER was [redacted] per QALY gained, thus, [redacted] larger than the company base-case.

Table 3.1: ERG base-case deterministic results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]				
Based on the electronic model submitted alongside the company's response to TE.[1] BSC = best supportive care; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY = quality adjusted life year; TE = technical engagement.							

Table 3.2 shows the impact of each individual ERG change to the company's updated base-case on model results and the cumulative impact on the ICER. Removing the company's assumed disease progression had minimal impact on the ICER and the reduction in the resource use multiplier also had limited impact, increasing the ICER by approximately [redacted]. The change which had by far the largest impact was switching from the DCE HRQoL valuation approach to the vignette/TTO approach, which increased the ICER by approximately [redacted].

Table 3.2: ERG step-by-step preferred assumptions and cumulative impact on ICER

Preferred assumption (combined with previous lines)	Section	Mexiletine		BSC		Inc. Costs (£)	Inc. QALYs	Cumulative ICER
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company updated base-case after TE	2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG change 1 – Company disease progression assumptions removed	1.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 2 – Vignette/TTO valuation approach used instead of DCE	1.5.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 3 - Resource use	1.6.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on the electronic model submitted alongside the company's response to TE.[1] BSC = best supportive care; ERG = evidence review group; DCE = discrete choice experiment; ICER = incremental cost effectiveness ratio; Inc = incremental; QALY = quality adjusted life year; TE = technical engagement; TTO = time trade off.								

The ERG also ran a PSA on their preferred base-case. The probabilistic ICER of [redacted] aligns closely with the deterministic ICER of [redacted], as can be seen in Table 3.3 below. The cost effectiveness plane in Figure 3.1 shows that, similar to the company's updated base case, the vast majority of simulations fell into the north-east quadrant, with a few in the south-east quadrant. The majority of simulations fell above the £30,000 upper limit of the NICE threshold. The CEAC in Figure 3.2 shows that at thresholds of £20,000 and £30,000, mexiletine has a [redacted] and [redacted] probability of being cost-effective respectively.

Table 3.3: ERG base-case probabilistic results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]				
Based on the electronic model submitted alongside the company's response to TE.[1] BSC = best supportive care; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; QALYs = quality-adjusted life years.							

Figure 3.1: ERG base-case cost-effectiveness plane

Based on company model submitted alongside their Response to Technical Engagement. [1]
PSA = probabilistic sensitivity analysis; QALYs quality-adjusted life years, WTP = willingness to pay.

Figure 3.2: ERG base-case CEAC

Based on company model submitted alongside their Response to Technical Engagement.[1]
CEAC = cost effectiveness acceptability curve.

The DSA run on the ERG's updated base-case shows that the assumed dose, compliance rate and utility values have the largest impact on results as shown in Figure 3.3.

Figure 3.3: ERG base-case DSA tornado diagram

Based on company model submitted alongside their Response to Technical Engagement.[1]
ICER = incremental cost effectiveness ratio.

3.1 Additional scenarios conducted by the ERG

3.1.1 Scenario set 1: Mexiletine dosage

Given the substantial impact that the dosage has on results and the two options regarding either the use of a dose which reflects the efficacy data from the trial or the dose which is more representative of real world clinical practice, the ERG presents the results of both alternatives in Table 3.4. Using the trial dose of 600 mg to reflect the maximum dose increases the ICER to [redacted]. Although this dose matches with the efficacy and safety data used in the model as outlined in Section 1.2 it is likely to be very conservative, with real world data suggesting an average dosage around 400 mg.

Table 3.4: ERG mexiletine dosage scenarios

Mexiletine dosage	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Trial dose 600 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suetterlin dose 429 mg (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on the electronic model, updated from the company's response to technical engagement.[1]							

Mexiletine dosage	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
BC = base-case; BSC = best supportive care; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality-adjusted life years.							

3.1.2 Scenario set 2: Utilities

Many uncertainties remain in relation to the utilities used in the model as shown by the scenarios in Table 3.5. The ERG and company still disagree on which HRQoL valuation approach to use in the base-case, with the company preferring the DCE approached with lower anchor 33333 and upper anchor 1, while the ERG prefer to use the vignette/TTO approach. Using the company's preferred DCE approach reduces the ICER to [redacted] per QALY gained. The results of the ERG mapping of the Statland SF-36 data to UK EQ-5D-3L utilities are also provided, to give an idea of the potential impact on results. Using the utility values calculated from the SF-36 data averaged over the 2 Statland trial periods results in an ICER of [redacted] per QALY gained, while using only the period 1 trial data where possible (with averaged data for the remaining domains) results in an ICER of [redacted] per QALY gained. This indicates that the reduced treatment effect in terms of HRQoL observed using the mapped data has a substantial impact on the ICER. Although the limitations of the mapping analysis should be kept in mind this does provide support to the use of the vignette/TTO utilities in the base-case as this approach is the most conservative of the two company approaches selected.

Given the ERG's uncertainty regarding the size of the disutility used and the proportion of patients categorised as severe to whom it was applied, several scenarios were conducted in relation to carer utilities. Since Tables 61 and 62 and Figures 27 and 28 of the CS suggested that no participants in the MYOMEX trial required a wheelchair or walking aid, but that approximately 44% in the placebo group did have moderate difficulties in walking, asking for occasional assistance, the ERG explored a scenario with a reduced carer disutility of 0.06, applied to 40% of patients not on mexiletine.[9] This scenario had almost no impact on the ICER, with a reduction of approximately [redacted]. In order to explore the idea that the carer disutility of 0.11 assumed from non-ambulatory Duchenne patients was too large for a severe NDM population, the ERG also tested a scenario whereby the reduced disutility of 0.06 was applied to the company's assumed 20% of patients not receiving mexiletine. This scenario increased the ERG base-case ICER by approximately [redacted] to [redacted] per QALY gained, while assuming no carer disutility increased the ERG base-case ICER to [redacted] per QALY gained.

Table 3.5: ERG utility value scenarios

Utility values	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
HRQoL valuation approach							
DCE approach anchored to 33333 and 1 (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility values	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Vignette/TTO approach (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG mapping utility validation							
Statland period 1 utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statland averaged period utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutilities							
Carer disutility of 0.11 applied to 20% of NDM placebo patients and patients off mexiletine (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.06 applied to 40% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.06 applied to 20% of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No carer disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model, updated from the company's response to technical engagement.[1]
BC = base-case; BSC = best supportive care; DCE = discrete choice experiment; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; NDM = Non-dystrophic myotonia; QALYs = quality-adjusted life years.

3.1.3 Scenario set 3: Disease progression

This scenario set in Table 3.6 shows that the impact of removing the company's disease progression assumption in the ERG base-case has a minimal impact on the ICER.

Table 3.6: ERG disease progression scenarios

Disease progression	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
No disease progression (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated company BC (15% QoL decrease for 'progressed' BSC and mexiletine patients, with BSC patients progressing [redacted] quicker)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on the economic model, updated from the company's response to technical engagement.[1] BC = base-case; BSC = best supportive care; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALY s= quality-adjusted life years; QoL = quality of life.							

3.1.3 Scenario set 3: Resource use

The source of resource use estimates and the multiplier assumed have a small impact on results as shown in Table 3.7. The difference between the ERGs updated base-case assumption and the company's updated base-case assumption is small at approximately [redacted] and therefore this is not a substantial issue.

Table 3.7: ERG resource use scenarios

Resource use	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
Multiplier [redacted], Delphi panel (ERG updated BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier 3, Delphi panel (Company updated BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier 1, Nov 2018 advisory board (ERG original BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiplier 3, Nov 2018 advisory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Resource use	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
board (Company original BC)							

Based on the economic model, updated from the company's response to technical engagement.[1]

BC = base-case; BSC = best supportive care; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; QALYs = quality-adjusted life years.

4. ERG conclusions

In their response to the technical report, the company submitted responses to the key issues raised in the Technical Report written by the NICE technical team, as well as some additional evidence relevant to these issues, a new PAS and an updated company base-case.

The company submitted evidence from a recent clinical advisory board and Delphi panel in support of the generalisability of the MYOMEX trial as well as further evidence and arguments against the inclusion of additional comparators including lamotrigine. Evidence was also submitted from a variety of sources, including the Suetterlin study and real-world usage from the main UK NDM centre in Queens square, in support of their assumed mexiletine maintenance dose of 400 mg per day. The company acknowledged that the average dose of the Suetterlin data is between 14 and 15 capsules per week, and therefore updated their base case to a maintenance dose of 429 mg (15 capsules per week), which they argue is very conservative given that Queen Square provides approximate usage between 300 mg to 400 mg per day.

The company made a series of arguments in defence of their HRQoL valuation approaches, maintaining their preference for the use of the DCE values in their base-case. The company refused NICE's request to conduct a mapping of the published SF-36 data from the Statland trial, arguing that the SF-36 was not appropriate in NDM. Lastly the company included carer disutilities in their updated base-case, using a disutility of 0.11 based on a disutility observed for carers of non-ambulatory Duchenne patients found in the literature and the assumption that 20% of NDM patients not receiving mexiletine would require a carer.

The company conducted a new approach to estimate the difference in resource use between patients receiving mexiletine and BSC in the Delphi panel study. This created new resource use estimates, which were included in the company's updated base-case, and provided additional evidence for the resource use multiplier, which the company claimed supported their assumption of a multiplier of 3, which was retained in their updated base-case.

The company agreed to ERG base-case assumptions regarding discontinuation rates, AE rates and the age-adjustment of utilities and included these in their updated base-case, removing these as issues. A new PAS, which reduced the pack price of mexiletine to [redacted] (from [redacted]) was also agreed and incorporated into the model.

These changes resulted in an updated company base-case ICER of [redacted] per QALY gained (including PAS). The PSA showed that at thresholds of £20,000 and £30,000, mexiletine has a [redacted] and [redacted] chance of being considered cost-effective.

The ERG had some remaining issues with the updated company base-case. The ERG still believe that lamotrigine is a relevant comparator and should be included in the model. The company's updated implementation of disease progression within the model still does not reflect a steady progression of disease and worsening of HRQoL over time. Instead the company implemented a one-off progression event at the time that patients transition from alive on treatment to alive off treatment in each treatment arm, at which point patients' utility was assumed to decline by 15%. Patients in the BSC arm were assumed to reach this progression event [redacted] faster than patients in the mexiletine arm. The ERG felt there was a lack of evidence for these assumptions and that they were unlikely to reflect the real life progression

of the condition and therefore removed the disease progression assumption in their updated base-case, reverting to the original ERG base-case without disease progression.

The company did not present any additional evidence to alleviate the ERGs concerns regarding the design and results of the DCE study nor did they present sufficient evidence to prove that the SF-36 is not valid in NDM. Therefore, the ERG conducted the requested mapping of the SF-36 Statland data. Despite substantial limitations in the simplistic mapping analysis which could be conducted given the data available, the ERG note that the results suggest a smaller treatment effect in terms of utility than suggested by either the company's DCE or vignette/TTO study. This lends further support to using the more conservative vignette/TTO utility values and these were used in the updated ERG base-case. The ERG agrees that carer disutilities are likely to be appropriate for severe NDM patients, however there is uncertainty as to the appropriate disutility and proportion of patients to which this disutility would apply. The ERG did not change the company base-case assumptions in relation to carers but conducted a series of scenarios.

Given the evidence presented by the company, the ERG agree that the company's updated maintenance dose of 429 mg is likely to be more reflective of clinical practice than the 600 mg dose used in the trial. Therefore, the ERG retained the company's updated dose in their base-case, but conduct a scenario using the 600mg dose, given that this dose was used in the MYOMEX study to obtain the efficacy and safety data used in the model.

These changes by the ERG led to an ERG base-case ICER of [redacted] per QALY gained. The change which had by far the largest impact on results was using the utility produced by the vignette/TTO study rather than the DCE approach. The PSA showed that at thresholds of £20,000 and £30,000, mexiletine has a [redacted] and [redacted] chance of being cost-effective, respectively. The DSA showed that the assumed dose, compliance rate and utility values have the largest impact on results. The scenarios which had the largest impact on results were those surrounding utilities and assumed dose.

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Mexiletine for symptomatic myotonia in adults with non-dystrophic myotonic disorders

Extra model calculations after Technical engagement

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Date 5 October 2020

Updated scenario ERG after TE

Scenario set 3: lamotrigine as a comparator

No direct head-to-head evidence assessing the effectiveness of mexiletine compared to lamotrigine was identified. The cost of lamotrigine was identified from the BNF. The same AEs were assumed for lamotrigine as for mexiletine with the addition of the expected costs of Stevens-Johnson Syndrome (SJS), a rare but severe AE of lamotrigine. To estimate the expected costs of SJS, we multiplied the probability of 0.05% (based on SPC lamotrigine[1] which indicates a probability of between 0.1% and 0.01%) with the associated treatment costs of £9331 (based on HRG code JD07A, as a conservative estimate).[2]

Given that the impact of treatment on HRQoL is the only unit of effectiveness in the model, this scenario investigates different utility values for lamotrigine, relative to those observed for BSC and mexiletine. This provides scenarios regarding the potential cost effectiveness of mexiletine compared to lamotrigine, dependent on the utility value assumed for lamotrigine. Since there has been discussion during Technical Engagement (TE) regarding the dosage of mexiletine that should be assumed in the model, we present the results both for the lower dosage as observed in clinical practice, according to the company's response to the TE report, and for the dosage as observed in the MYOMEX trial. These results are shown in Table 1 and 2, and Figure 1. Assuming a utility value equal to that of best supportive care ([redacted]) resulted in an ICER of [redacted] for mexiletine compared to lamotrigine when using the lower dosage and [redacted] when using the higher dosage. It should be remarked here that in a full incremental comparison including BSC as well, lamotrigine would be dominated by BSC.

[1] https://www.medicines.org.uk/emc/product/8052/smpc#UNDESIRABLE_EFFECTS, accessed 5 October 2020

[2] Proposed 2020/21 National Tariff Payment System: national prices and prices for blended payments

Table 1: Results of scenario set 3: lamotrigine as a comparator – Dosage mexiletine as observed in daily practice

Utility lamotrigine	Mexiletine		Lamotrigine		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
[redacted] (U=BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] (U=mex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to Technical Engagement
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; mex = mexiletine; QALY = quality-adjusted life year

Table 2: Results of scenario set 3: lamotrigine as a comparator – Dosage mexiletine as in clinical study

Utility lamotrigine	Mexiletine		Lamotrigine		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
[redacted] (U=BSC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] (U=mex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Based on the economic model, updated from the response to Technical Engagement
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; mex = mexiletine; QALY = quality-adjusted life year

For the lower dosage of mexiletine, the ICER increases rapidly from this point to [redacted] at a lamotrigine utility of [redacted] and [redacted] at a utility of [redacted]. For the higher dosage of mexiletine a similar pattern is seen (see figure 1). At a utility of [redacted] (equal to the utility of mexiletine) [redacted]

Figure 1: The impact on the ICER of various assumed lamotrigine utility values

Source: Based on the economic model, updated from the response to Technical Engagement.

ICER = incremental cost effectiveness ratio