NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders [ID1488]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

treating the symptoms of myotonia in non-dystrophic myotonic disorders [ID1488]

Contents:

The following documents are made available to consultees and commentators:

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

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders [ID1488]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment (sic)	NICE Response
1	Consultee (company)	Lupin Healthcare (UK) Limited	The Company is disappointed with the Appraisal Committee's preliminary decision that NaMuscla is not recommended, within its marketing authorisation, for treating the symptoms of myotonia in adults with non-dystrophic myotonic disorders (NDM). NaMuscla is the only licensed established treatment for NDM patients. The Company is deeply concerned for those patients who are stable on this efficacious and well tolerated treatment following NICE's preliminary decision to depart from its usual practice for ensuring continuity of patient treatment. Instead commissioners are not required to continue to commission treatment if there is a negative guidance. The Company welcomes the opportunity to comment on the preliminary recommendation detailed in the appraisal consultation document (ACD) and are committed to working with NICE to address the Committee's key concerns, and to working with NHSE&I to ensure a continuity of treatment for adult NDM patients. The budget impact for this medicine in Year 3 at our revised PAS is circa [redacted], which represents a medicine already established in clinical practice. The Company has met with NHSE&I and NICE to discuss potential managed access arrangements to alleviate the uncertainty of cost to the NHS, and would welcome further discussions. NDM is a rare condition affecting 0.75 in 100,000 patients[1] with funded genetic diagnosis in only one key centre (Queen Square Highly Specialised Service (HSS)). There are no other licenced treatments in this disease area and no national clinical guidelines. As such the clinical symptoms and quality of life impact of the disease can be overlooked. Given the rarity, it is no surprise that there is little data for this disease and, as such, the Company consider that a Highly Specialised Technology review may have been more appropriate. Despite this, the Company has invested in this disease area and has provided a comprehensive package to demonstrate the long-term safety and efficacy of mexiletine, and the significantly improved quality of life for NDM patients. Supporting evidence includes three randomised controlled studies[2,3,4], that enrolled a total of 115 patients and demonstrated the significant treatment effect for mexiletine, and two long-term studies[5,6] that evidence long-term efficacy and safety. Additional long-term safety is supported by several periodic safety update reports (PSURs) (see Company submission B.2.10.5). This level of evidence is uncommon in such a rare disease. Further evidence has been provided to support this appraisal including a Delphi panel, clinical elicitation exercises, market research and patient surveys; insights that hitherto did not exist in this disease	Thank you for your comment. The further supporting data appendices were provided to the committee ahead of the second meeting.

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			area. The Company continues to invest in this disease area and to generate further insights for patients and caregivers alike, with the objective to ensure this disease and the patients are no longer “invisible”. These include, but are not limited to: ➢ The mapping of patient pathways and identification of system blockages to improve patient access and to decrease the significant time to diagnosis (approximately 8 to 12 years – see Company submission section B.1.3.4.), improving patient outcomes and improving education. ➢ The largest NDM patient survey to date, to increase the understanding of burden of disease and awareness of NDM (on-going)[7]. ➢ The first and only NDM caregiver survey to, for the first time, understand the burden of caring for patients with NDM (on-going)[7]. ➢ A prospective non-interventional post-approval safety study, which will also collects patient-reported outcomes over 5 years (including two sites in the UK)[8]. (NCT04616807) ➢ The first trial ever in paediatric patients, allowing efficacy and safety to be assessed in this age group with additional NaMuscla strengths[9]. NCT04624750) ➢ A 24 month open-label extension study for paediatric patients who have completed the clinical trial to continue to study the long-term safety and efficacy of treating myotonia symptoms in paediatric patients[10]. (NCT04622553) The Company is pleased to be able to provide further supporting data to the appraisal process, *which can be found in the Appendices to this response.* Appendix 1: Clinical Elicitation for utility comparisons and comparators Appendix 2a: Utility valuation analysis Appendix 2b: Updated company deterministic base case and scenario analyses At this extraordinarily difficult time during the COVID pandemic the Company would like to thank clinicians, patients, caregivers and the wider NICE & NHSE&I teams who continue to provide their time and expertise within this technology appraisal.	
2	Consultee (company)	Lupin Healthcare (UK) Limited	**1. The availability of unlicensed special mexiletine is uncertain and is very rarely used instead of NaMuscla to treat adult NDM patients.** In section 1, page 3 of the ACD it states: *“**Why the committee made these recommendations*** *Treatments for the symptoms of myotonia in adults with non-dystrophic myotonic disorders already include*	Thank you for your comment. The reference to unlicensed mexiletine was used as background to the disease area

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			imported mexiletine (that is not licensed in the UK)". This statement is supported in section 3.7 of the ADC where it states: *"The clinical experts stated that most patients currently have between 300 mg to 400 mg of imported mexiletine"* For clarity special unlicensed mexiletine alone is not currently routinely used to treat adult NDM patients; It is used in cases of exception, for purposes of titration or when the HCP uses doses which is outside that of the NaMuscla licence. The Company does not believe that the evidence reflects that most patients currently have 300mg to 400mg of imported (unlicensed) mexiletine hydrochloride. A dose of 300mg or 400mg mexiletine hydrochloride will almost certainly include NaMuscla. The place and usage of special unlicensed mexiletine is described in the commissioning expert statement as: *"to support titration"* and *"where the maximum tolerated dose cannot be met by the branded product".* This later point being supported by an example of paediatric patients who do not form a part of this appraisal. In their technical engagement response the Association of British Neurologists (ABN) also only describes special unlicensed mexiletine in the titration process: *"100mg tablets of mexiletine to slowly up titrate".* Indeed the use of special unlicensed mexiletine should only be used where the special need of the patient cannot be met by NaMuscla and would be inconsistent with the requirements for the use of "specials" as described in the MHRA's Guidance Note 14[11]. In the interest of patient safety the exemption for the use of a special import unlicensed medicine is narrowly drawn by the MHRA, because unlike a licensed medicine they may not have been assessed by the licensing authority in the same way against the criteria of safety, quality and efficacy. NaMuscla is the only licensed medicine for the treatment of myotonia in NDM patients, and is supported by a dedicated medical information team, with on-going post authorisation pharmacovigilance, PSURs, a NaMuscla risk management plan and a post authorisation observational study to monitor safety as a primary outcome, and efficacy and quality of life as a secondary outcome. The supply of any strength of special imported unlicensed mexiletine has been and continues to be uncertain[12-17], whilst the readily available licensed NaMuscla provides a "*uniformity of supply*" (see Clinical Expert statement). Clinicians routinely report to the Company that special mexiletine is not available to them from their hospital pharmacy, as pharmacy comply with the MHRA guidance note 14, or because of sporadic supply. In addition, the quality checks and release of special unlicensed medicines from quality assurance teams in hospital pharmacies can be a lengthy and time consuming process requiring specialist pharmacist checks, and could also impact healthcare provider teams. The Company understands in its most recent correspondence with the MHRA, that imports of special unlicensed 200mg mexiletine hydrochloride for patient use in the UK is negligible.	and the history of treatment in the NHS. NICE's remit for this appraisal was to appraise Namuscla.

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			The Company understands that the majority of clinicians now titrate using NaMuscla[18], and as the ABN describes in their Technical engagement response that if the 100mg unlicensed medicine is required for titration, but not available, the 200mg (NaMuscla) is used instead. Additionally prices for the unlicensed special mexiletine are unregulated and costs may vary[19]. Finally in section B.2.12 of the company submission, the results from the pan-European MyoPath survey[20] found that: "*disruption in mexiletine treatment harmed 85% of patients".* In summary, when it is available, special unlicensed mexiletine is very rarely used alone or instead of NaMuscla to treat myotonia symptoms in adults with non-dystrophic myotonic disorders. The recommendations outlined in section 1 of the ACD should be clear that this is not a suitable basis of the availability or use of unlicensed special mexiletine as an alternative to NaMuscla to treat adult NDM patients. This is particularly important for stable patients treated with NaMuscla. The Company is very concerned for patient welfare in the event of a negative recommendation for NaMuscla as special unlicensed mexiletine would not be a suitable alternative.	
3	Consultee (company)	Lupin Healthcare (UK) Limited	In section 3.3 of the ACD, the committee considered that "*established clinical management without mexiletine cannot currently be observed in the NHS because mexiletine is already established in clinical practice…..Therefore, the committee deemed the most appropriate comparison to be with what people currently taking mexiletine would have if mexiletine was not available*." Given that data for the efficacy and safety of the committee's most appropriate comparison cannot be observed, and there are no existing NICE NDM guidelines, inherently there will be a much greater uncertainty in this appraisal's decision problem. We ask the committee to give this the utmost consideration, given the potential significant risk to the wellbeing of stable NDM patients currently treated with NaMuscla from the recommendations of the ACD. **2.a Lamotrigine should not be considered a comparator as it is not in established clinical practice to treat NDM patients.** Lamotrigine does not have a marketing authorisation for the symptomatic treatment of myotonia in adults with non-dystrophic myotonic disorders as defined in the scope. The Guide to the methods of technology appraisal 2013 section 6.2.4 describes when an off-licensed medicine such as lamotrigine can be considered as a comparator: *Section 6.2.4: "The Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS."*	Thank you for your comment. The committee considered that the comparator for this appraisal would be the treatment people would have if mexiletine was not available. The clinical experts stated that patients would receive another sodium channel blocker in the absence of mexiletine. Lamotrigine is also sometimes used if mexiletine is contraindicated, not effective or not tolerated

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			In their technical engagement response form, the ABN states that lamotrigine, which they describe as being used at high doses, is not established in clinical practice to treat NDM patients, and state: *"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":* and it *"has the potential life-threatening side effects limiting its use*". The senior clinicians at the main treating centre Queen Square (HSS) confirm that lamotrigine is not in established use. Citing its much longer titration period to reach effective doses and potential severe and life-threatening side effect profile as reasons why they are "*cautious in its use*."[21]. Whilst in the clinical expert statement, the Clinical Expert confirms that she does not use lamotrigine to treat NDM patients. In the technical engagement response from Muscular Dystrophy UK (MDUK), the serious and potential life threatening side effects of lamotrigine, including Stevens-Johnson Syndrome, rashes, psychiatric side effects, emotional impairment, insomnia, hemophagocytic lymphohistiocytosis (HLH), aseptic meningitis as well as limitations regarding contraceptive use and issues with tapering (withdrawal), are described by a patient forum group, The Myotonia Project, and concludes: "*Lamotrigine is rarely used to treat myotonia because of the safety profile and the requirement for more intensive monitoring".* In the Company's technical engagement response (see Issue 3), the Company notes limitations of use outlined in the lamotrigine SmPC[22]: *"In its licensed indications, lamotrigine has a very common (≥1/10) undesirable effect of skin rash. For patients who develop a lamotrigine related rash, treatment should be withdrawn immediately. 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 behavioural change/ psychiatric disorders".* In addition, in contrast to other sodium channel blockers, the research conducted by the Company that shows circa 1% of NDM patients are treated or have ever been treated with lamotrigine in the UK[23], which only reflects its limitations of use and uncertain place in treatment of myotonia symptoms in patients with NDM highlighted in the evidence above. In summary, the evidence provided by the Professional Association (ABN), senior clinicians at the main treating centre at Queen Square (HSS), the Patient Organisation (MDUK), the Clinical Expert and the lamotrigine SmPC confirms that lamotrigine has limitations for use in adult NDM patients, based on:	(please see sections 3.2 and 3.3 in the FAD).

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			• Any available data is too new, and there is no long-term safety or efficacy data to support the safe use of high doses of lamotrigine in NDM patients. • Well-known and documented serious and life-threatening side-effects of lamotrigine, and requiring immediate treatment withdrawal in all patients who develop a common lamotrigine related rash, as well as other common undesirable side effects. • A much longer titration period and intensive monitoring to reach the required higher doses. Off-licensed lamotrigine is therefore not currently, nor has ever been, in established use in this indication. The issues presented here are inherent to lamotrigine, and therefore the committee's unobservable decision problem for comparison, the Company believes, is extremely uncertain. The Company also believes the evidence provided above confirms that lamotrigine is not currently part of established clinical practice for the indication in the NHS, and therefore cannot be considered a relevant comparator in accordance with section 6.2.4 of the Guide to methods of technology appraisal 2013. **2.b There is no quality evidence to support the safety or efficacy of the other sodium channel blockers carbamazepine, acetazolamide, flecainide and phenytoin in NDM treatment** The appraisal consultation document identifies that other sodium channel blockers are used to treat NDM patients. These are the off-licensed medicines carbamazepine, acetazolamide, flecainide and phenytoin. In section 6.2.4 of the Guide to the methods of technology appraisal it says *"Specifically when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use."* The Final Scope for this appraisal stated that these medicines do *"not form part of standard care"*. None of these medicines have proven or substantiated efficacy through clinical trials or long-term data supporting their use in NDM patients, and their clinical and safety profile is unfavourable based on evidence provided below. The ACD does not refer to the extent and quality of the safety or efficacy evidence for carbamazepine, acetazolamide, flecainide and phenytoin. Clinical evidence is unfavourable for these medicines. In the Professional Association's technical engagement response, the ABN says: *"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*	

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			profile to make their use rare in clinical practice". The EMA[24], in assessing other antiarrhythmics, state that *"most of them cannot be recommended as treatment for myotonia, because of associated severe side effects*". In the Clinical Expert statement, the expert states: "*have used phenytoin in the past and found that largely ineffective*", and in describing carbamazepine that "*there may be limitations to its use through side-effects such as rash, imbalance and so on*". Further specialist NDM clinical opinion has been elicited in November 2020 (please see Appendix 1). Clinicians stated: • *"Mexiletine cannot be compared to the other medicines and shouldn't be, as other medicines often just do not work".* • [From a clinician who used to work in Spain]: *"Mexiletine was not available for 2 years. It was despairing for the patients and clinicians. Nothing was working for them."* In contrast to the clinical and safety limitations of all the other sodium channel blockers (including lamotrigine), the Company understands from clinicians and patients alike that there would be no suitable alternative to mexiletine: • In the Clinical Expert statement, the expert states: "*In my experience, drug options other than mexiletine do not provide sufficient benefit for most patients*." • In the clinical opinion elicited in November 2020 (Appendix 1) a clinician stated "*No replacement for mexiletine*." • In the MDUK response to the technical engagement, as described by a patient forum group The Myotonia Project, it says *" If mexiletine is not available to NDM patients in the UK, I don't see a suitable replacement for our members at this time".* In summary there is no quality data evidence provided by the ACD to support the use of carbamazepine, flecainide, acetazolamide and phenytoin, and no due regard is given in the ACD to their safety and efficacy profile to treat NDM patients (which, from the above, clinicians and the Professional Association describe unfavourably). Therefore, in accordance with section 6.2.4 of the Guide to the methods of technology appraisal, the Company believes the recommendations in section 1 of the ACD are not sound or suitable on the basis of a comparison to the sodium channel blockers carbamazepine, acetazolamide, flecainide and phenytoin to treat NDM patients. **<u>2.c A comparison to sodium channel blockers is not appropriate or possible due to the lack of data</u>**	

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			An indirect treatment comparison with any of the off-licensed channel blockers is not possible, as confirmed by the technical team in the technical report. There is not the data to make a comparison. The Company has tried to elicit information for the use of the off-licensed sodium channel medicines to treat NDM patients (see Appendix 1), including a Freedom of Information request (see Company response to the Technical Engagement - Issue 3). The practicality of a study to compare these medicines would be challenging and significantly limited. The evidence provided in section 2a and 2b by the experts from the ABN, senior clinicians at the main treating centre at Queen Square (HSS), the Clinical Expert and the patient group (MDUK) have confirmed the limitations, and their caution of use of lamotrigine, and the ABN describe the other off-licensed sodium channel blockers use as rare in clinical practice to treat NDM patients. The findings of the advisory board in July 2020[18] suggest only 6% of NDM patients are currently treated with any of the other off-licensed sodium channel blockers (see the Company's response to the Technical Engagement Issue 3), and only confirms the evidence of the experts that very few NDM patients take the other off-licensed sodium channel blockers currently. An observational study to compare these medicines is not possible according to the decision problem as stated in the ACD which cannot be observed in the NHS, and specialist NDM clinicians in the elicitation November 2020 also confirmed they were not aware of any data to make a comparison between medicines either (See Appendix 1). In section 3.8 of the ACD it is explained that the ERG had provided an analysis for an indicative comparison with lamotrigine. The initial comparison by the ERG assumed the same Adverse Event (AE) profile, compliance, discontinuation, AE disutilities and utility range for NaMuscla. This analysis is extremely uncertain to inform decision making, given no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients at high doses, no treatment comparison is possible, and, other than medicine cost, no inputs were based on lamotrigine use. In the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, page 4 the ERG acknowledges the limitations to their comparison between mexiletine and lamotrigine: "*This was only intended to be an explorative scenario*". The Company has received further analysis from the ERG during the consultation period (26th February 2021), in which the ERG chooses to remove the disutilities associated with AEs. This new analysis completely disregards any impact of the serious and potential life-threatening side effects on patient quality of life when treated with lamotrigine. The company strongly objects to this analysis informing any decision making that disregards the evidence for the safety of lamotrigine provided by the Professional Association (ABN), Patient Organisation (MDUK) or the senior clinicians at the main treating centre at Queen Square (HSS) (see section 2a) that could affect the lives of currently stable treated NDM patients. The ERG's update to include an estimate	

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			for Stevens-Johnson Syndrome treatment costs, not based on a probability rate for NDM patients treated at a high dose of lamotrigine, is a scant amendment, and the Company believes only adds to the extreme uncertainty of the analysis to inform decision making. In section 3.15 of the ACD it states: "*The committee considered that this analysis would likely also be indicative of any comparison with other sodium channel blockers because of the similar costs of treatment*". In section 5.1.14 of the NICE reference case it states: "*In exceptional circumstances, if the comparators form part of a class of treatments, and evidence is available to support their clinical equivalence, estimates of QALYs gained for the class as a whole can be presented*." The Company does not believe there is any evidence of the clinical equivalence of these sodium channel blockers, and therefore the Company believes this exceptional circumstance as outlined in the NICE reference case is not met. Whilst the company acknowledges that for the minority of patients who do currently receive other off-licensed sodium channel blockers, some may benefit from their treatment, but there are no data (quality of life or otherwise) that can value that benefit. There are no specific national NDM clinical management guidelines and the landscape and efficacy of NHS clinical practice in the absence of mexiletine is not observable, and therefore unknown. The Company also acknowledges from the evidence of the Clinical Expert, the specialist NDM clinicians (see Appendix 1) and the Professional Association (ABN) that there may be many of the NDM patients who would not receive either sufficient benefit or any benefit at all from some of the other off-licensed sodium channel blockers. It is not known what the discontinuation rate would be for NDM patients treated with off-licensed sodium channel blockers if mexiletine was not available. Similarly, it is not known what AEs NDM patients may experience when treated with these medicines, although they are described unfavourably and/or significant in the evidence from the Clinical Expert, the specialist NDM clinicians, the Professional Association (ABN), and the Patient Organisation (MDUK). Nor is it known what impact those unfavourable and/or significant AEs would have on the NDM patients' quality of life. There are no long-term data of any kind that support the safety or efficacy of any of the off-licensed sodium channel blockers for treatment of NDM patients. Clinician feedback for the elicitation Nov 2020 described a comparison as "*impossible*" (See Appendix 1). In examples of a previous appraisal for TA346[25] and TA409[26], where data was lacking and insufficient evidence was available to make any robust economic comparisons, the committee could not confidently assess the off-licensed bevacizumab compared with aflibercept, and therefore accepted bevacizumab should be excluded from any comparator analysis.	

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			Based on the evidence above, any provisional recommendations based on the ERG's comparison to lamotrigine, or further applied to any other sodium channel blocker, the Company believes is entirely uncertain, and therefore any provisional recommendations in the ACD based on this analysis would not be a sound and a suitable basis for guidance to the NHS. The Company believes, to be consistent with previous guidance (e.g.TA346 & TA409), the ERG comparison to an off-licensed medicine should be excluded, based on a lack of any data to inform it.	
4	Consultee (company)	Lupin Healthcare (UK) Limited	**3. Longer term Dosing should reflect clinical practice** All evidence submitted in this appraisal suggests that the mean dosage of mexiletine hydrochloride in clinical practice over the long-term is on average around 400mg per day. This includes evidence from the NHS commissioning expert statement, the clinical experts (see ACD section 3.7), the Delphi panel[27], the follow up data from the MYOMEX study[6], the Suetterlin observational study[5], and the senior clinicians from the main treating centre Queen Square (HSS)[21]. The committee concludes the 600mg dose in the MYOMEX study "*does not reflect how mexiletine is currently used in clinical practice*" (ACD section 3.7). However the committee considered "*it appropriate to use the costs of the 600 mg dose in the economic modelling, as was seen in MYOMEX*." All of the trials were relatively short in duration, however evidence does exist for the effectiveness of mexiletine over the long-term with lower doses than those seen in MYOMEX. • In the 63 patients from the Suetterlin et al[5] observational study (mean duration 4.8 years - the study conducted at the main treating centre Queen Square (HSS)) doses were titrated "until symptoms resolved" on an average dose of 416.7 mg mexiletine hydrochloride. Some patients will have been on higher doses of 600mg mexiletine hydrochloride, and therefore many patients on lower doses will receive the same clinical benefit. The mean dose of 416.7mg 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 describes the patient dosing in the study as the "Mean Effective Dose". • More recently (Aug 2020) the senior clinicians from the main treating centre Queen Square (HSS)[21], have confirmed that the dosing they currently use (approximately on average 300mg to 400mg of mexiletine hydrochloride) is "usually sufficient to improve quality of life to normal". • The MYOMEX study supports current practice, with the EMA noting that some patients had already significant reduction of stiffness score on day four (200 mg mexiletine hydrochloride once a day)[24]. Lower doses are further supported by the long-term follow up (mean 48 months) data from MYOMEX[6]. The data shows at least maintained efficacy response to treatment at a mean dose of two capsules per day (400mg mexiletine hydrochloride).	Thank you for your comment. The committee considered it appropriate to consider the costs of the 429 mg dose (informed by Suetterlin et al. and clinician views on current NHS practice). It also considered a scenario with the costs of the 600 mg dose (as used in MYOMEX) in the economic modelling, as it was mindful that efficacy estimates in the MYOMEX trial were taken once patients had been titrated up to the 600 mg daily dose (please see sections 3.7 and 3.17 of the FAD).

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			The Company believes collectively, the long-term data and clinician feedback evidences that in clinical practice efficacy at a lower dose than used in the MYOMEX study is not diminished, and that a mean dose of 416.7mg mexiletine hydrochloride would still treat patients optimally, returning their quality of life to normal, regardless of the varying patient severity or dose, reflective of clinical practice in the NHS. Supporting long-term use, the patients who were non-naïve to mexiletine in the MYOMEX study (and who stopped taking mexiletine at screening) had an average treatment duration of circa a decade prior to study start[2], and the Patient Expert has been treated successfully for c20 years (see Patient Expert statement) which demonstrates that efficacy of mexiletine is maintained over the long-term. In the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, page 3, the ERG writes *"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."* The ERG therefore included 429mg in their preferred case, and the Company agrees with the ERG. The Company believes there cannot be a greater benefit for patients than using a mean dose of 416.7mg mexiletine hydrochloride from the Suetterlin et al study, as all symptoms were resolved at this mean dose. At a dose of 429mg mexiletine hydrochloride, the benefits derived from the MYOMEX study can only be a conservative estimate compared to the clinical practice reflected in the Suetterlin et al study. In summary, the Company acknowledges that there will be some uncertainty with the long-term patient benefits derived in clinical practice, especially for treatment in such a rare disease. However the Company believes that collectively the long-term evidence and data suggests that the efficacy derived from NaMuscla in the MYOMEX study are reflective, even conservatively, of those found in clinical practice use. The Company therefore believes that a conclusion to use the costs of the 600mg dose in the economic modelling would not be reflective of clinical practice, and therefore would not be sound or suitable basis for guidance to the NHS.	
5	Consultee (company)	Lupin Healthcare (UK) Limited	**4. Additional scenarios and options within model to reflect clinical practice** The Company acknowledges that some patients will be titrated using 100mg special import mexiletine hydrochloride. However, the Company also understands that the majority of clinicians now titrate using NaMuscla[27]. The Company has modelled the rate of titration from the NaMuscla SmPC and the dosing using the costs of NaMuscla, which might capture the costs conservatively. However, the Company acknowledges that some patients will be titrated at a more cautious rate.	Thank you for your comment.

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			To investigate the effect on the cost-effectiveness of mexiletine of using a more cautious dose titration in clinical practice, the Company has added functionality for a scenario in the model. This allows an extra two phases of titration, allowing the user to select up to 4 different titration doses before the final maintenance dose. Although NaMuscla is not currently available in other doses, the scenario costs these other doses on a per NaMuscla capsule cost basis, and therefore assumes a linear pricing strategy for any other capsule/pack sizes. However, should a cheaper 100mg mexiletine hydrochloride special import be used to titrate for some patients, the cost-effectiveness results for this scenario would be conservative. A sensitivity for cost effectiveness between the fastest and slowest dose titration is provided below: • The New Company base case in Appendix 2 (titration as per MYOMEX, up to 15 capsules per week, no disease progression, Hybrid model 1 to inform utilities and new PAS): [redacted] • 200mg (mexiletine hydrochloride) for 4 weeks, 300mg for 4 weeks, 400mg for 4 weeks, 429mg maintenance: [redacted] The Company believes there is no evidence that there might be any difference in the quality of life benefits over the lifetime of the patient when using the SmPC titration to that observed in clinical practice from the Suetterlin et al study, where patients were titrated until symptoms resolved, and where usually patients' quality of life will return to "normal"[21]. The Company believes these amendments in the model allow scenarios to provide a better reflection of the titration in clinical practice in the NHS.	
6	Consultee (company)	Lupin Healthcare (UK) Limited	**5. Utilities derived from SF36 are extremely uncertain** Section 3.10 of the ACD states that the committee "*concluded that the generic SF-36 data from the Statland et al. trial could be included in its considerations*" On page 8 of the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, the ERG acknowledges the many limitations associated with the mapping analysis of SF36 data from the Statland trial to EQ-5D-3L utilities. The ERG explains "*The intention was simply to estimate, even crudely, a set of utilities".* The ERG does not continue to recommend this analysis in its preferred case, but instead recommends the TTO/ Vignette valuation methodology. The Company agrees with the limitations of this mapping exercise outlined by the ERG. Particularly as only the mean SF-36 scores from the Statland trial are available (the Company understands the mapping cannot be conducted accurately without patient level data) and as the mapping algorithm by Rowen et al[28] was not designed or validated in NDM patients.	Thank you for your comment. The ERG considered that the company did not show that generic measures of quality of life are unable to measure health-related quality of life of people with NDM. The committee noted that generic quality-of-life instruments are

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			The Company also agrees with the Committee, who recognise in the ACD that the muscle locking function would be difficult to capture, which is in line with findings of Sansone et al, where the SF36 domains of Role physical and Physical functioning had a very weak correlation of -0.22 and -0.20 respectively with the Locking domain of INQoL[29]. The Delphi panel identified that muscle locking is the most impactful INQoL domain to NDM patients QoL[27]. The company also agrees with the ERG, who cautioned that the algorithm to map SF-36 to EQ-5D-3L utilities can underestimate severe health states (see ACD section 3.12). The company believe that utility scores for the BSC patients calculated using this methodology (mean [redacted]) could be higher than expected, which may be why they do not align with the TTO/vignette or revised Hybrid scenarios (see section 6 below). The authors of the Rowen et al[28] paper in their conclusions state: "*Our results raise doubt over the suitability of mapping for patient datasets which have a proportion of subjects with poorer health….Potential policy implications are that mapping the SF-36 onto the EQ-5D can be useful, but may not be suitable for all populations*." From the ERG analysis, the mapped utilities for mexiletine treatment using SF36 from the Statland et al trial are between [redacted] and [redacted] (average [redacted]). These 'on-treatment' utility scores seem extremely low, given that the senior clinicians at the main treatment centre Queen Square expect patient quality of life to improve "*to normal*"[21] when treated with mexiletine (see section 3). The EQ-5D calculated utility for a member of the UK population[30] is expected to be 0.87 (with an upper range of 1 or perfect health), whilst the SF36 derived on treatment utility score is at least 0.20 below this level, and much less at the lower range. The use of SF36 assessing patients with myotonic symptoms is not supported by the literature[29,31-33.] The clinicians agree, as noted in the ABN technical engagement response: *"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.".* Indeed the INQoL questionnaire is the only validated QoL questionnaire that refers specifically to the presence and impact of myotonic symptoms[29,32,34]. The Company strongly believes the Statland et al trial adds significant supportive evidence to mexiletine as an effective medicine. However the Company does have some concerns regarding how the SF36 data was collected in the trial. In the vast majority of SF36 questions[35], respondents are asked to review aspects of their health "During the past 4 weeks", whilst in another question the respondent is to consider a year. Given that 22% of patients were being treated with Mexiletine prior to the trial, it is not clear how the SF36 could show an accurate difference in HRQL between treatments. In summary, the Company believes the utilities derived from SF36 using the Statland trial are extremely uncertain, not solely based on the evidence provided by the ERG, but also based on the evidence provided	included in the NICE reference case to achieve consistency in decision making across different diseases. The committee considered that domains such as physical function and activity in the SF-36 matched issues described by the patient expert (please see sections 3.10 and 3.12 of the FAD).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment (sic)	NICE Response
			above.	
7	Consultee (company)	Lupin Healthcare (UK) Limited	**6.The DCE and TTO valuation methodologies confirm each other** The valuation methodologies were independently reviewed by three experts, none of whom suggested that the valuation exercises or results were highly uncertain. Specific comments from the experts included, "confidence in the general validity and supportiveness for both approaches", and "the overall approach is sound", referring to the TTO. (See company Technical engagement response – Issue 5) 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 scale, but also noted that the impact of the muscle coefficients are lower in the TTO model. As highlighted in section 5 of this response, muscle locking is identified as the most impactful to NDM patients' quality of life. In the Company's technical engagement response – Issue 5, it is highlighted that the incremental utility from the TTO result was very similar to DCE estimates using the same upper and lower anchors ([redacted] and [redacted] respectfully). Further analysis is highlighted in the additional information in Appendix 2a. When considering the utility values generated at a patient level from the MYOMEX study at baseline and in the placebo and mexiletine arms (i.e. all utility values derived within the model), the correlation between those derived from the DCE (using the same range as the TTO) and TTO model is very high (R^2 = 0.96). The two methodologies effectively provide the same utility values at the same range, validating each other and giving confidence and credence to the two datasets and methodologies as supported by the comments of the expert reviewers. However, the Company does agree with the author of the study in Appendix 2a, a senior health economist (who is also Exec Chair for the executive committee at EuroQoL, which developed the EQ-5D measure), who identified that the TTO appeared to undervalue the muscle locking dimension, confirming the findings of the expert reviewers (see the Company's response to Technical engagement - Issue 5). In the TTO study participants were provided with less description of the disease dimensions than in the DCE study, which may have had an effect on the results of muscle locking/ myotonia, as it is such a specific disease symptom. From the TTO study results the muscle locking utility weights were valued at zero for all of the levels except the highest level "an extreme amount", and for this level description it was scored the lowest of all of the 8 items of the INQoL dimension chosen in the valuation exercise (see the Company's Vignette utility report). The Company believes this is important because, as previously stated, muscle locking was identified by the specialist NDM clinicians in the Delphi panel[27] as the most impactful to NDM patients' quality of life. Therefore, the TTO study may underestimate the anchoring range, and thus the incremental utilities that inform the economic model.	Thank you for your comment. The ERG noted several problems with the DCE valuation studies including: a lack of clear ordering preference in describing health states, logical inconsistencies, lack of adequate quality control checks, complex health states, and issues relating to anchoring to the EQ-5D. The clinical experts also considered the range of utility values generated by the DCE studies to be implausible, and some patients to have implausibly low utility. The ERG considered the hybrid modelling had been well conducted and that linking data from the two studies resolved the anchoring issues for the

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			Addressing Limitations The quality controls for the DCE task are described in the Company's ERG clarification question responses (Question B7). The DCE was hosted online by Global Perspectives, an organisation that specialises in this type of survey. It was assumed that the subscribing respondents would likely have some experience in completing similar surveys of this kind. Nevertheless the respondents were provided contact details to contact the facilitators to ask questions to support their understanding of the task at any time. Quality checks such as checking that no respondent always answered A or B were performed, whilst other potential quality control checks were deemed not necessary[36]. However, the Company acknowledges some limitations of the results derived from the valuation methodologies as outlined in Appendix 2a, including sample size (limited by practicality), an unadjusted DCE, non-monotonicity, interpolation between levels, and the muscle locking valuation from the TTO. In the valuation studies, for practical reasons the INQoL questionnaire was substantially reduced to be amenable for valuation, and was guided by 3 expert NDM clinicians and a senior health economist (see company submission B.3.4.2). The literature suggests that an individual can only process between five and nine pieces of information at a time[37], therefore the Company acknowledges that the breadth of the descriptive system (8 dimensions) would be at the higher end of that range. In order to ameliorate the limitations, a new analysis of the data is reported (Appendix 2a). The report describes the appropriateness of modelling INQoL data using a DCE + TTO hybrid approach from more than 700 participants to inform the utility weights. Realignment of the dimensions in the design for the INQoL now addresses the issues for the conceptual mapping to EQ5D-3L upper bound anchoring for the DCE study (i.e. the response of "No" or "Not at all" for any of the selected INQoL items would be mapped to "No problems, "No" or "Not" on the EQ5D-3L domain responses), whilst the combined dataset does not suffer from unadjusted DCE predicted values on a latent scale (lower bound anchoring issues). Performance was judged in terms of out-of-sample predictive accuracy in a by-state (TTO) and by-state-pair (DCE) cross-validation approach. Out-of-sample likelihood was used in order to limit the risk of "overfitting" to any noise in the data, as use of direct model fit to the entire dataset increases the risk of erroneously attributing a set of incidental correlations occurring in that particular set of data. The results confirm the advantages of hybrid modelling and confirm the convergence and validity of the TTO and DCE valuation methodologies. The empirical finding supports the notion that the TTO and DCE tap into the	DCE but would not be able to resolve the DCE's design issues. In the absence of a burden of disease study, the committee considered both the vignette approach and the Statland et al. mapping in their decision making, and agreed that the utility increase from mexiletine would be somewhere between the values generated by these two approaches. The committee considered there was a high level of uncertainty associated with these two utility valuation approaches (please see sections 3.11 and 3.13 of the FAD).

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			same underlying preference structure in INQoL valuation, and information from DCE responses therefore improve our ability to predict TTO responses, and vice versa. In this study, we find that a model combining information from TTO and DCE improves our ability to predict both TTO values and DCE choice probabilities over using either in isolation. Models were tested both with and without intercepts, and the best 2 performing models were CALE (Cross-attribute level-effect**)** hybrid models, although the results were very similar. **Hybrid model results** The utility values for the hybrid models from the economic model are provided in table 1 below: Table 1 [redacted] **Health state BSC utility score validation** To validate the baseline levels of utility in MYOMEX (i.e. patients with NDM severe enough to be treated with NaMuscla), one method could be to use a proxy disease. NDM has some signs and symptoms which can make it difficult to choose a "closely related" condition. During the NICE meeting, Multiple sclerosis (MS) was used as a proxy measure by the chair, to understand better the plausibility of some of the results in particular from the Company's original base case. A clinical elicitation exercise was therefore conducted by proxy to MS patients (see Appendix 1). Expert NDM clinicians were asked if they could estimate where an average untreated adult NDM patient with symptoms that are severe enough for treatment with mexiletine might sit on the Expanded Disability Status Scale (EDSS)[38]. The results suggest that the total range would be between an EDSS score of 3.0 to 7.5 (very rarely), but more frequently predicted between a score of 3.0 to 6.0. Four of the six clinicians, who could make the proxy comparison, stated a specific usual mean score of 5.0 (one said 5.0+). A description of the EDSS scores is provided in Appendix 1. An EDSS patient with a score of 5.0 is described as: "*Disability severe enough to impair activities and ability to work a full day without special provisions. Able to*	

	Hybrid 1	Hybrid 2
u Mexiletine	[redacted]	[redacted]
u Placebo	[redacted]	[redacted]
Diff	[redacted]	[redacted]

Comment number	Type of stakeholder	Organisation name	Stakeholder comment (sic)	NICE Response
			walk without aid or rest for 200m". EDSS patients with a score of 3.0 have no mobility issues, but three or four mild or one moderate functional system impairment. A patient with an EDSS score of 6.0 would require a walking aid, and is able to walk 100m with or without resting. With an EDSS score of 7.5, which is described in Appendix 1 as very rare (which is aligned with the clinical expert's experience in section 3.13 of the ACD), the patient can only take a few steps and would require a wheelchair. The Patient Expert in his statement describes significant impairment to his activities prior to being treated with mexiletine, including climbing stairs, bathing, sitting down, sleeping, shaking hands, opening his eyes, speaking clearly, suffering falls and injuries, and the need to take time off work. In the MYOMEX study the vast majority of patients could not feed, dress, climb stairs, take care of their personal hygiene, walk, speak or write normally. 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] and [redacted] of patients could speak and write normally and only [redacted] described the ability to walk as normal. (Company submission document B, section B.1.3.5). During the placebo treatment period for the MYOMEX trial between two fifths and a half ([redacted]) of the patients required some help to walk 3m to 5m (see Company submission B.3.5.5), and in the stair test (5 stairs) nearly a third ([redacted]) required the use of a ramp, whilst circa a further fifth ([redacted]) had serious difficulties of ascending or descending step by step (see economic model patient level data). In the Patient Organisation submission, MDUK report from patients who describe what it is like to live with the condition: • ""*It's horrible, terrible", and also the words "awkward"; "tiring" "dangerous" and "invisible*"." • "*You can't get up from the chair…you just can't move*." • "*If I sneeze my eyes close and I can't open them*." • "*It's dangerous because of the risk of falling*." • **"***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*." • "*No one cares*". Further a carer described the condition of her sister as "*totally house bound and can't leave her flat*" In addition MDUK in their submission provided results of an online survey of 27 patients in the UK. It describes how daily lives are significantly impacted in terms of mobility, falls, activities and work. In this survey NDM patients were asked what were the symptoms that led to seeking a diagnosis, with 70.4% stating difficulty walking[39].	

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			In section B.1.3.5. of the company submission, the MYOPATH survey[12] provides insight into the multifaceted nature of disease impact from patient verbatims: • *'Lack of dexterity, movement'* • *'Difficult to breathe'* • *'Trouble swallowing – trouble eating because cannot open jaw'* • *'Always feeling on guard – being careful not to fall or have an accident'* • *'Challenges with independence' – working, walking, climbing stairs, speaking,– doing simple tasks'* • *'Difficulties at school - Bullying – social isolation – inability to participate in sports'* • *'Total desperation – feel paralysed'* Further evidence for untreated genetically confirmed NDM patients comes from a cross sectional study of 62 patients in the Netherlands[40,41]. In section B.1.3.5 of the company submission it states: "*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* "; and "*63% reported muscle weakness and 47% experienced painful myotonia. 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. Mobility impairments, such as difficulty climbing stairs (80%), standing up quickly (73%) and running (82%), were reported by patients in this study*." In a review of the literature, the two large cohort studies in the UK from Hawton et al[42] (1169 EQ-5D health state descriptions given by 565 respondents) and from Orme et al[43] (2048 respondents) have compared EDSS scores to EQ-5D scores, and the results are shown in Figure 1 of Appendix 1. Results were reported separately for relapse and remitting MS (RRMS) patients prior to primary or secondary progression for the Hawton et al study. The Company believes the evidence from the clinical elicitation exercise and the evidence provided by the Patient Expert, MDUK, the Company, available studies and patient surveys and the MYOMEX study provides some validation of the plausibility of the results of the placebo arm mean utility scores from the new Hybrid models when compared with findings of the clinical elicitation exercise. The Company appreciates that it is challenging to make comparisons across different disease areas. But NDM is a very rare disease with a significant impact on quality of life. A proxy exercise to better informed and studied disease areas could provide some plausibility of indicative NDM BSC utility estimates. Given the potential consequences for the welfare of NDM patients currently stable on NaMuscla resultant from a negative appraisal, the Company asks the committee to give the utmost consideration to the plausibility of our BSC arm	

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			mean utility scores from the new Hybrid models, based on all of the evidence provided above. **Health state Treatment utility score validation** The Patient Expert in his statement states that "with Mexiletine, the situation improved considerably" and as highlighted in section 3.2 of the ACD the "*patient expert explained that using mexiletine addressed most of the symptoms of NDM with near normal muscle function".* In the clinical elicitation process (Appendix M of the Company submission), clinicians confirmed a greater than 0.3 utility gain, supportive of the significantly positive impact mexiletine can have on an NDM patients' quality of life. This is further supported by NDM patient feedback. The clinician advisory board in July 2020 describes an NDM patient who is able to play rugby in the winter[18]. Further in the MDUK Patient Organisation submission, patients describe mexiletine as: • "*a wonder drug*" • "*I wouldn't have a proper life without it*" In the Company submission section B.2.12, the results of the pan-European MyoPath survey are provided. The ability to access mexiletine 'drastically' or 'substantially' reduced frequency of falling in 77% of NDM patients, and as a result of being treated with mexiletine, NDM patients reported a significant or drastic improvement in their ability to work (72%), exercise or play sports (75%), overall mobility (85%), drive a car (82%), child care (80%), socialise and communicate (speaking in pubic, shaking hands) (77%), and in their emotional well-being (91%). Additionally the senior clinicians from the main treating centre Queen Square (HSS), have confirmed that it is usual for mexiletine "*to improve quality of life to normal*"[21] for NDM patients (see section 3). As stated in section 5 above, the EQ-5D calculated utility for a member of the UK population is expected to be 0.87 (with an upper range of 1 or perfect health). Given the evidence from the Patient Expert, the Patient Organisation MDUK, available patient surveys and the senior clinicians from the main treatment centre Queen Square (HSS), the Company believes that there is validity of the plausibility of the results of the mexiletine arm mean utility scores from the hybrid models. **New Base case and Scenario**	

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			Given the validation evidence above, the Company now considers the Hybrid 1 model as the base case, as it is the best statistically performing model, and provided utility estimates in line with the validation results described above. The second-best performing model, Hybrid 2, is used as a sensitivity analysis. The revised Company base case (Hybrid 1) in Appendix 2b gives a cost effectiveness ratio of [redacted] The new sensitivity case (Hybrid 2) in Appendix 2b gives a cost effectiveness ratio of [redacted]	
8	Consultee (company)	Lupin Healthcare (UK) Limited	**7. Care Giver disutilities** The Company had planned to present results from a caregiver survey in order to provide further data to demonstrate the impact of NDM on carers to support the inclusion of a carer disutility within the cost-effectiveness model. However, due to ethical approval delays, the survey remains on-going[7]. The Company however agrees with the ACD that NDM can affect the quality of life of both patients and caregivers (ACD section 3.1). In the Patient Organisation submission, MDUK report from caregivers who describe what it is like to care for someone with NDM: • **"***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*." • "*I feel embarrassed for him. It triggers Myotonia and people think he's drunk*". • "*You feel helpless. I'm always worrying that they'll fall when (they) get a spasm*." • "*It's the pain side that you can't help with and you feel really bad because you can't do anything*." • "*It's really hard*." Furthermore, a caregiver explained that for her sister suffering from NDM 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*." As such, the Company believes it is appropriate to consider the impact on carer HRQL within the cost-effectiveness estimates. In the technical engagement, scenarios were presented based on caregiver studies for both Duchenne Muscular Dystrophy (DMD) caregivers and Multiple Sclerosis (MS) caregivers. The ACD suggests that the disutility values described in the Company technical engagement response and also used in the appraisal for	Thank you for your comment. The committee acknowledged the impact that being a carer for someone with NDM has. However, the number of patients that require care is highly uncertain, and the disutility that would occur was also highly uncertain. The committee concluded that it had not seen enough evidence to justify including consideration of carer quality of life, and that inclusion of this assumption is highly uncertain and should be removed (please see section 3.14 of the FAD).

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			ataluren for treating DMD are inappropriate for this appraisal because the disutility represents carers of non-ambulatory patients, who are very rare in NDM. However, this was incorrectly reported by the Company in the technical engagement response, as the primary source does not differentiate between ambulatory and non-ambulatory patients for this carer disutility (both ambulatory [56%] and non-ambulatory [44%] DMD patients were included in the study)[44]. The Company applied a conservative [redacted] as the input for the proportion of DMD caregiver disutility, based on feedback from the clinical ad board[45] in November 2018 (see Company's response to technical engagement Issue 5). In order to explore further scenarios regarding NDM carer disutilities, the study by Acaster et al[46] , previously submitted during the technical engagement response, showing carer HRQL for MS patients, was further explored. The study examines caregiver disutilities against patient determined disease steps (PDSS) score[47] for MS patients. EDSS and PDSS scores have been shown to be highly correlated, and a score of 4.0 or 5.0 on the EDSS scale could be interpreted as approximate to a score of 2.0 to 3.0 on the Patient determined disease steps (PDSS) scale[48]. The more severe PDSS score of 3.0 is described as: "*Gait Disability: MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually doesn't need a cane or other assistance to walk, but I might need some assistance during an attack*." Given this description, the Company believes it is plausible that the health state for a NDM BSC patient could be justified by disease proxy comparison given the evidence provided by the Patient Expert, MDUK, the Company, available studies and patient surveys and the MYOMEX study in section 6 above. From the evidence of the Patient Expert, the Patient Organisation MDUK, available patient surveys, the senior clinicians from the main treatment centre Queen Square (HSS) (see section 6 above), and from the Delphi panel[27], there is a clear expectation that the quality of life of caregivers of NDM patients treated with NaMuscla would be positively impacted. From the Acaster et al study the estimated disutility of a caregiver of an MS patient with a PDSS score of 2.0 to 3.0 was found to be -0.045. This value is greater than those investigated by the Company at technical engagement, and suggests that the Company base case value used previously (an average of -0.022 per patient) may even be conservative. The ERG agrees with the inclusion of the -0.022 caregiver disutility and therefore, given the evidence above, the Company proposes to not change the -0.022 disutility in its revised base case (see Appendix 2b). The Company acknowledges that its revised base case compares NaMuscla with placebo, however given the	

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			potentially extreme uncertainties highlighted in Section 2 above for other sodium channel blockers, the Company believes placebo is the most appropriate..	
9	Consultee (company)	Lupin Healthcare (UK) Limited	In section 3.6 of the ACD, the potential for carry over effect and unblinding is raised for the MYOMEX trial. "*The committee concluded that potential for unblinding and carry-over effects, short trial duration and few patients contribute substantial uncertainty to the MYOMEX results*" The Company acknowledges the short duration of the trial and patient numbers, however this is a very rare condition, and long-study durations 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 from both the MYOMEX long-term follow up[6] (mean duration 48 months) and the Suetterlin et al study[5] (mean duration 4.8 years). Supporting long-term use, the patients who were non-naïve to mexiletine in the MYOMEX study (and who stopped taking mexiletine at screening) had an average treatment duration of circa a decade[2] prior to study start, and the Patient Expert has been successfully treated for c20 years (see Patient Expert statement) which demonstrates that efficacy of mexiletine is maintained over the long-term. The Company has evidenced in its submission (sections B.2.6.1 and B.2.13.2) and its response to the ERG's clarification questions (Question B12), that for 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. In the Company's response to the ERG's clarification questions (Question A8), and in the Company's response to the Technical engagement (Issue 5), the Company evidences in the statistical analysis that there are no differences between naïve and non-naïve subjects, either in the placebo or in the mexiletine groups. Those patients naïve to mexiletine perceived the treatment event more efficacious than those that were previously exposed suggesting that there was no bias effect in non-naive patients. Therefore, any previous treatment with mexiletine did not influence the expectations of the patients with respect to treatment effect. In the Company's submission (Section: B.2.6.1, and section B.2.13.1), and in its response to the ERG questions (Question A10), the Company evidences that the statistical analysis did not show a difference in treatment effect for treatment periods with no evidence of a carry-over effect (treatment sequence effect). A mixed effect linear model on ranks and statistical analysis used to assess the efficacy results showed that treatment sequence did not have significant effect. Since the p-value associated with the sequence fixed effect was > [redacted], the carry-over effect was to be ruled out. Results for the VAS score showed that treatment sequence did not have significant effect (p [redacted]), ruling out any potential carry-over effect. Lastly the 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	Thank you for your comment. The ERG noted and the clinical expert agreed that the recognisable side effects of mexiletine could have effectively unblinded patients to which treatment they had. This is supported by the Statland et al. study in which around 80% of patients correctly guessed which treatment they had. People in the MYOMEX trial had a 4 to 8 day wash-out period. The ERG noted the Statland et al. trial had at least a 7 day wash-out period and there was a statistically significant carry-over effect. The committee concluded that potential for unblinding and carry-over effects, short trial

Comment number	Type of stakeholder	Organisation name	Stakeholder comment (sic)	NICE Response
			bias found for MYOMEX (see section D1.3 of the company submission, and the company's factual accuracy check of the ERG report – Issue 1). In summary, this evidence was required by and accepted by the EMA[49] in order for NaMuscla to receive its licence. The potential carry over effect and unintentional blinding were not evidenced in the MYOMEX trial, and no risk of bias has been found. The Company therefore does not believe that relevant evidence provided above has been taken into account.	duration and few patients contribute substantial uncertainty to the MYOMEX results (please see section 3.6 of the FAD)
10	Consultee (company)	Lupin Healthcare (UK) Limited	**9.Resource use should remain 3 x multiplier** In round 1 of the Delphi panel clinical experts were asked to provide the frequency of resource use and the estimated number of people using the resource. These questions were asked for both patients treated with NaMuscla and those of Best Supportive Care (BSC). In the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, Page 9, the ERG notes: *However, within Round 1 of the Delphi process, the experts were asked to estimate the frequency of resource use for adult NDM patients receiving 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.* The relevant questions from round 1 of the Delphi panel[27] pertaining to BSC are provided below: *"Question 10: From your experience, please provide an estimation of the percentage of adult patients with NDM, who receive BSC, that would use each type of resource in the table below. Please ensure that the values are between 0-100%".* *"Question 13: Of the adult patients with NDM who receive BSC who make use of a resource, please provide an estimation of how often that patient would use the resource per year (in numbers)".* In Question 13 it is clear that the number of visits are conditional on the patient using the resource in the first place, and not applicable to all patients. It should be noted the questions for BSC patients were posed the same way for NaMuscla treated patients in the Delphi panel questionnaire, and in the model for NaMuscla treated patients the number of patient visits are conditional to the patient using the resource in the first place. The Company believes consistency should apply for both NaMuscla and BSC arms.	Thank you for your comment. The x multiplier includes both the estimated frequency of resource use and the estimated number of people using the resource, when only the frequency of resource use is needed for use in the model (please see section 3.15 of the FAD).

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			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. As such a multiplier of [redacted] is applied in the Company's model, which may be conservative. Additional Delphi panel[27] findings suggesting that there could be additional support needed for NDM patients in the form of mental health visits to a psychologist or general practitioner were not considered in the cost-effectiveness model. 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 further underestimate the difference in resource use costs between arms. The Round 1 questionnaire of the Delphi panel has been submitted again separately to the main report.	
11	Consultee (company)	Lupin Healthcare (UK) Limited	**Disease Progression** Given the uncertainty of the natural history of the disease, the Company has removed any disease progression assumptions from its base and scenario economic cases. **Statland trial** In section 3.4 of the ACD it states "*Statland et al. (2012) – a randomised crossover trial of 56 patients*". The Company understands that the number of patients recruited for the Statland trial was 62, with 59 patients randomised for treatment **NDM patients over 65** In the section 3.5 of the ACD it states: "*The Company noted that most people over 65 with NDM are on treatment with mexiletine*". The Company doesn't believe it has noted this in the evidence. **Mexiletine Formulation** In section 3.7 of the ADC it states: "*NaMuscla is a new formulation of mexiletine that uses different dose measurements to previous off-label use (a 167 mg capsule of NaMuscla formulation [mexiletine base] is equivalent to 200 mg of imported mexiletine [mexiletine hydrochloride]). However, all the clinical evidence uses the imported formulation of mexiletine."* The Company believes this section of the ACD seems confusing. For clarity, NaMuscla contains mexiletine hydrochloride, and 200 mg mexiletine hydrochloride corresponds to 167 mg of mexiletine[50]. **Adverse Events (AEs)** In section 3.7 of the ACD it says *"The committee considered that because of the short duration of the MYOMEX trial, some adverse events might not have been reported. In clinical practice, such adverse events could take much longer than the MYOMEX trial duration to emerge."*	Thank you for your comments. Section 3.4 of the FAD has been updated to reflect the number of patients in the ITT population in Statland et al. The wording in section 3.5 of the FAD has been altered to better reflect the company's input at technical engagement regarding the treatment of people with NDM over 65. The wording in section 3.7 of the FAD has been altered to make it clearer for the reader. The wording in section 3.10 of

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			In our response to the technical engagement, the Company noted that it believed 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[5]. The Company amended its base case because the MYOMEX study and the Suetterlin et al study have relatively similar AE rates, and AEs are not a large driver of the cost-effectiveness results, and to align with the Technical teams assumption of the MYOMEX AE input in to the base case. Comparison analysis of our revised base case with MYOMEX AEs, and with Suetterlin AEs is provided below: The revised Company base case (Hybrid 1) with MYOMEX AEs gives a cost effectiveness ratio of [redacted] The revised Company base case (Hybrid 1) with Suetterlin et al AEs gives a cost effectiveness ratio of [redacted] **MYOMEX and Suetterlin responders** In section 3.8 of the ACD it states: "*The committee also noted that not everyone in clinical practice would be expected to respond to treatment with mexiletine; MYOMEX and the Suetterlin et al. study selected patients that would be more likely to respond (see section 3.6).*" For the Company's revised base case (see Appendix 2b), the model does not assume every patient responds. The discontinuation applied to the revised base case the Company believes is conservatively applied (8% from Myomex trial is higher than others reported from Statland et al[3], Stunnenberg et al[4] or Suetterlin et al[5]). There are a number of patients ([redacted]) who didn't respond with lower utility values on mexiletine than on placebo in the revised base case (see Economic model patient level data). Additionally it isn't clear in section 3.6 why the MYOMEX or the Suetterlin et al. would have selected patients that would be more likely to respond. Suetterlin et al is a retrospective study of clinical practice, whereas for the MYOMEX study the Company evidences that any previous treatment with mexiletine did not influence the expectations of the patients with respect to treatment effect (see section 8). **EQ-5D-3L** In section 3.10 of the ACD it states: "*The Company considered that generic quality-of-life measurement tools such as the Short Form 36 (SF-36) or EuroQoL 5 dimensions (EQ-5D-3L) are unable to effectively capture the quality-of-life implications of muscle locking in NDM*". The Company doesn't believe it has stated in the evidence that EuroQoL 5 dimensions (EQ-5D-3L) are unable to effectively capture the quality-of-life implications of muscle locking in NDM in the evidence. From a review of the literature, EQ-5D has never been used in this disease area, and therefore the suitability of this tool in capturing quality of life in this patient population is unknown. **Mobility** In section 3.13 of the ACD it states "*no patients in MYOMEX needed to use wheelchairs or walking aids*." For	the FAD has been amended to reflect that the company considered that suitability of EQ-5D to capture quality of life implications of muscle locking is unknown. Section 3.14 has been amended to note the walking test aspect of the MYOMEX trial.

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			clarity, Company is only aware that no patients in the MYOMEX trial needed a wheelchair or walking aid to complete a walking test of 3 to 5 meters (see section B.3.5.5 of the Company submission). **467mg mean effective dose** In the lead team slides, slide 15, it states "*Applying mean doses stratified by genetic subgroup from Suetterlin et al. population to the Statland et al./MYOMEX population gives a mean effective dose of 467mg*" This calculation is provided by the ERG in their ADDENDUM: Critique of the Company's response to Technical Engagement, page 3, which relies on 40 patients with a chloride channel mutation requiring a mean dose of 550mg mexiletine hydrochloride. This is incorrect from the Suetterlin et al[5] study, only 10 patients are reported to be on this dose, and therefore the calculation is an error. **MS Patient utility** In the lead team slides, slide 26, it states that "*the company compares utility of NDM to multiple sclerosis. Reference EQ-5D utility value for an ambulatory but relatively severely disabled multiple sclerosis patient – and provides a utility value of 0.59."* The Company does not believe it has compared the utility of NDM to a multiple sclerosis patient with a utility value of 0.59.	
12	Consultee (professional organisation)	Association of British Neurologists	We do not feel it is reasonable to consider that lamotrigine and other sodium channel blockers are equivalent or a comparator to mexiletine. In our practical experience going back several decades, drugs such as carbamazepine, flecainde and phenytoin have not been efficacious and patients do not stay on them in the long term due to lack of efficacy and side effects. Lamotrigine is very rarely used at present and in current practice we have not found it to be as effective and has a high discontinuation rate amongst patients. We have found that we require high doses of over 150mg a day to see an effect and that a number of patients report not having any improvement in symptoms. A direct comparator trial of mexiletine and lamotrigine is currently being set up but the results for this are likely to take several years.	Thank you for your comment. The committee considered that the comparator for this appraisal would be the treatment people would have if mexiletine was not available. Due to evidence from clinical and patient experts, this was determined to be lamotrigine or another sodium channel blocker (please see sections 3.2 and 3.3 of the FAD).
13	Consultee (professional organisation)	Association of British Neurologists	We feel that it is unethical for the appraisal to recommend discontinuation of mexiletine for those patients already established on treatment. We have found in our clinical experience and during the Statland et al study	Thank you for your comment. The remit of this

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			that sudden termination of mexiletine results in a significant worsening of symptoms for patients for a prolonged period. We are concerned that those patients who are already established on the drug would be left worse off because of this recommendation.	appraisal was to assess the clinical and cost effectiveness of mexiletine (Namuscla).
14	Consultee (professional organisation)	Association of British Neurologists	Although the National Hospital for Neurology and Neurosurgery in London are currently able to get some supply of the generic mexiletine in 100mg doses. This supply is intermittent and frequently unavailable. This results in patients frequently being unable to access treatment when they need it and has been a frequent occurrence in the past 10 years prior to the availability of Namuscla. It is our understanding that other neuromuscular centres around the country do not have access to any supply of generic mexiletine and therefore when Namuscla is no longer available it is likely to cause significant problems with supply in other parts of the country and an inequality in treatment across England.	Thank you for your comment. NICE's remit for this appraisal was to appraise Namuscla.
15	Clinical expert (Fiona Norwood)	N/A	A proven and effective drug – mexiletine – potentially will not be available for patients with non-dystrophic myotonia (NDM). This drug is currently used first-line for the vast majority of NDM patients. To date comparators such as lamotrigine have been used in only a very small number of patients nationally.	Thank you for your comment.
16	Clinical expert (Fiona Norwood)	N/A	The only licensed drug for this group of conditions will not be available.	Thank you for your comment.
17	Clinical expert (Fiona Norwood)	N/A	An unlicensed drug for NDM – lamotrigine – is recommended by NICE as first-line treatment, on the basis of one small trial. The justification for this, especially given the licensed drug availability and efficacy, is unclear.	Thank you for your comment. Lamotrigine was not recommended as first-line treatment for NDM but rather considered as a comparator to mexiletine. The committee concluded that comparing mexiletine with best supportive care was not appropriate because, if mexiletine were not available, people would be

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				offered other active treatments such as lamotrigine or other sodium channel blockers (please see sections 3.2 and 3.3 of the FAD).
18	Clinical expert (Fiona Norwood)	N/A	There has been no evidence to show that lamotrigine is superior – or equal to – mexiletine in an RCT. A comparator trial would be useful but is not available, hence the rationale for changing the status quo is unclear.	Thank you for your comment. The committee concluded that comparing mexiletine with best supportive care was not appropriate because people would be offered other active treatments such as lamotrigine or other sodium channel blockers if mexiletine was not available (please see sections 3.2 and 3.3 of the FAD).
19	Clinical expert (Fiona Norwood)	N/A	Patients who are established on the licensed form of mexiletine (NaMuscla) will have this treatment withdrawn, with likely recurrence of symptoms. A number of my patients have expressed alarm at this possible outcome.	Thank you for your comment. The remit of this appraisal was to assess the clinical and cost effectiveness of mexiletine (Namuscla).
20	Clinical expert (Fiona Norwood)	N/A	As a prescriber I will not be able to justify prescribing an unlicensed, unproven drug when the licensed drug is available. Having discussed with my pharmacist, this puts us in a very difficult and uncertain position.	Thank you for your comment.

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21	Consultee (patient organisation)	Muscular Dystrophy UK	We are concerned that this recommendation would mean that patients who are currently successfully managing their condition with Namuscla would no longer have access to this treatment. Following conversations with clinical experts, we feel that it is wrong to suggest that there is a supply of mexiletine readily available from alternative sources that patients could access instead. Cessation of Namuscla treatment is likely to cause widespread anxiety due to the uncertainty of supply of other forms of mexiletine from alternative sources, and places an undue onus on individual clinicians to source supplies of mexiletine; time that would be better dedicated to supporting patients if a guaranteed supply of Namuscla was available. An individual who has been successfully managing their condition with mexiletine/Namuscla for several years told us of their concerns, which are two fold – for their own experience and for those of their family members: 1) I am well aware of the impact that not having this medication has on my quality of life and the thought that this would how I would have to live my life in the future is very stressful indeed. The lack of control over my condition means that the resultant implications for all aspects of my future life would be would be dramatic. I foresee a lack of mobility and increasing pain and muscle stiffness leading very quickly to me becoming far more housebound, which as I am in my 50s is a pretty frightening thought. This consequence as well significantly impacting my physical health through reduced mobility will also impact my quality of life with my family and have resultant mental wellbeing implications not just for me but for them as well. As a parent of a child with complex special needs who enjoys our daily walk as a particular highlight of both their and my day as a shared experience, the thought that this will not be possible as we look to the future is really actually very upsetting. 2) And then for those who will be denied access to this treatment in the future I am equally worried. I am very conscious of the impact this medication has on my quality of life and therefore I fear for my other teenage child, who has been diagnosed with myotonia (but is not yet taking medication) as to their future because that option will not be available to them. They already struggle with stiff and aching muscles, and the thought that they will have to endure this for the rest of their life, without the benefits this medication provides, is very upsetting. They are bright, clever and ambitious and I am confident that in the future they will add much to society but my fear is that without medication they will be unable to fulfil that potential, which as a parent causes me great sadness.	Thank you for your comment. The remit for this appraisal was to appraise Namuscla. The committee heard from stakeholders and members of the public about their concerns regarding access to treatment.
22	Consultee (patient organisation)	Muscular Dystrophy UK	Mexiletine is the first line of treatment for non-dystrophic myotonia in adults and it alleviates symptoms rapidly. We are therefore concerned that patients who have to switch to a new treatment, and newly diagnosed patients, will have to spend many months adjusting the dosage of a new drug (e.g. lamotrigine) before it is acceptable and tolerated. In addition, we are concerned by reports from clinicians about the possible harmful side-effects of lamotrigine. We are concerned that the removal of an effective treatment that is well-tolerated would be unfair and unethical.	Thank you for your comment. Comments regarding the impact of withdrawal and the need for a withdrawal

Comment number	Type of stakeholder	Organisation name	Stakeholder comment (sic)	NICE Response
				regimen were discussed at the second meeting. The remit for this appraisal was to appraise Namuscla. The committee heard from stakeholders and members of the public about their concerns regarding access to treatment.
23	Consultee (patient organisation)	Muscular Dystrophy UK	We are concerned by reports from clinicians that the symptoms of myotonia can be more severe if treatment stops suddenly, therefore, a careful withdrawal regimen would need to be worked out for each patient. This again will cause unnecessary stress and anxiety to patients and their families.	Thank you for your comment. Comments regarding the impact of withdrawal and the need for a withdrawal regimen were discussed at the second meeting.
24	Consultee (patient organisation)	Muscular Dystrophy UK	We are extremely disappointed that current recommendation is that “The cost-effectiveness estimates for mexiletine are much higher than what NICE considers a cost-effective use of NHS resources and would potentially be higher if compared with other sodium channel blockers rather than best supportive care”. Clinical evidence has shown that mexiletine/Namuscla is effective in managing non-dystrophic myotonia in adults. Given the concerns raised by clinicians with whom we have spoken regarding the potential use of other sodium channel blockers to treat this condition we hope that measures can be taken to readdress the cost-effectiveness and reverse this recommendation.	Thank you for your comment.
25	Consultee (patient organisation)	Muscular Dystrophy UK	Together with other patient groups, we are deeply concerned by the precedent that would be set by the proposed removal of Namuscla from patients who are already receiving the treatment. As noted in the ADC document, this is a significant departure from previous practice and one that would have a profound impact not only on those patients immediately effected in this case but on future patients receiving other treatments for other conditions where this approach could be repeated.	Thank you for your comment. The remit of this appraisal was to assess the clinical and cost effectiveness of mexiletine

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				(Namuscla).
26	Members of the public	Web comments	*Impact of removing mexiletine* • Without the provision of mexilitine by the NHS my quality of living and would likely return to that of the time of my diagnosis where I struggled to perform everyday activity's likely also causing negative impacts on my mental health and well-being. • In 2008 Boehringer Ingelheim discontinued manufacturing of Mexitil (mexiletine hydrocholoride). Many patients in Europe were taking mexiletine at the time to treat non-dystrophic myotonia. It caused a great deal of concern in a support group for NDMs and I followed the subsequent attempts to find an adequate replacement. Most were put back on carbamazepine or phenytoin and a few on flecainide. The anti-epilepsy drugs (AEDs) helped somewhat with the myotonia, but had significant psychiatric side effects in younger adults in particular, including depression. The flecainide was helpful for the sodium ion channel myotonias, but not as effective as mexiletine for the chloride ion channel myotonias. Some patients lost their jobs over this change because they had been functioning so well on the mexiletine and lost that functionality or had to deal with the mental side effects of the AEDs. • Mexiletine is the most effective medication used by the members of our group. While some may experience GI side effects, Lupin has demonstrated that their formulation is better tolerated than the generic mexiletine. Taking away that option for people with NDMs is going to cause problems for many of our members who have been functioning at a level they consider significantly higher compared to no treatments or the other alternatives. • I am disappointed that the committee rejected the study recommendations and that they will discontinue access to mexiletine completely in the UK, even for those already taking the medication successfully. This is going to be devastating to many of our support group members. Unlike AEDs, mexiletine works immediately and has no withdrawal period. • I fear that some will lose their jobs because going through the process of adapting to a new medication will take time and disrupt many lives. • It is no exaggeration to say that if I was unable to have this medication, and without a suitable alternative that delivered the same results, I would not be able to live any kind of normal life. • if this guidance remains unchanged we will have a situation whereby patients that are largely asymptomatic on mexiletine will have to be transferred to an unlicensed and as yet unproven treatment. • The draft guidance if finalised unaltered will deny known effective treatment for those disabled by myotonia and prevent them from having a much fuller life than is possible.	Thank you for your comments. The concerns raised regarding possible side effects and mental health consequences of treatments were discussed at the second meeting, as well as potential impact on the ability to work.

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			• Some members reported that supply of the generic version of Mexiletine is erratic, and sometimes may not be available for weeks or months. Thus, patients taking this form of Mexiletine may sometimes have to interrupt treatment. Suddenly stopping treatment worsens their symptoms. Thus colleagues, particularly from the larger centres, expressed concern that this decision by NICE would impact significantly upon patient quality of life. • Not having the stress and worry of my partner falling over when her legs lock and potentially causing further bodily harm (and potential further costs to the NHS through hospital visits) by hitting her head, or cutting her hand if she was carrying a glass for instance, both of these scenarios have already been played out before mexiletine. • We have together a much much better quality of life with mexiletine in our lives, of course with lockdown we have been limited, but even going out for walks together or doing exercise regimes has greatly helped our fitness and weight, and just as importantly our mindfulness and wellbeing, all of this is lost without mexiletine. The disease will progress at the quick rate it was before the appropriate treatment and cause a significant life long impact on daily life for my partner and those close.	
27	Members of the public	Web comments	*Comparison with other sodium channel blockers* • most of the patients on mexiletine at our neuromuscular centre have already tried and failed other sodium channel blockers. • The availability of other sodium channel blocking agents with lamotrigine having the highest level of evidence (RCT placebo-controlled) cannot be compared to Namuscla due to study capture outcome measures and therefore the standardised effect sizes cannot be compared. • The BMS council members do not consider Lamotrigine to be first line treatment for non-dystrophic myotonia because it may take many months to be effective and there is a risk of serious side-effects. • Other drugs mentioned in this report: Carbamazepine and Phenytoin were not deemed to be clinically effective, which is why there have not been trials comparing these agents with Mexiletine. • the evidence and the personal experience of trialing sodium channel blockers such as lamotrigine has been very limited. It has not thus far impressed me as being a dramatically successful and I am uncertain as to the outcome of any RCT evidence in its favour that might arise. • The clinical effectiveness of lamotrigine as an alternative treatment for NDM has been over-stated.	Thank you for your comments. The committee considered that the comparator for this appraisal would be the treatment people would have if mexiletine was not available. The clinical experts stated that patients would receive another sodium channel blocker in the absence of mexiletine. Lamotrigine is also sometimes used if mexiletine is contraindicated,

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			• Although other sodium channel blockers are used (such as Lamotrigine and Carbamazepine), in my clinical experience their efficacy is less well established and the literature reflects this. • The alternative drugs mentioned are not going to be acceptable for many patients and will result in diminished quality of life for those who are currently taking the medication and thriving. • Lamotrigine has been proposed as a primary substitute by the committee. Feedback from our support group indicates that it has been helpful for some who were being treated concomitantly for depression and were able to combine that and myotonia treatment into one medication. However many have noted psychiatric side effects with lamotrigine as well. • flecainide was helpful for the sodium ion channel myotonias, but not as effective as mexiletine for the chloride ion channel myotonias.	not effective or not tolerated (please see sections 3.2 and 3.3 in the FAD). The concerns regarding possible side effects and mental health consequences of lamotrigine were discussed at the second meeting.
28	Members of the public	Web comments	*Outcome measures* • I would comment on the use of INQoL as the QoL measure that has been used in the Namuscla trial, results of which have been part of the evidence submission to NICE. [redacted]. It is a muscle disease specific QoL and it includes specific questions on myotonia that are of course particularly relevant to ask of those on treatment for myotonia. It has been around for 20 years and is a validated measure in widespread use for muscle disease studies and trials, including muscle diseases with myotonia. • I believe the INQOL and other outcome measures in the MYOMEX study are entirely appropriate for this population, albeit short term. I do not think the ERG has given enough credit to these clear-cut outcome measures and positive effect sizes of Namuscla treatment. These cannot be compared with other RCTs. • The availability of other sodium channel blocking agents with lamotrigine having the highest level of evidence (RCT placebo-controlled) cannot be compared to Namuscla due to study capture outcome measures and therefore the standardised effect sizes cannot be compared. • The neuromuscular outcome measures captured in the Myomex trial where much more comprehensive and reflective of this population, albeit being a short-term trial.	Thank you for your comment. The ERG considered that the company did not show that generic measures of quality of life are unable to measure health-related quality of life of people with NDM. The committee noted that generic quality-of-life instruments are included in the NICE reference case to achieve consistency in decision making across different diseases. The committee considered that

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				domains such as physical function and activity in the SF-36 matched issues described by the patient expert (please see sections 3.10 and 3.12 of the FAD).
29	Members of the public	Web comments	*Carer quality of life* • If funding for mexiletine is withdrawn, then I am faced with a lifetime of care, helping my partner get up from a chair, or move about the house for fear of falling. This could lead to me having to give up my job to be a full time carer for my partner, I may have to claim benefits, yet another cost to funding. • As a partner of somebody diagnosed with Paramyotonia Congenita I cannot agree with this recommendation, especially 3.13 'The reduction in quality of life for carers of people with NDM should be removed as an assumption'. • Since starting mexiletine there has been a 'night & day' change to my partner's life but also my own. • Not having the stress and worry of my partner falling over when her legs lock and potentially causing further bodily harm (and potential further costs to the NHS through hospital visits) by hitting her head, or cutting her hand if she was carrying a glass for instance, both of these scenarios have already been played out before mexiletine.	Thank you for your comments. The committee acknowledges the impact that being a carer for someone with NDM has. There was not enough evidence regarding the prevalence and magnitude of carer disutility in NDM to be able to include it as an assumption (please see section 3.14 of the FAD).
30	Members of the public	Web comments	*Supply of generic mexiletine* • Some members reported that supply of the generic version of Mexiletine is erratic, and sometimes may not be available for weeks or months. Thus, patients taking this form of Mexiletine may sometimes have to interrupt treatment. • sourcing reliable supplies of an rarely used drug became increasingly problematic.	Thank you for your comments. The remit of this appraisal was to assess the clinical and cost effectiveness of mexiletine (Namuscla).
31	Members of the public	Web comments	*Possible equality considerations* • I hope disability from a rare disorder has been appropriately addressed	Thank you for your comments. The committee considered

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			• It is a discrimination against the disabled to take away the drugs that allow them to lead a normal life • The draft guidance if finalised unaltered will deny known effective treatment for those disabled by myotonia and prevent them from having a much fuller life than is possible. • I do believe this is discrimination based on disability. By stating that the impact on quality of life is not significant enough to warrant the cost is discriminatory. The committee members have no idea what it is like to live with this condition 24 hours a day; wheelchair use should not be the criteria for the government's support. The alternative drugs mentioned are not going to be acceptable for many patients and will result in diminished quality of life for those who are currently taking the medication and thriving. Mexiletine is life-changing for so many patients, and removing it completely as one of the options for treatment is harsh and insensitive. • Lamotrigine has been proposed as a primary substitute by the committee. Feedback from our support group indicates that it has been helpful for some who were being treated concomitantly for depression and were able to combine that and myotonia treatment into one medication. However many have noted psychiatric side effects with lamotrigine as well. It is also affected by estrogen and must be monitored if women use birth control or hormone replacement therapy. And there are studies showing possibility of an increase in cleft palate or cleft lip if a woman becomes pregnant while taking lamotrigine.	equality issues that apply to this topic. There were no equalities issues that could be addressed by the committee. Please see sections 3.18 and 3.19 of the FAD and the Equalities Impact Assessment for further discussion on the potential equalities issues identified in this appraisal.

No consultation comments were received from other stakeholders.

NICE National Institute for Health and Care Excellence

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders [ID1488]

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 5 March 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The appraisal committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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**]

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Consultation on the appraisal consultation document – deadline for comments 5:00pm on 5 March 2021 **email:** NICE DOCS

Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	The Company is disappointed with the Appraisal Committee's preliminary decision that NaMuscla is not recommended, within its marketing authorisation, for treating the symptoms of myotonia in adults with non-dystrophic myotonic disorders (NDM). NaMuscla is the only licensed established treatment for NDM patients. The Company is deeply concerned for those patients who are stable on this efficacious and well tolerated treatment following NICE's preliminary decision to depart from its usual practice for ensuring continuity of patient treatment. Instead commissioners are not required to continue to commission treatment if there is a negative guidance. The Company welcomes the opportunity to comment on the preliminary recommendation detailed in the appraisal consultation document (ACD) and are committed to working with NICE to address the Committee's key concerns, and to working with NHSE&I to ensure a continuity of treatment for adult NDM patients. The budget impact for this medicine in Year 3 at our revised PAS is circa [redacted], which represents a medicine already established in clinical practice. The Company has met with NHSE&I and NICE to discuss potential managed access arrangements to alleviate the uncertainty of cost to the NHS, and would welcome further discussions. NDM is a rare condition affecting 0.75 in 100,000 patients[1] with funded genetic diagnosis in only one key centre (Queen Square Highly Specialised Service (HSS)). There are no other licenced treatments in this disease area and no national clinical guidelines. As such the clinical symptoms and quality of life impact of the disease can be overlooked. Given the rarity, it is no surprise that there is little data for this disease and, as such, the Company consider that a Highly Specialised Technology review may have been more appropriate. Despite this, the Company has invested in this disease area and has provided a comprehensive package to demonstrate the long-term safety and efficacy of mexiletine, and the significantly improved quality of life for NDM patients. Supporting evidence includes three randomised controlled studies[2,3,4], that enrolled a total of 115 patients and demonstrated the significant treatment effect for mexiletine, and two long-term studies[5,6] that evidence long-term efficacy and safety. Additional long-term safety is supported by several periodic safety update reports (PSURs) (see Company submission B.2.10.5). This level of evidence is uncommon in such a rare disease. Further evidence has been provided to support this appraisal including a Delphi panel, clinical elicitation exercises, market research and patient surveys; insights that hitherto did not exist in this disease area. The Company continues to invest in this disease area and to generate further insights for patients and caregivers alike, with the objective to ensure this disease and the patients are no longer "invisible". These include, but are not limited to: ➢ The mapping of patient pathways and identification of system blockages to improve patient access and to decrease the significant time to diagnosis (approximately 8 to 12

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	years – see Company submission section B.1.3.4.), improving patient outcomes and improving education. ➢ The largest NDM patient survey to date, to increase the understanding of burden of disease and awareness of NDM (on-going)[7]. ➢ The first and only NDM caregiver survey to, for the first time, understand the burden of caring for patients with NDM (on-going)[7]. ➢ A prospective non-interventional post-approval safety study, which will also collects patient-reported outcomes over 5 years (including two sites in the UK)[8]. (NCT04616807) ➢ The first trial ever in paediatric patients, allowing efficacy and safety to be assessed in this age group with additional NaMuscla strengths[9]. NCT04624750) ➢ A 24 month open-label extension study for paediatric patients who have completed the clinical trial to continue to study the long-term safety and efficacy of treating myotonia symptoms in paediatric patients[10]. (NCT04622553) The Company is pleased to be able to provide further supporting data to the appraisal process, *which can be found in the Appendices to this response.* Appendix 1: Clinical Elicitation for utility comparisons and comparators Appendix 2a: Utility valuation analysis Appendix 2b: Updated company deterministic base case and scenario analyses At this extraordinarily difficult time during the COVID pandemic the Company would like to thank clinicians, patients, caregivers and the wider NICE & NHSE&I teams who continue to provide their time and expertise within this technology appraisal.
1 Usage of special mexiletine	**1. The availability of unlicensed special mexiletine is uncertain and is very rarely used instead of NaMuscla to treat adult NDM patients.** In section 1, page 3 of the ACD it states: *"**Why the committee made these recommendations*** *Treatments for the symptoms of myotonia in adults with non-dystrophic myotonic disorders already include imported mexiletine (that is not licensed in the UK)".* This statement is supported in section 3.7 of the ADC where it states: *"The clinical experts stated that most patients currently have between 300 mg to 400 mg of imported mexiletine"* For clarity special unlicensed mexiletine alone is not currently routinely used to treat adult NDM patients; It is used in cases of exception, for purposes of titration or when the HCP uses doses which is outside that of the NaMuscla licence. The Company does not believe that the evidence reflects that most patients currently have 300mg to 400mg of imported (unlicensed) mexiletine hydrochloride. A dose of 300mg or 400mg mexiletine hydrochloride will almost certainly include NaMuscla. The place and usage of special unlicensed mexiletine is described in the commissioning expert statement as: *"to support titration"* and *"where the maximum tolerated dose cannot be met by the branded product".* This later point being supported by an example of paediatric patients who do not form a part of this appraisal. In their technical engagement response the Association of British Neurologists (ABN) also only describes special unlicensed mexiletine in the titration process: *"100mg tablets of mexiletine to slowly up titrate".* Indeed the use of special unlicensed mexiletine should only be used where the special need of the patient cannot be met by NaMuscla and would be inconsistent with the requirements for the use of "specials" as described in the MHRA's Guidance Note 14[11].

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	In the interest of patient safety the exemption for the use of a special import unlicensed medicine is narrowly drawn by the MHRA, because unlike a licensed medicine they may not have been assessed by the licensing authority in the same way against the criteria of safety, quality and efficacy. NaMuscla is the only licensed medicine for the treatment of myotonia in NDM patients, and is supported by a dedicated medical information team, with on-going post authorisation pharmacovigilance, PSURs, a NaMuscla risk management plan and a post authorisation observational study to monitor safety as a primary outcome, and efficacy and quality of life as a secondary outcome. The supply of any strength of special imported unlicensed mexiletine has been and continues to be uncertain[12-17], whilst the readily available licensed NaMuscla provides a "*uniformity of supply*" (see Clinical Expert statement). Clinicians routinely report to the Company that special mexiletine is not available to them from their hospital pharmacy, as pharmacy comply with the MHRA guidance note 14, or because of sporadic supply. In addition, the quality checks and release of special unlicensed medicines from quality assurance teams in hospital pharmacies can be a lengthy and time consuming process requiring specialist pharmacist checks, and could also impact healthcare provider teams. The Company understands in its most recent correspondence with the MHRA, that imports of special unlicensed 200mg mexiletine hydrochloride for patient use in the UK is negligible. The Company understands that the majority of clinicians now titrate using NaMuscla[18], and as the ABN describes in their Technical engagement response that if the 100mg unlicensed medicine is required for titration, but not available, the 200mg (NaMuscla) is used instead. Additionally prices for the unlicensed special mexiletine are unregulated and costs may vary[19]. Finally in section B.2.12 of the company submission, the results from the pan-European MyoPath survey[20] found that: "*disruption in mexiletine treatment harmed 85% of patients".* In summary, when it is available, special unlicensed mexiletine is very rarely used alone or instead of NaMuscla to treat myotonia symptoms in adults with non-dystrophic myotonic disorders. The recommendations outlined in section 1 of the ACD should be clear that this is not a suitable basis of the availability or use of unlicensed special mexiletine as an alternative to NaMuscla to treat adult NDM patients. This is particularly important for stable patients treated with NaMuscla. The Company is very concerned for patient welfare in the event of a negative recommendation for NaMuscla as special unlicensed mexiletine would not be a suitable alternative.
2 Sodium channel blockers as a comparator	In section 3.3 of the ACD, the committee considered that "*established clinical management without mexiletine cannot currently be observed in the NHS because mexiletine is already established in clinical practice…..Therefore, the committee deemed the most appropriate comparison to be with what people currently taking mexiletine would have if mexiletine was not available*." Given that data for the efficacy and safety of the committee's most appropriate comparison cannot be observed, and there are no existing NICE NDM guidelines, inherently there will be a much greater uncertainty in this appraisal's decision problem. We ask the committee to give this the utmost consideration, given the potential significant risk to the wellbeing of stable NDM patients currently treated with NaMuscla from the recommendations of the ACD. **2.a Lamotrigine should not be considered a comparator as it is not in established clinical practice to treat NDM patients.**

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	Lamotrigine does not have a marketing authorisation for the symptomatic treatment of myotonia in adults with non-dystrophic myotonic disorders as defined in the scope. The Guide to the methods of technology appraisal 2013 section 6.2.4 describes when an off-licensed medicine such as lamotrigine can be considered as a comparator: *Section 6.2.4: "The Appraisal Committee can consider as comparators technologies that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS."* In their technical engagement response form, the ABN states that lamotrigine, which they describe as being used at high doses, is not established in clinical practice to treat NDM patients, and state: *"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":* and it *"has the potential life-threatening side effects limiting its use*". The senior clinicians at the main treating centre Queen Square (HSS) confirm that lamotrigine is not in established use. Citing its much longer titration period to reach effective doses and potential severe and life-threatening side effect profile as reasons why they are "*cautious in its use*."[21]. Whilst in the clinical expert statement, the Clinical Expert confirms that she does not use lamotrigine to treat NDM patients. In the technical engagement response from Muscular Dystrophy UK (MDUK), the serious and potential life threatening side effects of lamotrigine, including Stevens-Johnson Syndrome, rashes, psychiatric side effects, emotional impairment, insomnia, hemophagocytic lymphohistiocytosis (HLH), aseptic meningitis as well as limitations regarding contraceptive use and issues with tapering (withdrawal), are described by a patient forum group, The Myotonia Project, and concludes: "*Lamotrigine is rarely used to treat myotonia because of the safety profile and the requirement for more intensive monitoring".* In the Company's technical engagement response (see Issue 3), the Company notes limitations of use outlined in the lamotrigine SmPC[22]: *"In its licensed indications, lamotrigine has a very common (≥1/10) undesirable effect of skin rash. For patients who develop a lamotrigine related rash, treatment should be withdrawn immediately. 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 behavioural change/ psychiatric disorders".* In addition, in contrast to other sodium channel blockers, the research conducted by the Company that shows circa 1% of NDM patients are treated or have ever been treated with lamotrigine in the UK[23], which only reflects its limitations of use and uncertain place in treatment of myotonia symptoms in patients with NDM highlighted in the evidence above. In summary, the evidence provided by the Professional Association (ABN), senior clinicians at the main treating centre at Queen Square (HSS), the Patient Organisation (MDUK), the Clinical Expert and the lamotrigine SmPC confirms that lamotrigine has limitations for use in adult NDM patients, based on:

- Any available data is too new, and there is no long-term safety or efficacy data to support the safe use of high doses of lamotrigine in NDM patients.
- Well-known and documented serious and life-threatening side-effects of lamotrigine, and requiring immediate treatment withdrawal in all patients who develop a common lamotrigine related rash, as well as other common undesirable side effects.
- A much longer titration period and intensive monitoring to reach the required higher doses.

Off-licensed lamotrigine is therefore not currently, nor has ever been, in established use in this indication. The issues presented here are inherent to lamotrigine, and therefore the committee's unobservable decision problem for comparison, the Company believes, is extremely uncertain.

The Company also believes the evidence provided above confirms that lamotrigine is not currently part of established clinical practice for the indication in the NHS, and therefore cannot be considered a relevant comparator in accordance with section 6.2.4 of the Guide to methods of technology appraisal 2013.

2.b There is no quality evidence to support the safety or efficacy of the other sodium channel blockers carbamazepine, acetazolamide, flecainide and phenytoin in NDM treatment

The appraisal consultation document identifies that other sodium channel blockers are used to treat NDM patients. These are the off-licensed medicines carbamazepine, acetazolamide, flecainide and phenytoin.

In section 6.2.4 of the Guide to the methods of technology appraisal it says *"Specifically when considering an 'unlicensed' medicine, the Appraisal Committee will have due regard for the extent and quality of evidence, particularly for safety and efficacy, for the unlicensed use."*

The Final Scope for this appraisal stated that these medicines do *"not form part of standard care"*.

None of these medicines have proven or substantiated efficacy through clinical trials or long-term data supporting their use in NDM patients, and their clinical and safety profile is unfavourable based on evidence provided below. The ACD does not refer to the extent and quality of the safety or efficacy evidence for carbamazepine, acetazolamide, flecainide and phenytoin.

Clinical evidence is unfavourable for these medicines. In the Professional Association's technical engagement response, the ABN says:

"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".

The EMA[24], in assessing other antiarrhythmics, state that *"most of them cannot be recommended as treatment for myotonia, because of associated severe side effects*".

In the Clinical Expert statement, the expert states: "*have used phenytoin in the past and found that largely ineffective*", and in describing carbamazepine that "*there may be limitations to its use through side-effects such as rash, imbalance and so on*".

Further specialist NDM clinical opinion has been elicited in November 2020 (please see Appendix 1). Clinicians stated:

- *"Mexiletine cannot be compared to the other medicines and shouldn't be, as other medicines often just do not work".*
- [From a clinician who used to work in Spain]: *"Mexiletine was not available for 2 years. It was despairing for the patients and clinicians. Nothing was working for them."*

In contrast to the clinical and safety limitations of all the other sodium channel blockers (including lamotrigine), the Company understands from clinicians and patients alike that there would be no suitable alternative to mexiletine:

- In the Clinical Expert statement, the expert states: "*In my experience, drug options other than mexiletine do not provide sufficient benefit for most patients*."
- In the clinical opinion elicited in November 2020 (Appendix 1) a clinician stated "*No replacement for mexiletine*."
- In the MDUK response to the technical engagement, as described by a patient forum group The Myotonia Project, it says *" If mexiletine is not available to NDM patients in the UK, I don't see a suitable replacement for our members at this time".*

In summary there is no quality data evidence provided by the ACD to support the use of carbamazepine, flecainide, acetazolamide and phenytoin, and no due regard is given in the ACD to their safety and efficacy profile to treat NDM patients (which, from the above, clinicians and the Professional Association describe unfavourably). Therefore, in accordance with section 6.2.4 of the Guide to the methods of technology appraisal, the Company believes the recommendations in section 1 of the ACD are not sound or suitable on the basis of a comparison to the sodium channel blockers carbamazepine, acetazolamide, flecainide and phenytoin to treat NDM patients.

2.c A comparison to sodium channel blockers is not appropriate or possible due to the lack of data

An indirect treatment comparison with any of the off-licensed channel blockers is not possible, as confirmed by the technical team in the technical report. There is not the data to make a comparison. The Company has tried to elicit information for the use of the off-licensed sodium channel medicines to treat NDM patients (see Appendix 1), including a Freedom of Information request (see Company response to the Technical Engagement - Issue 3).

The practicality of a study to compare these medicines would be challenging and significantly limited. The evidence provided in section 2a and 2b by the experts from the ABN, senior clinicians at the main treating centre at Queen Square (HSS), the Clinical Expert and the patient group (MDUK) have confirmed the limitations, and their caution of use of lamotrigine, and the ABN describe the other off-licensed sodium channel blockers use as rare in clinical practice to treat NDM patients. The findings of the advisory board in July 2020[18] suggest only 6% of NDM patients are currently treated with any of the other off-licensed sodium channel blockers (see the Company's response to the Technical Engagement Issue 3), and only confirms the evidence of the experts that very few NDM patients take the other off-licensed sodium channel blockers currently.

An observational study to compare these medicines is not possible according to the decision problem as stated in the ACD which cannot be observed in the NHS, and specialist NDM clinicians in the elicitation November 2020 also confirmed they were not aware of any data to make a comparison between medicines either (See Appendix 1).

In section 3.8 of the ACD it is explained that the ERG had provided an analysis for an indicative comparison with lamotrigine. The initial comparison by the ERG assumed the same Adverse Event (AE) profile, compliance, discontinuation, AE disutilities and utility range for NaMuscla. This

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	analysis is extremely uncertain to inform decision making, given no long-term safety or efficacy data exists for lamotrigine for the treatment of NDM patients at high doses, no treatment comparison is possible, and, other than medicine cost, no inputs were based on lamotrigine use. In the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, page 4 the ERG acknowledges the limitations to their comparison between mexiletine and lamotrigine: "*This was only intended to be an explorative scenario*". The Company has received further analysis from the ERG during the consultation period (26th February 2021), in which the ERG chooses to remove the disutilities associated with AEs. This new analysis completely disregards any impact of the serious and potential life-threatening side effects on patient quality of life when treated with lamotrigine. The company strongly objects to this analysis informing any decision making that disregards the evidence for the safety of lamotrigine provided by the Professional Association (ABN), Patient Organisation (MDUK) or the senior clinicians at the main treating centre at Queen Square (HSS) (see section 2a) that could affect the lives of currently stable treated NDM patients. The ERG's update to include an estimate for Stevens-Johnson Syndrome treatment costs, <u>not</u> based on a probability rate for NDM patients treated at a high dose of lamotrigine, is a scant amendment, and the Company believes only adds to the extreme uncertainty of the analysis to inform decision making. In section 3.15 of the ACD it states: "*The committee considered that this analysis would likely also be indicative of any comparison with other sodium channel blockers because of the similar costs of treatment*". In section 5.1.14 of the NICE reference case it states: "*In exceptional circumstances, if the comparators form part of a class of treatments, and evidence is available to support their clinical equivalence, estimates of QALYs gained for the class as a whole can be presented*." The Company does not believe there is any evidence of the clinical equivalence of these sodium channel blockers, and therefore the Company believes this exceptional circumstance as outlined in the NICE reference case is not met. Whilst the company acknowledges that for the minority of patients who do currently receive other off-licensed sodium channel blockers, some may benefit from their treatment, but there are no data (quality of life or otherwise) that can value that benefit. There are no specific national NDM clinical management guidelines and the landscape and efficacy of NHS clinical practice in the absence of mexiletine is not observable, and therefore unknown. The Company also acknowledges from the evidence of the Clinical Expert, the specialist NDM clinicians (see Appendix 1) and the Professional Association (ABN) that there may be many of the NDM patients who would not receive either sufficient benefit or any benefit at all from some of the other off-licensed sodium channel blockers. It is not known what the discontinuation rate would be for NDM patients treated with off-licensed sodium channel blockers if mexiletine was not available. Similarly, it is not known what AEs NDM patients may experience when treated with these medicines, although they are described unfavourably and/or significant in the evidence from the Clinical Expert, the specialist NDM clinicians, the Professional Association (ABN), and the Patient Organisation (MDUK). Nor is it known what impact those unfavourable and/or significant AEs would have on the NDM patients' quality of life. There are no long-term data of any kind that support the safety or efficacy of any of the off-licensed sodium channel blockers for treatment of NDM patients. Clinician feedback for the elicitation Nov 2020 described a comparison as "*impossible*" (See Appendix 1).

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	In examples of a previous appraisal for TA346[25] and TA409[26], where data was lacking and insufficient evidence was available to make any robust economic comparisons, the committee could not confidently assess the off-licensed bevacizumab compared with aflibercept, and therefore accepted bevacizumab should be excluded from any comparator analysis. Based on the evidence above, any provisional recommendations based on the ERG's comparison to lamotrigine, or further applied to any other sodium channel blocker, the Company believes is entirely uncertain, and therefore any provisional recommendations in the ACD based on this analysis would not be a sound and a suitable basis for guidance to the NHS. The Company believes, to be consistent with previous guidance (e.g.TA346 & TA409), the ERG comparison to an off-licensed medicine should be excluded, based on a lack of any data to inform it.
3 Longer term Dosing	**3. Longer term Dosing should reflect clinical practice** All evidence submitted in this appraisal suggests that the mean dosage of mexiletine hydrochloride in clinical practice over the long-term is on average around 400mg per day. This includes evidence from the NHS commissioning expert statement, the clinical experts (see ACD section 3.7), the Delphi panel[27], the follow up data from the MYOMEX study[6], the Suetterlin observational study[5], and the senior clinicians from the main treating centre Queen Square (HSS)[21]. The committee concludes the 600mg dose in the MYOMEX study "*does not reflect how mexiletine is currently used in clinical practice*" (ACD section 3.7). However the committee considered "*it appropriate to use the costs of the 600 mg dose in the economic modelling, as was seen in MYOMEX.*" All of the trials were relatively short in duration, however evidence does exist for the effectiveness of mexiletine over the long-term with lower doses than those seen in MYOMEX. • In the 63 patients from the Suetterlin et al[5] observational study (mean duration 4.8 years - the study conducted at the main treating centre Queen Square (HSS)) doses were titrated "until symptoms resolved" on an average dose of 416.7 mg mexiletine hydrochloride. Some patients will have been on higher doses of 600mg mexiletine hydrochloride, and therefore many patients on lower doses will receive the same clinical benefit. The mean dose of 416.7mg 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 describes the patient dosing in the study as the "Mean Effective Dose". • More recently (Aug 2020) the senior clinicians from the main treating centre Queen Square (HSS)[21], have confirmed that the dosing they currently use (approximately on average 300mg to 400mg of mexiletine hydrochloride) is "usually sufficient to improve quality of life to normal". • The MYOMEX study supports current practice, with the EMA noting that some patients had already significant reduction of stiffness score on day four (200 mg mexiletine hydrochloride once a day)[24]. Lower doses are further supported by the long-term follow up (mean 48 months) data from MYOMEX[6]. The data shows at least maintained efficacy response to treatment at a mean dose of two capsules per day (400mg mexiletine hydrochloride). The Company believes collectively, the long-term data and clinician feedback evidences that in clinical practice efficacy at a lower dose than used in the MYOMEX study is not diminished, and that a mean dose of 416.7mg mexiletine hydrochloride would still treat patients optimally,

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	returning their quality of life to normal, regardless of the varying patient severity or dose, reflective of clinical practice in the NHS. Supporting long-term use, the patients who were non-naïve to mexiletine in the MYOMEX study (and who stopped taking mexiletine at screening) had an average treatment duration of circa a decade prior to study start[2], and the Patient Expert has been treated successfully for c20 years (see Patient Expert statement) which demonstrates that efficacy of mexiletine is maintained over the long-term. In the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, page 3, the ERG writes *"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."* The ERG therefore included 429mg in their preferred case, and the Company agrees with the ERG. The Company believes there cannot be a greater benefit for patients than using a mean dose of 416.7mg mexiletine hydrochloride from the Suetterlin et al study, as all symptoms were resolved at this mean dose. At a dose of 429mg mexiletine hydrochloride, the benefits derived from the MYOMEX study can only be a conservative estimate compared to the clinical practice reflected in the Suetterlin et al study. In summary, the Company acknowledges that there will be some uncertainty with the long-term patient benefits derived in clinical practice, especially for treatment in such a rare disease. However the Company believes that collectively the long-term evidence and data suggests that the efficacy derived from NaMuscla in the MYOMEX study are reflective, even conservatively, of those found in clinical practice use. The Company therefore believes that a conclusion to use the costs of the 600mg dose in the economic modelling would not be reflective of clinical practice, and therefore would not be sound or suitable basis for guidance to the NHS.
4 Dose titration	**4. Additional scenarios and options within model to reflect clinical practice** The Company acknowledges that some patients will be titrated using 100mg special import mexiletine hydrochloride. However, the Company also understands that the majority of clinicians now titrate using NaMuscla[27]. The Company has modelled the rate of titration from the NaMuscla SmPC and the dosing using the costs of NaMuscla, which might capture the costs conservatively. However, the Company acknowledges that some patients will be titrated at a more cautious rate. To investigate the effect on the cost-effectiveness of mexiletine of using a more cautious dose titration in clinical practice, the Company has added functionality for a scenario in the model. This allows an extra two phases of titration, allowing the user to select up to 4 different titration doses before the final maintenance dose. Although NaMuscla is not currently available in other doses, the scenario costs these other doses on a per NaMuscla capsule cost basis, and therefore assumes a linear pricing strategy for any other capsule/pack sizes. However, should a cheaper 100mg mexiletine hydrochloride special import be used to titrate for some patients, the cost-effectiveness results for this scenario would be conservative. A sensitivity for cost effectiveness between the fastest and slowest dose titration is provided below:

	• The New Company base case in Appendix 2 (titration as per MYOMEX, up to 15 capsules per week, no disease progression, Hybrid model 1 to inform utilities and new PAS): [redacted] • 200mg (mexiletine hydrochloride) for 4 weeks, 300mg for 4 weeks, 400mg for 4 weeks, 429mg maintenance: [redacted] The Company believes there is no evidence that there might be any difference in the quality of life benefits over the lifetime of the patient when using the SmPC titration to that observed in clinical practice from the Suetterlin et al study, where patients were titrated until symptoms resolved, and where usually patients' quality of life will return to "normal"[21]. The Company believes these amendments in the model allow scenarios to provide a better reflection of the titration in clinical practice in the NHS.
5 Suitability of utilities derived from SF36 from the Statland et al trial	**5. Utilities derived from SF36 are extremely uncertain** Section 3.10 of the ACD states that the committee "*concluded that the generic SF-36 data from the Statland et al. trial could be included in its considerations*" On page 8 of the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, the ERG acknowledges the many limitations associated with the mapping analysis of SF36 data from the Statland trial to EQ-5D-3L utilities. The ERG explains "*The intention was simply to estimate, even crudely, a set of utilities".* The ERG does not continue to recommend this analysis in its preferred case, but instead recommends the TTO/ Vignette valuation methodology. The Company agrees with the limitations of this mapping exercise outlined by the ERG. Particularly as only the mean SF-36 scores from the Statland trial are available (the Company understands the mapping cannot be conducted accurately without patient level data) and as the mapping algorithm by Rowen et al[28] was not designed or validated in NDM patients. The Company also agrees with the Committee, who recognise in the ACD that the muscle locking function would be difficult to capture, which is in line with findings of Sansone et al, where the SF36 domains of Role physical and Physical functioning had a very weak correlation of -0.22 and -0.20 respectively with the Locking domain of INQoL[29]. The Delphi panel identified that muscle locking is the most impactful INQoL domain to NDM patients QoL[27]. The company also agrees with the ERG, who cautioned that the algorithm to map SF-36 to EQ-5D-3L utilities can underestimate severe health states (see ACD section 3.12). The company believe that utility scores for the BSC patients calculated using this methodology (mean [redacted]) could be higher than expected, which may be why they do not align with the TTO/vignette or revised Hybrid scenarios (see section 6 below). The authors of the Rowen et al[28] paper in their conclusions state: "*Our results raise doubt over the suitability of mapping for patient datasets which have a proportion of subjects with poorer health….Potential policy implications are that mapping the SF-36 onto the EQ-5D can be useful, but may not be suitable for all populations*." From the ERG analysis, the mapped utilities for mexiletine treatment using SF36 from the Statland et al trial are between [redacted] and [redacted] (average [redacted]). These 'on-treatment' utility scores seem extremely low, given that the senior clinicians at the main treatment centre Queen Square expect patient quality of life to improve "*to normal*"[21] when treated with mexiletine (see section 3). The EQ-5D calculated utility for a member of the UK population[30] is expected to be 0.87 (with an upper range of 1 or perfect health), whilst the SF36 derived on treatment utility score is at least 0.20 below this level, and much less at the lower range.

	The use of SF36 assessing patients with myotonic symptoms is not supported by the literature[29,31-33]. The clinicians agree, as noted in the ABN technical engagement response: *"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.".* Indeed the INQoL questionnaire is the only validated QoL questionnaire that refers specifically to the presence and impact of myotonic symptoms[29,32,34]. The Company strongly believes the Statland et al trial adds significant supportive evidence to mexiletine as an effective medicine. However the Company does have some concerns regarding how the SF36 data was collected in the trial. In the vast majority of SF36 questions[35], respondents are asked to review aspects of their health "During the past 4 weeks", whilst in another question the respondent is to consider a year. Given that 22% of patients were being treated with Mexiletine prior to the trial, it is not clear how the SF36 could show an accurate difference in HRQL between treatments. In summary, the Company believes the utilities derived from SF36 using the Statland trial are extremely uncertain, not solely based on the evidence provided by the ERG, but also based on the evidence provided above.
6 Valuation methodologies and derived Clinical benefit	**6.The DCE and TTO valuation methodologies confirm each other** The valuation methodologies were independently reviewed by three experts, none of whom suggested that the valuation exercises or results were highly uncertain. Specific comments from the experts included, "confidence in the general validity and supportiveness for both approaches", and "the overall approach is sound", referring to the TTO. (See company Technical engagement response – Issue 5) 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 scale, but also noted that the impact of the muscle coefficients are lower in the TTO model. As highlighted in section 5 of this response, muscle locking is identified as the most impactful to NDM patients' quality of life. In the Company's technical engagement response – Issue 5, it is highlighted that the incremental utility from the TTO result was very similar to DCE estimates using the same upper and lower anchors ([redacted] and [redacted] respectfully). Further analysis is highlighted in the additional information in Appendix 2a. When considering the utility values generated at a patient level from the MYOMEX study at baseline and in the placebo and mexiletine arms (i.e. all utility values derived within the model), the correlation between those derived from the DCE (using the same range as the TTO) and TTO model is very high (R^2 = 0.96). The two methodologies effectively provide the same utility values at the same range, validating each other and giving confidence and credence to the two datasets and methodologies as supported by the comments of the expert reviewers. However, the Company does agree with the author of the study in Appendix 2a, a senior health economist (who is also Exec Chair for the executive committee at EuroQoL, which developed the EQ-5D measure), who identified that the TTO appeared to undervalue the muscle locking dimension, confirming the findings of the expert reviewers (see the Company's response to Technical engagement - Issue 5). In the TTO study participants were provided with less description of the disease dimensions than in the DCE study, which may have had an effect on the results of muscle locking/ myotonia, as it is such a specific disease symptom. From the TTO

	study results the muscle locking utility weights were valued at zero for all of the levels except the highest level "an extreme amount", and for this level description it was scored the lowest of all of the 8 items of the INQoL dimension chosen in the valuation exercise (see the Company's Vignette utility report). The Company believes this is important because, as previously stated, muscle locking was identified by the specialist NDM clinicians in the Delphi panel[27] as the most impactful to NDM patients' quality of life. Therefore, the TTO study may underestimate the anchoring range, and thus the incremental utilities that inform the economic model. **Addressing Limitations** The quality controls for the DCE task are described in the Company's ERG clarification question responses (Question B7). The DCE was hosted online by Global Perspectives, an organisation that specialises in this type of survey. It was assumed that the subscribing respondents would likely have some experience in completing similar surveys of this kind. Nevertheless the respondents were provided contact details to contact the facilitators to ask questions to support their understanding of the task at any time. Quality checks such as checking that no respondent always answered A or B were performed, whilst other potential quality control checks were deemed not necessary[36]. However, the Company acknowledges some limitations of the results derived from the valuation methodologies as outlined in Appendix 2a, including sample size (limited by practicality), an unadjusted DCE, non-monotonicity, interpolation between levels, and the muscle locking valuation from the TTO. In the valuation studies, for practical reasons the INQoL questionnaire was substantially reduced to be amenable for valuation, and was guided by 3 expert NDM clinicians and a senior health economist (see company submission B.3.4.2). The literature suggests that an individual can only process between five and nine pieces of information at a time[37], therefore the Company acknowledges that the breadth of the descriptive system (8 dimensions) would be at the higher end of that range. In order to ameliorate the limitations, a new analysis of the data is reported (Appendix 2a). The report describes the appropriateness of modelling INQoL data using a DCE + TTO hybrid approach from more than 700 participants to inform the utility weights. Realignment of the dimensions in the design for the INQoL now addresses the issues for the conceptual mapping to EQ5D-3L upper bound anchoring for the DCE study (i.e. the response of "No" or "Not at all" for any of the selected INQoL items would be mapped to "No problems, "No" or "Not" on the EQ5D-3L domain responses), whilst the combined dataset does not suffer from unadjusted DCE predicted values on a latent scale (lower bound anchoring issues). Performance was judged in terms of out-of-sample predictive accuracy in a by-state (TTO) and by-state-pair (DCE) cross-validation approach. Out-of-sample likelihood was used in order to limit the risk of "overfitting" to any noise in the data, as use of direct model fit to the entire dataset increases the risk of erroneously attributing a set of incidental correlations occurring in that particular set of data. The results confirm the advantages of hybrid modelling and confirm the convergence and validity of the TTO and DCE valuation methodologies. The empirical finding supports the notion that the TTO and DCE tap into the same underlying preference structure in INQoL valuation, and information from DCE responses therefore improve our ability to predict TTO responses, and vice versa. In this study, we find that a model combining information from TTO and DCE improves our ability to predict both TTO values and DCE choice probabilities over using either in isolation.

Models were tested both with and without intercepts, and the best 2 performing models were CALE (Cross-attribute level-effect**)** hybrid models, although the results were very similar.

Hybrid model results
The utility values for the hybrid models from the economic model are provided in table 1 below:

Table 1

	Hybrid 1	Hybrid 2
u Mexiletine	[redacted]	[redacted]
u Placebo	[redacted]	[redacted]
Diff	[redacted]	[redacted]

Health state BSC utility score validation

To validate the baseline levels of utility in MYOMEX (i.e. patients with NDM severe enough to be treated with NaMuscla), one method could be to use a proxy disease. NDM has some signs and symptoms which can make it difficult to choose a "closely related" condition. During the NICE meeting, Multiple sclerosis (MS) was used as a proxy measure by the chair, to understand better the plausibility of some of the results in particular from the Company's original base case.

A clinical elicitation exercise was therefore conducted by proxy to MS patients (see Appendix 1). Expert NDM clinicians were asked if they could estimate where an average untreated adult NDM patient with symptoms that are severe enough for treatment with mexiletine might sit on the Expanded Disability Status Scale (EDSS)[38]. The results suggest that the total range would be between an EDSS score of 3.0 to 7.5 (very rarely), but more frequently predicted between a score of 3.0 to 6.0.

Four of the six clinicians, who could make the proxy comparison, stated a specific usual mean score of 5.0 (one said 5.0+).

A description of the EDSS scores is provided in Appendix 1. An EDSS patient with a score of 5.0 is described as:

"*Disability severe enough to impair activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m*".

EDSS patients with a score of 3.0 have no mobility issues, but three or four mild or one moderate functional system impairment. A patient with an EDSS score of 6.0 would require a walking aid, and is able to walk 100m with or without resting. With an EDSS score of 7.5, which is described in Appendix 1 as very rare (which is aligned with the clinical expert's experience in section 3.13 of the ACD), the patient can only take a few steps and would require a wheelchair.

The Patient Expert in his statement describes significant impairment to his activities prior to being treated with mexiletine, including climbing stairs, bathing, sitting down, sleeping, shaking hands, opening his eyes, speaking clearly, suffering falls and injuries, and the need to take time off work.

In the MYOMEX study the vast majority of patients could not feed, dress, climb stairs, take care of their personal hygiene, walk, speak or write normally. 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] and [redacted] of patients could speak and write normally and only [redacted] described the ability to walk as normal. (Company submission document B, section B.1.3.5). During the placebo treatment period for the MYOMEX trial between two fifths and a half ([redacted]) of the patients required some help to walk 3m to 5m (see Company submission

B.3.5.5), and in the stair test (5 stairs) nearly a third ([redacted]) required the use of a ramp, whilst circa a further fifth ([redacted]) had serious difficulties of ascending or descending step by step (see economic model patient level data).

In the Patient Organisation submission, MDUK report from patients who describe what it is like to live with the condition:

- ""*It's horrible, terrible", and also the words "awkward"; "tiring" "dangerous" and "invisible*"."
- "*You can't get up from the chair…you just can't move*."
- "*If I sneeze my eyes close and I can't open them*."
- "*It's dangerous because of the risk of falling*."
- **"***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*."
- "*No one cares*".

Further a carer described the condition of her sister as "*totally house bound and can't leave her flat*"

In addition MDUK in their submission provided results of an online survey of 27 patients in the UK. It describes how daily lives are significantly impacted in terms of mobility, falls, activities and work. In this survey NDM patients were asked what were the symptoms that led to seeking a diagnosis, with 70.4% stating difficulty walking[39].

In section B.1.3.5. of the company submission, the MYOPATH survey[12] provides insight into the multifaceted nature of disease impact from patient verbatims:

- *'Lack of dexterity, movement'*
- *'Difficult to breathe'*
- *'Trouble swallowing – trouble eating because cannot open jaw'*
- *'Always feeling on guard – being careful not to fall or have an accident'*
- *'Challenges with independence' – working, walking, climbing stairs, speaking,– doing simple tasks'*
- *'Difficulties at school - Bullying – social isolation – inability to participate in sports'*
- *'Total desperation – feel paralysed'*

Further evidence for untreated genetically confirmed NDM patients comes from a cross sectional study of 62 patients in the Netherlands[40,41]. In section B.1.3.5 of the company submission it states:

"*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* "; and

"*63% reported muscle weakness and 47% experienced painful myotonia. 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. Mobility impairments, such as difficulty climbing stairs (80%), standing up quickly (73%) and running (82%), were reported by patients in this study*."

In a review of the literature, the two large cohort studies in the UK from Hawton et al[42] (1169 EQ-5D health state descriptions given by 565 respondents) and from Orme et al[43] (2048 respondents) have compared EDSS scores to EQ-5D scores, and the results are shown in Figure 1 of Appendix 1. Results were reported separately for relapse and remitting MS (RRMS) patients prior to primary or secondary progression for the Hawton et al study.

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	The Company believes the evidence from the clinical elicitation exercise and the evidence provided by the Patient Expert, MDUK, the Company, available studies and patient surveys and the MYOMEX study provides some validation of the plausibility of the results of the placebo arm mean utility scores from the new Hybrid models when compared with findings of the clinical elicitation exercise. The Company appreciates that it is challenging to make comparisons across different disease areas. But NDM is a very rare disease with a significant impact on quality of life. A proxy exercise to better informed and studied disease areas could provide some plausibility of indicative NDM BSC utility estimates. Given the potential consequences for the welfare of NDM patients currently stable on NaMuscla resultant from a negative appraisal, the Company asks the committee to give the utmost consideration to the plausibility of our BSC arm mean utility scores from the new Hybrid models, based on all of the evidence provided above. **Health state Treatment utility score validation** The Patient Expert in his statement states that "with Mexiletine, the situation improved considerably" and as highlighted in section 3.2 of the ACD the "*patient expert explained that using mexiletine addressed most of the symptoms of NDM with near normal muscle function".* In the clinical elicitation process (Appendix M of the Company submission), clinicians confirmed a greater than 0.3 utility gain, supportive of the significantly positive impact mexiletine can have on an NDM patients' quality of life. This is further supported by NDM patient feedback. The clinician advisory board in July 2020 describes an NDM patient who is able to play rugby in the winter[18]. Further in the MDUK Patient Organisation submission, patients describe mexiletine as: • "*a wonder drug*" • "*I wouldn't have a proper life without it*" In the Company submission section B.2.12, the results of the pan-European MyoPath survey are provided. The ability to access mexiletine 'drastically' or 'substantially' reduced frequency of falling in 77% of NDM patients, and as a result of being treated with mexiletine, NDM patients reported a significant or drastic improvement in their ability to work (72%), exercise or play sports (75%), overall mobility (85%), drive a car (82%), child care (80%), socialise and communicate (speaking in pubic, shaking hands) (77%), and in their emotional well-being (91%). Additionally the senior clinicians from the main treating centre Queen Square (HSS), have confirmed that it is usual for mexiletine "*to improve quality of life to normal*"[21] for NDM patients (see section 3). As stated in section 5 above, the EQ-5D calculated utility for a member of the UK population is expected to be 0.87 (with an upper range of 1 or perfect health). Given the evidence from the Patient Expert, the Patient Organisation MDUK, available patient surveys and the senior clinicians from the main treatment centre Queen Square (HSS), the Company believes that there is validity of the plausibility of the results of the mexiletine arm mean utility scores from the hybrid models. **New Base case and Scenario** Given the validation evidence above, the Company now considers the Hybrid 1 model as the base case, as it is the best statistically performing model, and provided utility estimates in line

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	with the validation results described above. The second-best performing model, Hybrid 2, is used as a sensitivity analysis. The revised Company base case (Hybrid 1) in Appendix 2b gives a cost effectiveness ratio of [redacted] The new sensitivity case (Hybrid 2) in Appendix 2b gives a cost effectiveness ratio of [redacted]
7 Caregiver disutilities	**7. Care Giver disutilities** The Company had planned to present results from a caregiver survey in order to provide further data to demonstrate the impact of NDM on carers to support the inclusion of a carer disutility within the cost-effectiveness model. However, due to ethical approval delays, the survey remains on-going[7]. The Company however agrees with the ACD that NDM can affect the quality of life of both patients and caregivers (ACD section 3.1). In the Patient Organisation submission, MDUK report from caregivers who describe what it is like to care for someone with NDM: • **"***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*." • "*I feel embarrassed for him. It triggers Myotonia and people think he's drunk*". • "*You feel helpless. I'm always worrying that they'll fall when (they) get a spasm*." • "*It's the pain side that you can't help with and you feel really bad because you can't do anything*." • "*It's really hard*." Furthermore, a caregiver explained that for her sister suffering from NDM 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*." As such, the Company believes it is appropriate to consider the impact on carer HRQL within the cost-effectiveness estimates. In the technical engagement, scenarios were presented based on caregiver studies for both Duchenne Muscular Dystrophy (DMD) caregivers and Multiple Sclerosis (MS) caregivers. The ACD suggests that the disutility values described in the Company technical engagement response and also used in the appraisal for ataluren for treating DMD are inappropriate for this appraisal because the disutility represents carers of non-ambulatory patients, who are very rare in NDM. However, this was incorrectly reported by the Company in the technical engagement response, as the primary source does not differentiate between ambulatory and non-ambulatory patients for this carer disutility (both ambulatory [56%] and non-ambulatory [44%] DMD patients were included in the study)[44]. The Company applied a conservative [redacted] as the input for the proportion of DMD caregiver disutility, based on feedback from the clinical ad board[45] in November 2018 (see Company's response to technical engagement Issue 5). In order to explore further scenarios regarding NDM carer disutilities, the study by Acaster et al[46] , previously submitted during the technical engagement response, showing carer HRQL for MS

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	patients, was further explored. The study examines caregiver disutilities against patient determined disease steps (PDSS) score[47] for MS patients. EDSS and PDSS scores have been shown to be highly correlated, and a score of 4.0 or 5.0 on the EDSS scale could be interpreted as approximate to a score of 2.0 to 3.0 on the Patient determined disease steps (PDSS) scale[48]. The more severe PDSS score of 3.0 is described as: "*Gait Disability: MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually doesn't need a cane or other assistance to walk, but I might need some assistance during an attack*." Given this description, the Company believes it is plausible that the health state for a NDM BSC patient could be justified by disease proxy comparison given the evidence provided by the Patient Expert, MDUK, the Company, available studies and patient surveys and the MYOMEX study in section 6 above. From the evidence of the Patient Expert, the Patient Organisation MDUK, available patient surveys, the senior clinicians from the main treatment centre Queen Square (HSS) (see section 6 above), and from the Delphi panel[27], there is a clear expectation that the quality of life of caregivers of NDM patients treated with NaMuscla would be positively impacted. From the Acaster et al study the estimated disutility of a caregiver of an MS patient with a PDSS score of 2.0 to 3.0 was found to be -0.045. This value is greater than those investigated by the Company at technical engagement, and suggests that the Company base case value used previously (an average of -0.022 per patient) may even be conservative. The ERG agrees with the inclusion of the -0.022 caregiver disutility and therefore, given the evidence above, the Company proposes to not change the -0.022 disutility in its revised base case (see Appendix 2b). The Company acknowledges that its revised base case compares NaMuscla with placebo, however given the potentially extreme uncertainties highlighted in Section 2 above for other sodium channel blockers, the Company believes placebo is the most appropriate.
8. Clinical trial/ unblinding – Trial design	In section 3.6 of the ACD, the potential for carry over effect and unblinding is raised for the MYOMEX trial. "*The committee concluded that potential for unblinding and carry-over effects, short trial duration and few patients contribute substantial uncertainty to the MYOMEX results*" The Company acknowledges the short duration of the trial and patient numbers, however this is a very rare condition, and long-study durations 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 from both the MYOMEX long-term follow up[6] (mean duration 48 months) and the Suetterlin et al study[5] (mean duration 4.8 years). Supporting long-term use, the patients who were non-naïve to mexiletine in the MYOMEX study (and who stopped taking mexiletine at screening) had an average treatment duration of circa a decade[2] prior to study start, and the Patient Expert has been successfully treated for c20 years (see Patient Expert statement) which demonstrates that efficacy of mexiletine is maintained over the long-term.

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	The Company has evidenced in its submission (sections B.2.6.1 and B.2.13.2) and its response to the ERG's clarification questions (Question B12), that for 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. In the Company's response to the ERG's clarification questions (Question A8), and in the Company's response to the Technical engagement (Issue 5), the Company evidences in the statistical analysis that there are no differences between naïve and non-naïve subjects, either in the placebo or in the mexiletine groups. Those patients naïve to mexiletine perceived the treatment event more efficacious than those that were previously exposed suggesting that there was no bias effect in non-naive patients. Therefore, any previous treatment with mexiletine did not influence the expectations of the patients with respect to treatment effect. In the Company's submission (Section: B.2.6.1, and section B.2.13.1), and in its response to the ERG questions (Question A10), the Company evidences that the statistical analysis did not show a difference in treatment effect for treatment periods with no evidence of a carry-over effect (treatment sequence effect). A mixed effect linear model on ranks and statistical analysis used to assess the efficacy results showed that treatment sequence did not have significant effect. Since the p-value associated with the sequence fixed effect was > [redacted], the carry-over effect was to be ruled out. Results for the VAS score showed that treatment sequence did not have significant effect (p [redacted]), ruling out any potential carry-over effect. Lastly the 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 (see section D1.3 of the company submission, and the company's factual accuracy check of the ERG report – Issue 1). In summary, this evidence was required by and accepted by the EMA[49] in order for NaMuscla to receive its licence. The potential carry over effect and unintentional blinding were not evidenced in the MYOMEX trial, and no risk of bias has been found. The Company therefore does not believe that relevant evidence provided above has been taken into account.
9. Resource use	**9.Resource use should remain 3 x multiplier** In round 1 of the Delphi panel clinical experts were asked to provide the frequency of resource use and the estimated number of people using the resource. These questions were asked for both patients treated with NaMuscla and those of Best Supportive Care (BSC). In the ERG ADDENDUM: Critique of the Company's response to Technical Engagement, Page 9, the ERG notes: *However, within Round 1 of the Delphi process, the experts were asked to estimate the frequency of resource use for adult NDM patients receiving 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.* The relevant questions from round 1 of the Delphi panel[27] pertaining to BSC are provided below: *"Question 10: From your experience, please provide an estimation of the percentage of adult patients with NDM, who receive BSC, that would use each type of resource in the table below. Please ensure that the values are between 0-100%".*

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	"Question 13: Of the adult patients with NDM who receive BSC who make use of a resource, please provide an estimation of how often that patient would use the resource per year (in numbers)". In Question 13 it is clear that the number of visits are conditional on the patient using the resource in the first place, and not applicable to all patients. It should be noted the questions for BSC patients were posed the same way for NaMuscla treated patients in the Delphi panel questionnaire, and in the model for NaMuscla treated patients the number of patient visits are conditional to the patient using the resource in the first place. The Company believes consistency should apply for both NaMuscla and BSC arms. 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. As such a multiplier of [redacted] is applied in the Company's model, which may be conservative. Additional Delphi panel[27] findings suggesting that there could be additional support needed for NDM patients in the form of mental health visits to a psychologist or general practitioner were not considered in the cost-effectiveness model. 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 further underestimate the difference in resource use costs between arms. The Round 1 questionnaire of the Delphi panel has been submitted again separately to the main report.
10. Other comments	**Disease Progression** Given the uncertainty of the natural history of the disease, the Company has removed any disease progression assumptions from its base and scenario economic cases. **Statland trial** In section 3.4 of the ACD it states "*Statland et al. (2012) – a randomised crossover trial of 56 patients*". The Company understands that the number of patients recruited for the Statland trial was 62, with 59 patients randomised for treatment **NDM patients over 65** In the section 3.5 of the ACD it states: "*The Company noted that most people over 65 with NDM are on treatment with mexiletine*". The Company doesn't believe it has noted this in the evidence. **Mexiletine Formulation** In section 3.7 of the ADC it states: "*NaMuscla is a new formulation of mexiletine that uses different dose measurements to previous off-label use (a 167 mg capsule of NaMuscla formulation [mexiletine base] is equivalent to 200 mg of imported mexiletine [mexiletine hydrochloride]). However, all the clinical evidence uses the imported formulation of mexiletine."* The Company believes this section of the ACD seems confusing. For clarity, NaMuscla contains mexiletine hydrochloride, and 200 mg mexiletine hydrochloride corresponds to 167 mg of mexiletine[50]. **Adverse Events (AEs)** In section 3.7 of the ACD it says *"The committee considered that because of the short duration of the MYOMEX trial, some adverse events might not have been reported. In clinical practice, such adverse events could take much longer than the MYOMEX trial duration to emerge."*

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In our response to the technical engagement, the Company noted that it believed 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[5]. The Company amended its base case because the MYOMEX study and the Suetterlin et al study have relatively similar AE rates, and AEs are not a large driver of the cost-effectiveness results, and to align with the Technical teams assumption of the MYOMEX AE input in to the base case.

Comparison analysis of our revised base case with MYOMEX AEs, and with Suetterlin AEs is provided below:

The revised Company base case (Hybrid 1) with MYOMEX AEs gives a cost effectiveness ratio of [redacted]

The revised Company base case (Hybrid 1) with Suetterlin et al AEs gives a cost effectiveness ratio of [redacted]

MYOMEX and Suetterlin responders

In section 3.8 of the ACD it states: "*The committee also noted that not everyone in clinical practice would be expected to respond to treatment with mexiletine; MYOMEX and the Suetterlin et al. study selected patients that would be more likely to respond (see section 3.6).*"

For the Company's revised base case (see Appendix 2b), the model does not assume every patient responds. The discontinuation applied to the revised base case the Company believes is conservatively applied (8% from Myomex trial is higher than others reported from Statland et al[3], Stunnenberg et al[4] or Suetterlin et al[5]). There are a number of patients ([redacted]) who didn't respond with lower utility values on mexiletine than on placebo in the revised base case (see Economic model patient level data).

Additionally it isn't clear in section 3.6 why the MYOMEX or the Suetterlin et al. would have selected patients that would be more likely to respond. Suetterlin et al is a retrospective study of clinical practice, whereas for the MYOMEX study the Company evidences that any previous treatment with mexiletine did not influence the expectations of the patients with respect to treatment effect (see section 8).

EQ-5D-3L

In section 3.10 of the ACD it states: "*The Company considered that generic quality-of-life measurement tools such as the Short Form 36 (SF-36) or EuroQoL 5 dimensions (EQ-5D-3L) are unable to effectively capture the quality-of-life implications of muscle locking in NDM*". The Company doesn't believe it has stated in the evidence that EuroQoL 5 dimensions (EQ-5D-3L) are unable to effectively capture the quality-of-life implications of muscle locking in NDM in the evidence. From a review of the literature, EQ-5D has never been used in this disease area, and therefore the suitability of this tool in capturing quality of life in this patient population is unknown.

Mobility

In section 3.13 of the ACD it states "*no patients in MYOMEX needed to use wheelchairs or walking aids*." For clarity, Company is only aware that no patients in the MYOMEX trial needed a wheelchair or walking aid to complete a walking test of 3 to 5 meters (see section B.3.5.5 of the Company submission).

467mg mean effective dose

In the lead team slides, slide 15, it states "*Applying mean doses stratified by genetic subgroup from Suetterlin et al. population to the Statland et al./MYOMEX population gives a mean effective dose of 467mg*" This calculation is provided by the ERG in their ADDENDUM: Critique of the Company's response to Technical Engagement, page 3, which relies on 40 patients with a

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	chloride channel mutation requiring a mean dose of 550mg mexiletine hydrochloride. This is incorrect from the Suetterlin et al[5] study, only 10 patients are reported to be on this dose, and therefore the calculation is an error. **MS Patient utility** In the lead team slides, slide 26, it states that "*the company compares utility of NDM to multiple sclerosis. Reference EQ-5D utility value for an ambulatory but relatively severely disabled multiple sclerosis patient – and provides a utility value of 0.59."* The Company does not believe it has compared the utility of NDM to a multiple sclerosis patient with a utility value of 0.59.
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Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Appendix 1: Clinical Expert Elicitation November 2020

Overview of Clinical Expert Elicitation Process

Adapted from recommended guideline by Iglesias et al, 2016.

Iglesias CP, Thompson A, Rogowski WH, Payne K. Reporting Guidelines for the Use of Expert Judgement in Model-Based Economic Evaluations. Pharmacoeconomics. 2016 Nov;34(11):1161-1172.

Criterion	Description
Research rationale	The need for using an expert elicitation exercise should be described There were two aspects that needed to be addressed in this research rationale. 1. The systematic literature review reported in Appendix G, H and I of the submission did not identify any published studies regarding utilities for Non-Dystrophic Myotonia (NDM) adult patients. Therefore experts in the management of NDM were consulted in order to identify key parameters for the cost effectiveness model. No utility data has been published for NDM. The QoL measured by the INQoL instrument in the MYOMEX study has been valued using two methodologies; a discrete choice experiment (DCE), and Vignette time to trade off exercise (Company Submission). Clinicians who treat NDM adult patients with Mexiletine, have stated that more usually their Quality of life returns to normal[1]. This clinical elicitation seeks to validate the utilities of Best Supportive Care (BSC) NDM adult patients who require treatment with mexiletine in clinical practice, by proxy to the more highly researched neurological condition Multiple Sclerosis (as highlighted in the committee slide 20), using the Expanded Disability Status Scale (EDSS). 2. Alternative medicines that have been used to treat NDM adult patients have been identified as either not established in clinical practise or currently rarely used[1,2,3,4] and due to the lack of available or common data[1,3,5,6] , a comparison to BSC has only been possible for established clinical management without mexiletine. Current data collection for patient outcomes is uncommon and the use of patient outcome tools are not standardised[4]. It is deemed necessary to validate whether any data does exist, or whether a comparison with other medicines is possible based on expert opinion (as highlighted in the Technical report)
Research problem	All uncertain quantities (model input parameters) that will be elicited should be described 1. For the health economic (cost-utility) model the following input parameters needed to be elicited/ validated a. Average BSC NDM adult patient utility b. Can alternative medicines established in clinical management be compared without mexiletine
Measurement type of uncertain quantities	The rationale for the measure type of each uncertain quantity elicited should be described Uncertain quantities were captured as numbers where appropriate.
Definition of an expert	The nature of the expert population should be described to clearly state what topic of expertise they represent and why Experts are defined as consultant neurologists in England and Wales with experience of NDM disorders. All consultant neurologists in England are consultants at a designated specialised service hospital commissioned by NHS England.
Number of experts	The selection criteria and final number of experts recruited to provide expert judgement should be reported 7 NDM specialist clinical experts. The medical director emailed any of the July 2020 advisory participants, to ask that they take part in clinical elicitation within the next few weeks. Due to short timelines, a total of 6 clinicians responded to be available in this time period. In addition 1 further specialist clinical expert had an appointment booked with the medical director, and agreed to participate. There was no intended selection bias, and no experts directly involved in the NICE appraisal participated.
Preparation	There should be clear reference made to a protocol that describes the design and conduct of the elicitation exercise A protocol was not developed but rather a list of questions and materials were developed to inform the aspects of the NICE submission described above.
Piloting	It should be clearly reported if the elicitation exercise process was piloted and a summary of any modifications made No piloting of the elicitation exercise was undertaken.
Data collection and administration	The approach to collect the data should be reported. The mode of administering the elicitation exercise should be reported Data were collected by individual Microsoft teams meeting interviews (30 mins per interview) • Key topic areas were developed into a PowerPoint presentation for a facilitated discussion with individual experts for the clinical elicitation – this was led by the Medical director at Lupin Healthcare (UK) Limited. The

	same person led the discussion on each occasion with the Market Access Director able to contribute and ask clarification questions to the experts • The findings and interpretation of the findings were sent to the consultant for factual accuracy and consent to use in the NICE process provided
Training	The use of training materials should be reported and made available No training or background materials were sent to the participants before the interviews.
The exercise	The number and framing of questions used in the exercise should be reported and made available Copies of the slides that were used to facilitate the meetings with the experts in relation to this submission are provided (See Annex 1) Question asked: • Can the impact to a patients daily activities as described by the EDSS scale be used as a proxy to compare the likely impact to daily activities for untreated adult NDM patients? • If it is possible, then where might an average untreated adult NDM patient with symptoms that are severe enough for treatment with mexiletine sit on the EDSS scale? • Do you maintain a database or can you provide others way to compare treatments, in line with the NICE scope?
Data aggregation	The type of aggregation method (mathematical or behavioural) should be reported together with a description of the method or process used to aggregate the data • The findings were aggregated into this Word report and provided as a reference in this NICE submission • EDSS scale utility scores from two large cohort studies within the UK are provided in the interpretation of the findings
Measures of performance for data aggregation	The processes followed to estimate measures of performance (calibration/information) for data aggregation need to be fully described Not applicable.
Ethical issues	The ethical issues for the expert sample and research community should be described Experts participating in the meetings did not know who the other experts that were engaged where, and no fees were provided in the elicitation process.
Presentation of results	The individual, and aggregated, point estimate(s) and distribution for each uncertain quantity (quantities) should be presented Results were gathered and presented as a synthesis of the feedback and insights gathered from the face to face interactions with the experts. Key questions that were asked were grouped into key themes and a summary of the findings are presented in a tabular form (see below).
Interpretation of results	The interpretation of uncertain quantities elicited should be presented together with a description of how the results will be used in the model-based economic analysis An interpretation of the results from the synthesis of the findings in a tabular format is presented (see below). This includes the degree of uncertainty in the results.

Expert Elicitation Findings

Topic	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6	Expert 7
Topic 1: Can the impact to a patients daily activities as described by the EDSS scale be used as a proxy to compare the likely impact to daily activities for untreated adult NDM patients?							
	Yes I believe the impact to the mobility between the patients is possible	Yes. However the diseases are different. However having such a scale for NDM would be useful	Yes. The MS patients disease is progressive, and the patients cannot move back dramatically to the lower scores on the scale.	No. Very aware of the EDSS scale. It is used in trials, and not helpful for NDM as the disease is so heterogeneous	Yes. However it is difficult as NDM patients have different symptoms on different days	Yes. However the EDSS validated for another disease area and other patients	Yes as a proxy
Topic 2: If it is possible, then where might an average untreated adult NDM patient with symptoms that are severe enough for treatment with mexiletine sit on the EDSS scale?							
	Patients vary between 3.0 and 7.5. However the majority of patients from experience would be circa 5.0	NDM patients would be between 3.0 to 6.0. But difficult to ascertain as NDM patients can change quickly based on other factors such as the temperature.	Larger cohort of patients are around 5.0, however range from 3.0 to 7.0, with a couple of patients slightly milder as construction workers who need treatment in order to do their work	Very difficult to say due to differences in the diseases.	Its probably 5 plus. But difficult to know	If I had to estimate a range it would be 3 to 6 for most NDM patients, very rarely up to 7.5	Most patients are a 5.0.
Topic 3: Do you maintain a database or provide other details to compare different treatments?							
	No. All patients on Mexiletine. There isn't the data to support any other medicine	No. Used to work in Spain. Mexiletine was not available for 2 years. It was despairing for the patients and clinicians. Nothing was working for them.	Mexiletine is first line. Phenytoin is from the old text books, we don't use it any more. Hold some patient data, but a comparison would be impossible	No. Mexiletine is used at the centre. The data doesn't exist for the other medicines	No, and such a dataset doesn't exist. No replacement for Mexiletine. Used Lamotrigine for pregnant patient but failed	Asking the impossible to compare.	Mexiletine cannot be compared to the other medicines and shouldn't be, as other medicines often just do not work

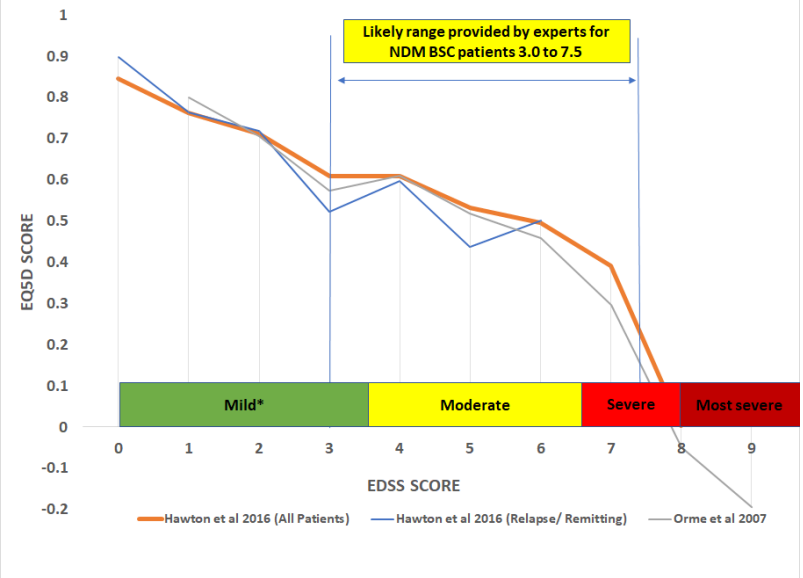
Interpretation of findings and use in NICE submission

Utility comparison BSC

- It is acknowledged that the disease severity tool the EDSS, is designed for Multiple Sclerosis (MS), and the assessment of MS patients. Some clinicians found (to differing degrees) that using such a tool for a proxy for NDM patients difficult.
- This said 6 of the 7 clinicians were able to provide their opinion on where an untreated NDM patients with symptoms that are severe enough for treatment with mexiletine might sit on the EDSS scale
    - The total range provided was between a score of 3.0 and 7.5 (very rarely) in terms of the different severity of the patients that they treat. However one clinician noted that a couple of patients were being treated who were milder than a 3.0 as they were construction workers and needed the medication to carry out their work.
    - Four of the 6 clinicians estimated that the majority of the NDM patients that they would treat would be at an EDSS proxy score of 5 (1 expert saying 5+).

- Two large cohort studies in the UK from the literature from Hawton et al.[7] (1169 EQ-5D health state descriptions given by 565 respondents) and from Orme et al[8] (2048 respondents) have compared EDSS scores to EQ-5D scores, and the results shown in Figure 1 below:

Figure 1



*Disease severity provided by Orme et al 2007

		EDSS Score									
		0	1	2	3	4	5	6	7	8	9
EQ5D	Hawton et al patients	0.846	0.762	0.711	0.608	0.609	0.531	0.496	0.392	0.0025	
	SD (Mean +/-)	*0.182*	*0.220*	*0.221*	*0.281*	*0.256*	*0.286*	*0.269*	*0.278*	*0.314*	
	Hawton et al Relapse/ Remitting	0.897	0.763	0.719	0.523	0.596	0.438	0.502			
	SD (Mean (+/-)	*0.132*	*0.186*	*0.229*	*0.317*	*0.274*	*0.359*	*0.275*			
	Orme et al 2007		0.799	0.705	0.574	0.61	0.518	0.458	0.297	-0.049	-0.195

Comparators

- All clinicians stated that they did not hold any data that could be used for a treatment comparison, and that it was not possible to do so.

Uncertainties in findings

- Experts recruited were driven by their availability to meet with Lupin within a short time frame. A sample size of 7 clinical experts may seem small, but acceptable for such a rare disease
- The EDSS is designed for Multiple Sclerosis (MS), and the assessment of MS patients. MS and NDM are different diseases and naturally using the EDSS as a proxy tool is difficult
- Qualitative nature of research, potential subjective bias
- Lack of data and sources of data meant experts drew upon experience for providing estimates

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8. Orme et al; The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value in Health 2007, 10: 54-60

Annex 1 – Slides used in Clinical Elicitation November 2020

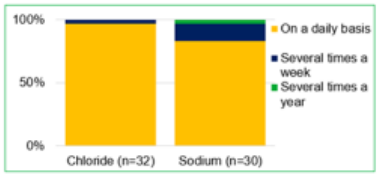
NaMuscla®Mexiletine comparisons

October 2020

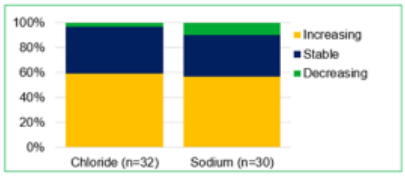
LUPIN NEUROSCIENCES

Disease burden and unmet need

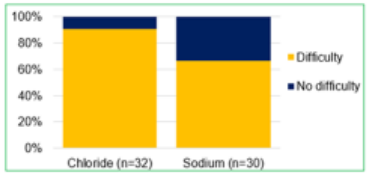
Frequency of myotonic symptoms[1]



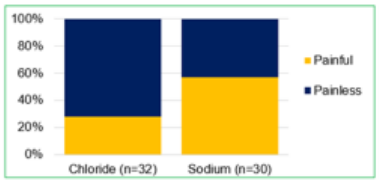
Changes in severity of myotonia since onset[1]



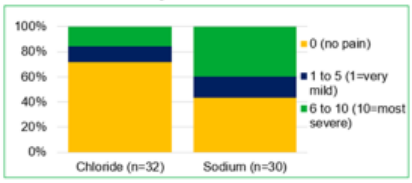
Difficulty in climbing stairs, standing up or running[1]



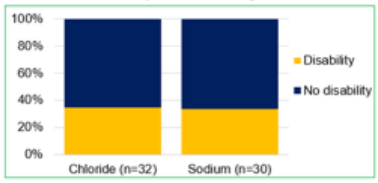
Painful vs. Painless Myotonia[1]



Severityof Pain[1]



Full or partial disability[2]



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EDSS Scale -Multiple Sclerosis Trust (1)

Reference 1: www.mstrust.org.uk

Comparators

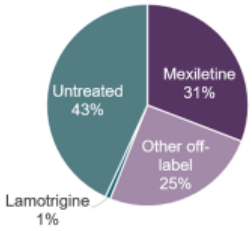
NICE Scope (1)

Current practice includes using mexiletine used off-label for treating symptomatic myotonia. 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.

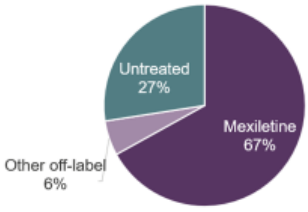
Comparators:

Established clinical management without mexiletine, including but not limited to:

- lamotrigine
- best support care.



Market research data (2)(Oct 2019)



Advisory Board (3) (July 2020- based on last 2 years of treatment)

Market research in October 2019 included patients who were registered to the main centre. The other off label medicines identified in the Market Research (Oct 2019) were Phenytoin, flecainide, acetazolamide.

Data in the Advisory board (July 2020) the main centre declared only patients under active care in the last two years.

References

1. NICE Final Scope mexiletine: https://www.nice.org.uk/guidance/gid-ta10432/documents/final-scope
2. Lupin Healthcare (UK) Limited. Market research on non-dystrophic myotonia clinical management. LUP-NAM-063. Data on file. 2019.
3. Lupin Healthcare (UK) Limited. UK Clinical Advisory Board. LUP-NAM-122. Data on file. 2020

Comparators

Queen Square: Lamotrigine - "precise place in the management of NDM is not fully established"[1]

Queen Square: "At present we are unable to compare mexiletine with Lamotrigine"[1]

Queen Square: Other medicines: "have less efficacy than mexiletine"[1]

Patient Group: "Lamotrigine is rarely used to treat myotonia because of the safety profile and the requirement for more intensive monitoring"[2]

Patient Group: "If mexiletine is not available to NDM patients in the UK, I don't see a suitable replacement for our members at this time"[2]

EMEA: Other antiarrhythmics: "most of them can not be recommended as a treatment for myotonia, because of associated severe side effects"[3]

References

1. Clinicians statement UCL website https://www.ucl.ac.uk/centre-for-neuromuscular-diseases/file/1843. Accessed 19.09.2020
2. Myotonia Foundation, August 27, 2020. Lupin DoF
3. Namuscla EPAR

Back up

EDSS Scale -Multiple Sclerosis Trust (1)

Score	Description
0	Normal neurological exam, no disability in any FS
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m

Score	Description
6.0	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transfering. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

* **FS** = eight functional systems criteria

Reference 1: Accessed 8.10.2020 https://www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss)

MS Eight Functional System criteria (1)

- muscle weakness and your ability to move your arms and legs
- balance, coordination and tremor
- eye movements you can't control, your speech and swallowing
- unusual sensations or numbness
- your bowel and bladder
- your eyesight
- your thinking and memory
- other functions

Reference 1: Accessed 8.10.2020 https://www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss)

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Appendix 2 - Utility valuation analysis

Appendix 2a Hybrid modeling of INQoL TTO and DCE data

Background

Acaster Lloyd Consulting have conducted valuation studies with the aim of using responses to the Individualized Neuromuscular Quality of Life (INQoL) questionnaire to generate utility estimates. INQoL was restricted to a set of 8 questions, covering Weakness, Locking, Pain, Tiredness, Daily activities, Leisure, Anxiety, and Depression. Preferences for INQoL health states were assessed in general population samples using two valuation methods: discrete choice tasks (DCE), and composite time trade-off (cTTO), both with task designs similar to those used in the EuroQol EQVT protocol. It should be noted that values derived using the DCE approach are on a latent scale, meaning that anchoring and rescaling is required for use in QALY analyses.

When considering the utility values generated at a patient level from the MYOMEX study at baseline, from the placebo arm, and for the mexiletine arm (ie all utility values derived), the correlation between those derived from the DCE model at the same range as the TTO model have an R^2 value of 0.96 (see figure 1). This supports the notion that DCE and TTO tap into the same underlying preference structure, and could be combined to maximize use of the available data.

Figure 1

However the models have certain limitations, in terms of sample size, necessary underlying assumptions regarding anchoring of the DCE scale, non-monotonicity (as typically observed in comparable sample sizes), and interpolation between levels. For an unadjusted DCE, predicted values on a latent scale are not appropriate for QALY calculation. The TTO values may display a substantial gap between full health (by convention set to 1) and the best imperfect health states, and the muscle locking dimension appeared undervalued. To ameliorate these issues, analyses were conducted, designed to develop an INQoL scoring system by use of a hybrid modelling approach, combining the DCE and cTTO data from more than 700 participants to inform the utility weights.

This study was conducted by Maths in Health B.V., a specialist Health Economic organisation based in Rotterdam, The Netherlands. This document describes the approach of modeling INQoL data using a DCE + TTO hybrid. Performance was judged in terms of out-of-sample predictive accuracy in a by-state (TTO) and by-state-pair (DCE) cross-validation approach. Out-of-sample likelihood was used in order to limit the risk of overfitting to noise in the data; prediction accuracy over left-out state values (TTO) and state pair probabilities (DCE) is used as a proxy for accuracy over health states and state pairs not included in the study.

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Empirical study design

In the cTTO study, 200 respondents were each administered 16 INQoL states, organized in two blocks, for a total of 32 unique states. In the DCE study 508 respondents were each administered a total of 32 state pairs. The states were designed using different combinations of INQoL levels between the TTO study and DCE study.

Dimension design

The 8 INQoL questions valued in this study were not identically presented in the questionnaire.

The first four dimensions, Weakness, Locking, Pain, and Tiredness, were presented as in **Figure 2**, with an initial choice for the presence/absence of the symptom, followed by a Likert scale if the respondent stated yes. The Likert scale had 7 levels, 1 ("Very little"), 2 ("Some"), 3 ("A fair amount"), 4 ("A moderate amount"), 5 ("A considerable amount"), 6 ("A lot"), and 7 ("An extreme amount").

Figure 2

For the remaining four dimensions, there was no initial binary question, and while the format was a 7-point likert scale, the levels differed somewhat from the other group of questions, numbered differently, as in **Figure 3**: 0 ("Not at all"), 1 ("Slightly"), 2 ("A fair amount"), 3 ("Moderately"), 4 ("Considerably"), 5 ("Very much"), and 6 ("Extremely").

Figure 3:

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A tabular description of the labels and levels of INQoL is presented in **Table 1A**. The selected mapping to numerical levels in found in **Table 1B**, with the levels and descriptions which were included in the DCE and cTTO designs.

Table 1: INQoL levels for the dimensions used.

A) level structure present in instrument, with numerical values (where explicit)

INQoL Level	Weakness	Locking	Pain	Tiredness	Daily activities	Leisure	Anxiety	Depression
0	No*	No*	No*	No*	Not at all	Not at all	Not at all	Not at all
1	Very little	Very little	Very little	Very little	Slightly	Slightly	Slightly	Slightly
2	Some	Some	Some	Some	A fair amount	A fair amount	A fair bit	A fair bit
3	A fair amount	A fair amount	A fair amount	A fair amount	Moderately	Moderately	Moderately	Moderately
4	A moderate amount	A moderate amount	A moderate amount	A moderate amount	Considerably	Considerably	Considerably	Considerably
5	A considerable amount	A considerable amount	A considerable amount	A considerable amount	Very much	Very much	Very much	Very much
6	A lot	A lot	A lot	A lot	Extremely	Extremely	Extremely	Extremely
7	An Extreme amount	An Extreme amount	An Extreme amount	An Extreme amount				

B) Mapping

Map Level	Weakness	Locking	Pain	Tiredness	Daily activities	Leisure	Anxiety	Depression
0	No*	No*	No*	No*	Not at all	Not at all	Not at all	Not at all
1	Very little	Very little	Very little	Very little	Slightly	Slightly	Slightly	Slightly
2	Some	Some	Some	Some	--	--	--	--
3	A fair amount	A fair amount	A fair amount	A fair amount	A fair amount	A fair amount	A fair bit	A fair bit
4	A moderate amount	A moderate amount	A moderate amount	A moderate amount	Moderately	Moderately	Moderately	Moderately
5	A considerable amount	A considerable amount	A considerable amount	A considerable amount	Considerably	Considerably	Considerably	Considerably
6	A lot	A lot	A lot	A lot	Very much	Very much	Very much	Very much
7	An Extreme amount	An Extreme amount	An Extreme amount	An Extreme amount	Extremely	Extremely	Extremely	Extremely

* Separate Question Used in DCE study design Used in TTO study design Used in Both study designs

Non-randomized order of presentation in DCE

The left-right order of presentation for the DCE can result in a bias in favour of the leftmost state. This suggests that the DCE models should include an intercept, which should then be discarded.

Censoring and heteroscedasticity in TTO data

As observed in EQ-5D studies employing the same TTO procedure, the resulting data tends to be highly heteroscedastic in severity; for mild states, there is relatively limited variation in how much time is traded away by different individuals. The worse the state, the greater the variation. Applying regular regression methods with the homoscedasticity assumption in place results in standard errors that are representative of some medium severity states, but higher than empirical for mild states, and lower for worse. For TTO data, we recommend inclusion of heteroscedasticity in the error term, improving precision over the milder range, and better reflecting the underlying data.

In the intial analysis the cTTO design employed allows a lowest possible expressed value of -1. However, some respondents would likely assign lower values if given the option. Values at -1 were therefore considered left censored (i.e. in the interval $[-\infty, -1]$). Health preference data is conventionally modeled using disutilities, i.e. $u' = -(u-1)$.

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Likelihood estimation

Regression modeling was done using the *xreg*[1] package in R, as this is designed specifically for bespoke hybrid modeling, including optional characteristics such as heteroscedastic models and censoring/interval regression,etc. DCE models were fitted using conditional logistic regression by way of modeling differences between the presented states using regular logistic. For TTO data, we used censored linear regression with a heteroscedastic error term, linear in the predicted value.

The hybrid model maximizes the product likelihood (sum logLikelihood) over DCE and TTO data, given a set of shared parameters and a linear transform between the two[2]. This transformation is necessary, given the latent scale of the DCE model parameters.

Models were tested with and without intercepts for TTO. The DCE data were always with intercept. The "base case" model employed a parameter for each observed level/dimension combination (Full model). Given the size of the descriptive system, and the available sample size, this model may be susceptible to overfitting. Alternative linear models tested a single parameter per dimension. Cross-attribute level-effect (CALE, see section below) models were fitted with different combinations of level parameters.

In order to prevent non-monotonicity (logically worse health states modeled as having higher utility), the primary model parameters were fitted using box-constraints, such that incremental disutility of moving to a worse level along any INQoL dimension had a lower bound of 0.

Model performance and result

Model performance was judged in terms of out-of-sample predictive accuracy, measured using out-of-sample log-likelihood in a leave-out by state/state pair cross-validation analysis.

The best two performing models (**Table 2**) were CALE hybrid models without TTO intercepts; fitting a single parameter per dimension, which takes the disutility value of the worst level, multiplied by level parameters shared by several dimensions. Hybrid 1 employed shared level parameters over all dimensions, while Hybrid 2 employed separate level parameters for the first four and last four dimensions, reflecting the difference in wording (see table 1). Hybrid 1 slightly outperformed Hybrid 2 in out-of-sample likelihood. Both models displayed substantially improved out-of-sample predictive accuracy compared to the base case model. The tested hybrid models indicate improved out-of-sample predictive accuracy both for TTO and DCE than corresponding models fitted to either data type in isolation. In other words, information from DCE responses improve our ability to predict TTO responses, and vice versa.

These results confirm the advantages of hybrid modelling. In this study out of sample predictiveness of the DCE and cTTO perform better in the CALE hybrid models. This empirical finding supports the notion that TTO and DCE tap into the same underlying preference structure in INQoL valuation.

Table 2 The best performing hybrid model results

			Out-of-sample predictive accuracy							
			logLikelihood			Pearson's R	ICC	CCC	MAE	RMSE
Model	Type	Description	TTO	DCE	Combined					
Hybrid 1	Hybrid	"CALE"	-2755.2	-4751.3	-7506.4	0.9154	0.9012	0.9012	0.0672	0.0790
Hybrid 2	Hybrid	"CALE" + sep. L3, L4, L5	-2756.4	-4750.9	-7507.3	0.9152	0.9017	0.9017	0.0633	0.0787
Base case hybrid	Hybrid	All dimension/level combinations	-2776.6	-4765.1	-7541.7	0.8354	0.8280	0.8286	0.0734	0.0920
Separate DCE and cTTO	Regular	"CALE"	-2784.2	-5268.3	-8052.5	0.8894	0.8693	0.8694	0.0761	0.0927
Separate DCE and cTTO	Regular	"CALE" + sep. L3, L4, L5	-2788.3	-5307.7	-8096.1	0.8846	0.8632	0.8632	0.0784	0.0954
Separate DCE and cTTO	Regular	All dimension/level combinations	-2778.9	-4769.1	-7548.0	0.8403	0.8372	0.8375	0.0729	0.0929

[1] Xreg: flexible multi-frame likelihood-based regression modeling, Kim Rand https://www.github.com/intelligentaccident/xreg
[2] Preference-Based Assessments: Handling Data Quality Issues to Estimate the Spanish EQ-5D-5L Value Set Using a Hybrid Interval Regression Approach. Juan M. Ramos-Goñi, Value in Health 21 (2018) 596-604

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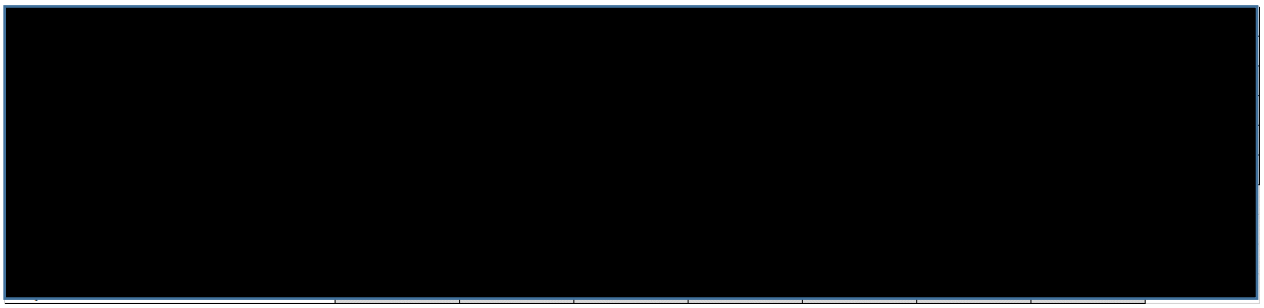
The improvements are in line with what should be expected, given the added stability of predictions from the Hybrid, as the DCE and cTTO data tend to converge, and the Hybrid models leverage substantially more data.

Table 3: Standard Error and P values

The disutilites for each dimension and for each level of INQoL are provided in **tables 4 a, 4b**

Table 4a - Hybrid 1

Table 4b - Hybrid 2



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A layman's perspective of the findings

The use of out-of-sample predictive accuracy in model selection aims to reflect the extent to which we are able to predict how a similar group of respondents would value other INQoL health states. For a review of the TTO, DCE and Hybrid studies, an analogy is provided.

Consider a betting situation in a street car race. You have access to historic track records of a number of races, including various characteristics of the cars, drivers, and the tracks involved. Additionally, you have information on a number of aesthetic properties, such as the color of the cars, the attire of the drivers, etc. If knowledge of e.g. the color of a car improves our ability to predict the winner, it is useful. This empiricist approach works in the absence of theory: while the color of car is not known to directly influence racing speed, faster cars could more often be colored red.

The out-of-sample approach applies; in order to determine which factors are useful in predicting a winner, we could sequentially leave out historic races one by one, and see how well models including different predictors allow us to determine the winner in each. Use of direct model fit to the entire dataset increases the risk of erroneously attributing the chance of winning to a set of incidental correlations occurring in that particular set of data.

In this study, we find that a model combining information from TTO and DCE improves our ability to predict both TTO values and DCE choice probabilities over using either in isolation. Furthermore, the combination of TTO and DCE is less like combining historic race statistics and aesthetic properties, and more analogous to combining information on race times (TTO) with pairwise car orderings (DCE); predictors of high TTO values correspond very well with predictors of preferred health state in paired comparisons.

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2a Annex

DCE

DCE models were fitted using conditional logistic regression by way of modeling differences between the presented states using regular logistic. Let *x* denote the the independent variables of the model, *β* the modeled coefficients, and x*β* + *ε* represent the regression model (which may be non-linear). As TTO and DCE coefficients given the same model setup could have different scales, let *β'* be the coefficients for DCE. Furthermore let *j* denote observations, and *j∈D* represent the dichotomous observations (i.e. DCE observations). The log-likelihood function maximized was

$$\underset{\beta\prime}{\operatorname{argmax}}(D) = \sum_{j\epsilon \mathrm{D}} \left\{ \ln\left(\frac{1}{1+e^{-x\beta\prime}}\right) y_j + \ln\left(\frac{e^{-x\beta\prime}}{1+e^{-x\beta\prime}}\right) \right\}$$

TTO

For TTO, we used censored linear regression with a heteroscedastic error term, linear in the predicted value. If *j∈C* represents discrete continuous observations, and *j∈R* represents right-censored observations, the loglikelihood function that was maximized was

$$\underset{\beta}{\operatorname{argmax}}(C,R) = -\frac{1}{2}\sum_{j\epsilon \mathrm{C}} \left\{ \ln\left(2\pi\sigma_j^2\right) + \left(\frac{y_j - x\beta}{\sigma_j}\right)^2 \right\} + \sum_{j\epsilon \mathrm{R}} ln\left\{ \phi\left(\frac{-\left(y_{Rj} - x\beta\right)}{\sigma_j}\right) \right\}$$

Heteroscedastic error

If $x_{\beta j}$ is the predicted value for observation *j*, the standard deviation in the normal-distribution-based likelihood estimation was modeled as:

$$\sigma_j = \alpha_\sigma + \beta_\sigma * X_{\beta j}$$

Hybrid model

The hybrid model maximizes the product likelihood (sum logLikelihood) over DCE and TTO data, given a set of shared parameters and a linear transform between the two, using the parameter *θ*.

$$\begin{aligned}\underset{\beta}{\operatorname{argmax}} = & -\frac{1}{2}\sum_{j\epsilon \mathrm{C}} \left\{ \ln\left(2\pi\sigma_j^2\right) + \left(\frac{y_j - x\beta}{\sigma_j}\right)^2 \right\} \\ & + \sum_{j\epsilon \mathrm{R}} ln\left\{ \phi\left(\frac{-\left(y_{Rj} - x\beta\right)}{\sigma_j}\right) \right\} \\ & + \sum_{j\epsilon \mathrm{D}} \left\{ \ln\left(\frac{1}{1+e^{(-x\beta/\theta)}}\right) y_j + \ln\left(\frac{e^{(-x\beta/\theta)}}{1+e^{(-x\beta/\theta)}}\right) \right\}\end{aligned}$$

Full models

The "default" model is one with a parameter for each observed level/dimension combination

Full model:

$$\alpha + \sum_{l,dim} \left(\mathrm{dim}_l\, \beta_{dim,l}\right) + \varepsilon$$

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This model format is the most flexible, but also most susceptible to overfitting and non-monotonicity. With the different levels used in DCE and TTO, the total number of primary parameters in the hybrid model is 40 (42 including intercepts, 45 including θ, α_σ and β_σ).

Linear models

The most constrained models tested used a single parameter per dimension, assuming linearity in levels. If *dim* denotes observed variables for each dimension (integers from 0 to 7), the simplest model was on the form

Linear model:

$$\alpha + \sum_{dim} (dim * \beta_{dim}) + \varepsilon$$

Cross-attribute level-effect (CALE) models

CALE models employ a parameter per dimension, taking the disutility of the worst level, multiplied by level parameters shared by several dimensions, each taking the incremental proportion of the worst level. Variants were tested with level parameters shared by all dimensions, and with separate parameters for levels 3, 4, and 5 for the first four dimensions (weakness, locking, pain, tiredness), and the last four (daily activities, leisure, anxiety, depression).

The general format is

Cale model:

$$\alpha + \sum_{l} \left(\beta_l \sum_{dim} \mathrm{dim}_l \, \beta_{dim} \right) + \varepsilon$$

Appendix 2b

Updated company deterministic base case and scenario analyses

The company ACD response describes the company's preferences on each of the committee's key concerns, including mexilitine dosing and titration, health-related quality of life utility estimates, and disease progression. Some of these preferences require an update to the company base case cost-effectiveness results. In addition, the company has proposed an update to the existing patient access scheme, reducing the price per pack of mexilitine to [redacted]. The results using the company's updated preferrred assumptions and PAS are shown in Table 1.

Table 1: Updated company deterministic base case and scenario analyses results

	Incremental cost-effectiveness ratio	
	ACM1 PAS	**Updated PAS**
Company base case (ACM1)	[redacted]	[redacted]
+ removal of disease progression	[redacted]	[redacted]
+ use of Hybrid 1 for utilties	[redacted]	[redacted]
Updated company base case	[redacted]	[redacted]
Scenario using slower mexilitine titration*	[redacted]	[redacted]
Scenario using Hybrid 2 for utilities	[redacted]	[redacted]
Scenario using a carer disutilities of 0.045 for all placebo patients and patients off mexilitine	[redacted]	[redacted]
Scenario using Suetterlin et al (2015) AEs	[redacted]	[redacted]
Note: *, 4 weeks at 200mg, 4 weeks at 300mg, 4 weeks at 400mg, 4 weeks at 500mg, 429mg maintenance dose		

Updated company probabilistic base case

The company has also updated the probabilistic base case cost-effectiveness results. These results align closely with the deterministic results (Table 2 and Figure 1), and estimate that mexiletine has a [redacted]% probability of being cost-effective at a willingness-to-pay threshold of £30,000 (Figure 2).

Table 2: Updated company deterministic and probabilistic base case results

	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Deterministic results							
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]				
Probabilistic results							
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]				

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.

Figure 1: Updated company base case cost-effectiveness plane

Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness to pay.

Figure 2: Updated company base case CEAC

Key: CEAC, cost-effectiveness acceptability curve.

Updated company base case one-way sensitivity analysis

The updated one-way sensitivity analyses show the same key parameters as drivers of model results: mexiletine dose, compliance rate and utility values (Figure 3).

Figure 3: Updated company base case one-way sensitivity analysis

Key: ICER, incremental cost-effectiveness ratio.

LUPIN HEALTHCARE (UK) Limited

CONFIDENTIAL

[redacted]
NICE

15/06/21

Dear [redacted],

Lupin is very pleased to update you with a new revised PAS price following our ACD response. In the appendix of this letter, you will find the updated PAS price, revised base case company ICER and deterministic and probabilistic results.

Some uncertainity will exist in such a rare disease area, and specifically we present scenarios to our base case which consider carer disutilities, utility valuation, health resource utilitiation multiplier and maintenance dosing.

We believe that this new updated PAS price goes a significant way to address these uncertainties, and is highly supportive of Namuscla (mexiletine) as cost effective in the symptomatic treatment of Non Dystrophic Myotonia (NDM) patients.

We would like to thank you for your time on the 31st March where we discussed the clarification of the decision problem for comparators for Namuscla (mexiletine). Lupin remains frustrated, and continue to consider that clause 6.2.4 of the Guide to the methods of technology appraisal 2013 is unambiguous regarding the unsuitability of the unlicensed medicines as comparators in this assessment.

This said we hope the committee can consider the significantly reduced ICER to address their concerns for cost effectiveness, allowing access for NDM patients to a highly effective treatment.

Yours sincerely

[redacted]
General Manager

LUPIN HEALTHCARE (UK) Limited

Appendix

Updated company deterministic base case and scenario analyses

The company has proposed an update to the existing patient access scheme, reducing the price per pack of Namuscla (mexiletine) to [redacted]. The results using the company's updated PAS are shown in Table 1.

The company has included a number of scenarios including varying the utilities derived from the Hybrid 1 results and the Hybrid 2 results (see appendix 2b of the ACD company response), the carer disutilities derived from the Acaster et al study (see section 7 of the ACD company response), and sceanrios considering the committee's feedback in the ACD regarding carer disutiities and dosing. The company has further provided scenarios considering the ERG base case.

Table 1: Updated company deterministic base case and scenario analyses results

	Incremental cost-effectiveness ratio	
	ACD PAS	**Updated PAS**
Updated company base case	[redacted]	[redacted]
Scenario using Hybrid 2 for utilities	[redacted]	[redacted]
Scenario using a carer disutilities of 0.045 for all placebo patients and patients off mexilitine	[redacted]	[redacted]
Scenario with no carer disutility for all placebo patients and patients off mexilitine	[redacted]	[redacted]
Scenario using 21 doses	[redacted]	[redacted]
ERG base case*	[redacted]	[redacted]
ERG base case with carer disutilities of 0.045 for all placebo patients and patients off mexilitine	[redacted]	[redacted]
ERG base case with no carer disutility for all placebo patients and patients off mexilitine	[redacted]	[redacted]
Note: *ERG base case is the company base case with the following amendments: TTO data for utilities Multiplier for healthcare resource use for no treatment of [redacted] (company base case uses a multiplier of [redacted])		

Updated company probabilistic base case

The company has also updated the probabilistic base case cost-effectiveness results. These results align closely with the deterministic results (Table 2 and Figure), and estimate that mexiletine has a % probability of being cost-effective at a willingness-to-pay threshold of £30,000 (Figure 2).

Table 2: Updated company deterministic and probabilistic base case results

	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Deterministic results							
Mexiletine		37.99			0		
BSC		37.99					
Probabilistic results							
Mexiletine		37.99			0		
BSC		37.99					
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.							

Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness to pay.

[redacted]

Key: CEAC, cost-effectiveness acceptability curve.

Updated company base case one-way sensitivity analysis

The updated one-way sensitivity analyses show the same key parameters as drivers of model results: mexiletine dose, compliance rate and utility values ([redacted]).

[redacted]

Key: ICER, incremental cost-effectiveness ratio.

Updated budget impact analysis

The net budget impact for this medicine in Year 3 at our revised PAS is circa [redacted], which represents a medicine already established in clinical practice.

NICE National Institute for Health and Care Excellence

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders [ID1488]

Consultation on the appraisal consultation document – deadline for comments 5:00pm on 5 March 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The appraisal committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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NICE National Institute for Health and Care Excellence

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders [ID1488]

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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation would mean that patients who are currently successfully managing their condition with Namuscla would no longer have access to this treatment. Following conversations with clinical experts, we feel that it is wrong to suggest that there is a supply of mexiletine readily available from alternative sources that patients could access instead. Cessation of Namuscla treatment is likely to cause widespread anxiety due to the uncertainty of supply of other forms of mexiletine from alternative sources, and places an undue onus on individual clinicians to source supplies of mexiletine; time that would be better dedicated to supporting patients if a guaranteed supply of Namuscla was available. An individual who has been successfully managing their condition with mexiletine/Namuscla for several years told us of their concerns, which are two fold – for their own experience and for those of their family members: 1) I am well aware of the impact that not having this medication has on my quality of life and the thought that this would how I would have to live my life in the future is very stressful indeed. The lack of control over my condition means that the resultant implications for all aspects of my future life would be would be dramatic. I foresee a lack of mobility and increasing pain and muscle stiffness leading very quickly to me becoming far more housebound, which as I am in my 50s is a pretty frightening thought. This consequence as well significantly impacting my physical health through reduced mobility will also impact my quality of life with my family and have resultant mental wellbeing implications not just for me but for them as well. As a parent of a child with complex special needs who enjoys our daily walk as a particular highlight of both their and my day as a shared experience, the thought that this will not be possible as we look to the future is really actually very upsetting. 2) And then for those who will be denied access to this treatment in the future I am equally worried. I am very conscious of the impact this medication has on my quality of life and therefore I fear for my other teenage child, who has been diagnosed with myotonia (but is not yet taking medication) as to their future because that option will not be available to them. They already struggle with stiff and aching muscles, and the thought that they will have to endure this for the rest of their life, without the benefits this medication provides, is very upsetting. They are bright, clever and ambitious and I am confident that in the future they will add much to society but my fear is that without medication they will be unable to fulfil that potential, which as a parent causes me great sadness.
2	Mexiletine is the first line of treatment for non-dystrophic myotonia in adults and it alleviates symptoms rapidly. We are therefore concerned that patients who have to switch to a new treatment, and newly diagnosed patients, will have to spend many months adjusting the dosage of a new drug (e.g. lamotrigine) before it is acceptable and tolerated. In addition, we are concerned by reports from clinicians about the possible harmful side-effects of lamotrigine. We are concerned that the removal of an effective treatment that is well-tolerated would be unfair and unethical.
3	We are concerned by reports from clinicians that the symptoms of myotonia can be more severe if treatment stops suddenly, therefore, a careful withdrawal regimen would need to be worked out for each patient. This again will cause unnecessary stress and anxiety to patients and their families.

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4	We are extremely disappointed that current recommendation is that "The cost-effectiveness estimates for mexiletine are much higher than what NICE considers a cost-effective use of NHS resources and would potentially be higher if compared with other sodium channel blockers rather than best supportive care". Clinical evidence has shown that mexiletine/Namuscla is effective in managing non-dystrophic myotonia in adults. Given the concerns raised by clinicians with whom we have spoken regarding the potential use of other sodium channel blockers to treat this condition we hope that measures can be taken to readdress the cost-effectiveness and reverse this recommendation.
5	Together with other patient groups, we are deeply concerned by the precedent that would be set by the proposed removal of Namuscla from patients who are already receiving the treatment. As noted in the ADC document, this is a significant departure from previous practice and one that would have a profound impact not only on those patients immediately effected in this case but on future patients receiving other treatments for other conditions where this approach could be repeated.
6	

Insert extra rows as needed

Checklist for submitting comments

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- Do not use abbreviations
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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.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	Comments

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1	We do not feel it is reasonable to consider that lamotrigine and other sodium channel blockers are equivalent or a comparator to mexiletine. In our practical experience going back several decades, drugs such as carbamazepine, flecainde and phenytoin have not been efficacious and patients do not stay on them in the long term due to lack of efficacy and side effects. Lamotrigine is very rarely used at present and in current practice we have not found it to be as effective and has a high discontinuation rate amongst patients. We have found that we require high doses of over 150mg a day to see an effect and that a number of patients report not having any improvement in symptoms. A direct comparator trial of mexiletine and lamotrigine is currently being set up but the results for this are likely to take several years.
2	We feel that it is unethical for the appraisal to recommend discontinuation of mexiletine for those patients already established on treatment. We have found in our clinical experience and during the Statland et al study that sudden termination of mexiletine results in a significant worsening of symptoms for patients for a prolonged period. We are concerned that those patients who are already established on the drug would be left worse off because of this recommendation.
3	Although the National Hospital for Neurology and Neurosurgery in London are currently able to get some supply of the generic mexiletine in 100mg doses. This supply is intermittent and frequently unavailable. This results in patients frequently being unable to access treatment when they need it and has been a frequent occurrence in the past 10 years prior to the availability of Namuscla. It is our understanding that other neuromuscular centres around the country do not have access to any supply of generic mexiletine and therefore when Namuscla is no longer available it is likely to cause significant problems with supply in other parts of the country and an inequality in treatment across England.
4	
5	
6	

Insert extra rows as needed

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- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[No links to tobacco industry]
Name of commentator person completing form:	[Fiona Norwood]
Comment number	**Comments**

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Example 1	We are concerned that this recommendation may imply that ……..
1	A proven and effective drug – mexiletine – potentially will not be available for patients with non-dystrophic myotonia (NDM). This drug is currently used first-line for the vast majority of NDM patients. To date comparators such as lamotrigine have been used in only a very small number of patients nationally.
2	The only licensed drug for this group of conditions will not be available.
3	An unlicensed drug for NDM – lamotrigine – is recommended by NICE as first-line treatment, on the basis of one small trial. The justification for this, especially given the licensed drug availability and efficacy, is unclear.
4	There has been no evidence to show that lamotrigine is superior – or equal to – mexiletine in an RCT. A comparator trial would be useful but is not available, hence the rationale for changing the status quo is unclear.
5	Patients who are established on the licensed form of mexiletine (NaMuscla) will have this treatment withdrawn, with likely recurrence of symptoms. A number of my patients have expressed alarm at this possible outcome.
6	As a prescriber I will not be able to justify prescribing an unlicensed, unproven drug when the licensed drug is available. Having discussed with my pharmacist, this puts us in a very difficult and uncertain position.

Insert extra rows as needed

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unlawful or otherwise inappropriate.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Mexilitine has helped me tremendously to cope with my Becker's type myotonia congenita, I am naturally a very sport and active person but a couple of years ago, when my symptoms for MC started to significantly worsen (just previous to and around the time of my diagnosis) it got to the point where I severely struggled with everyday activities, not only did this affect me physically but it also was detrimental to my mental health. Mexilitine has successfully suppressed all my MC symptoms enabling my quality of living to significantly increase again and makes everyday activities so much more manageable.

Without the provision of mexilitine by the NHS my quality of living and would likely return to that of the time of my diagnosis where I struggled to perform everyday activity's likely also causing negative impacts on my mental health and well-being.

Name	[redacted]
Organisation	Medicines team at NICE
Conflict	N/A
Comments on the ACD:	

recommendations

1 Recommendations

'This guidance does not require that patients having treatment with mexiletine (Namuscla) that was started in the NHS through the interim agreement for use as a 'pass through' drug for patients within specialised neurosciences centres, which came into effect on 1st April 2019, should continue to receive treatment with Namuscla. Commissioners are not required to continue to fund that treatment. This is a departure from NICE's usual practice that negative guidance ought not to affect NHS treatment started before the guidance is published.'

Is this standard wording that is used? It is quite difficult to read and understand on first glance. Could it be made clearer and start with the take home message 'Commissioners are not required to continue to fund treatment with mexiletine (Namuscla) for.....'

'Commissioners are not required to continue to fund that treatment.'

Assume this only relates only to Namuscla and not the imported versions of mexiletine? MHRA say that a licensed product should be used in preference to an unlicensed product. If the TA is not recommending the licensed product and saying that commissioners don't need to continue to fund this treatment, and prescribers are supposed to use a licensed product if one is available, then what happens to people who are established on mexiletine? Have the implications of not allowing people to continue been fully considered? Will NHSE update their policy after the TA is published?

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

In 2008 Boehringer Ingelheim discontinued manufacturing of Mexitil (mexiletine hydrocholoride). Many patients in Europe were taking mexiletine at the time to treat non-dystrophic myotonia. It caused a great deal of concern in a support group for NDMs and I followed the subsequent attempts to find an adequate replacement. Most were put back on carbamazepine or phenytoin and a few on flecainide. The anti-epilepsy drugs (AEDs) helped somewhat with the myotonia, but had significant psychiatric side effects in younger adults in particular, including depression. The flecainide was helpful for the sodium ion channel myotonias, but not as effective as mexiletine for the chloride ion channel myotonias. Some patients lost their jobs over this change because they had been functioning so well on the mexiletine and lost that functionality or had to deal with the mental side effects of the AEDs.

Lamotrigine has been proposed as a primary substitute by the committee. Feedback from our support group indicates that it has been helpful for some who were being treated concomitantly for depression and were able to combine that and myotonia treatment into one medication. However many have noted psychiatric side effects with lamotrigine as well. It is also affected by estrogen and must be monitored if women use birth control or hormone replacement therapy. And there are studies showing possibility of an increase in cleft palate or cleft lip if a woman becomes pregnant while taking lamotrigine.

Mexiletine is the most effective medication used by the members of our group. While some may experience GI side effects, Lupin has demonstrated that their formulation is better tolerated than the generic mexiletine. Taking away that option for people with NDMs is going to cause problems for many of our members who have been functioning at a level they consider significantly higher compared to no treatments or the other alternatives.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost effectiveness will be determined by contract negotiation which the public is not privy to, so there is no way to know how the final comparison will look. I do think that the gain of function that allows patients to lead normal lives is worth an investment. An effective treatment also greatly diminishes the risk of injury which, in turn, saves the NHS money. It does not reverse the conditions, but it allows patients to be productive members of society. It is hard to put a price tag on that when you look at the long-term physical and mental consequences of being disabled.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am disappointed that the committee rejected the study recommendations and that they will discontinue access to mexiletine completely in the UK, even for those already taking the medication successfully. This is going to be devastating to many

of our support group members. Unlike AEDs, mexiletine works immediately and has no withdrawal period. I fear that some will lose their jobs because going through the process of adapting to a new medication will take time and disrupt many lives. The majority of our patients start with the 200 mg equivalent twice a day and only increase to three times a day if that was not effective. Some only take an additional dose in cold weather. I don't think the committee should assume that all patients will need to be on the higher dose.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I do believe this is discrimination based on disability. By stating that the impact on quality of life is not significant enough to warrant the cost is discriminatory. The committee members have no idea what it is like to live with this condition 24 hours a day; wheelchair use should not be the criteria for the government's support. The alternative drugs mentioned are not going to be acceptable for many patients and will result in diminished quality of life for those who are currently taking the medication and thriving. Mexiletine is life-changing for so many patients, and removing it completely as one of the options for treatment is harsh and insensitive.

Name	[redacted]
Organisation	Cochrane Neuromuscular Disease Group
Conflict	N/A

Comments on the ACD:

Has all of the relevant evidence been taken into account?

There is an unpublished Cochrane review regarding the treatment of myotonia with Mexiletine that would not have been taken into consideration.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

My clinical experience and the outcomes of my unpublished Cochrane review would indicate that the evidence for the efficacy of Mexiletine is far greater than that for other treatments. I am writing on behalf of my fellow authors of the Cochrane review of the pharmacological treatment of myotonia.

Are the recommendations sound and a suitable basis for guidance to the NHS?

It is my opinion that the recommendations should take into account the randomised evidence regarding the use of Mexiletine in myotonia. Although other sodium channel blockers are used (such as Lamotrigine and Carbamazepine), in my clinical experience their efficacy is less well established and the literature reflects this

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

N/A

Comments

I am a consultant neurologist that is involved in the treatment of patients with myotonia. I am also the lead author of a Cochrane review on the treatment of myotonia. This review is in preparation and is currently unpublished. You will appreciate that we must keep the findings of the review confidential, pending publication, but the evidence that my team and I have gathered shows that Mexiletine is a safe and effective treatment for myotonia. There was far less robust evidence for any of other treatments we reviewed. My email address is [redacted] and I would be happy to confidentially share a draft version of that manuscript .

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

I have Paramyotonia Congenita. I have recently been diagnosed after years of doctors appointments and tests. These conditions are so rare they are not considered by many doctors, my own GP surgery still have no knowledge of the condition. This made getting a diagnosis difficult. Over the last 10 years my symptoms had developed to the point I could not work, I could not leave the house for fear of falling over and not being able to move. I lived in agony every day, affecting every part of my body. I would be woken up at night with the pain. It became difficult to swallow. I am 35 years old and I felt trapped by my own body, this was so distressing and exacerbated by the fact it is extremely difficult to describe and even harder to get a doctor to understand. This leads to a delay in being referred to the right specialist. I tried several different medications, acetazolamide, quinine tablets, none of which worked. I was prescribed mexilitine c.4 months ago. Within 2 weeks of taking this medication my life literally changed. It is no exaggeration to say I gained my independence back, the ability to look forward to events and enjoy time with family and outdoors. I have been able to start exercising again and have lost weight, I am able to sleep and eat with being in pain or feeling like I am choking on my food. I am able to laugh with my loved ones without having to hide the agony I was in. I still have the occasional “flare up” but the frequency and severity is drastically reduced. Please do not underestimate the impact this medication can have on someone’s physical and mental health. Until you suffer from a condition like this you are unable to comprehend how life limiting it really can be to some patients. While it is rare it does not mean there should be no time and funding spent trying to understand treat for those who suffer. It is no exaggeration to say that if I was unable to have this medication, and without a suitable alternative that delivered the same results, I would not be able to live any kind of normal life.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

I would comment on the use of INQoL as the QoL measure that has been used in the Namuscla trial, results of which have been part of the evidence submission to NICE. I am [redacted] of INQoL which was devised by [redacted]. It is a muscle disease specific QoL and it includes specific questions on myotonia that are of course particularly relevant to ask of those on treatment for myotonia. It has been around for 20 years and is a validated measure in widespread use for muscle disease studies and trials, including muscle diseases with myotonia. It has been translated into several languages. It follows the trend of using disease specific QoL that have more patient relevance and are more likely to be sensitive to change than are generic QoL such as SF36.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The clinical effectiveness of lamotrigine as an alternative treatment for NDM has been over-stated.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not. I am a neuromuscular specialist who has diagnosed and managed many cases of non-myotonic dystrophy for the last three decades. For the first two decades experts such as myself treated these cases with mexiletine. We did so on the basis of case reports and case series supported by personal experience of dramatic symptom improvement with this medication. We were criticised for using an off licence drug without a good evidence base especially when sourcing reliable supplies of an rarely used drug became increasingly problematic. Responding to this criticism RCTs were conducted that confirmed the benefit of mexiletine, as we suspected they would. By contrast the evidence and the personal experience of trialing sodium channel blockers such as lamotrigine has been very limited. It has not thus far impressed me as being a dramatically successful and I am uncertain as to the outcome of any RCT evidence in its favour that might arise. Thus if this guidance remains unchanged we will have a situation whereby patients that are largely asymptomatic on mexiletine will have to be transferred to an unlicensed and as yet unproven treatment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The draft guidance if finalised unaltered will deny known effective treatment for those disabled by myotonia and prevent them from having a much fuller life than is possible.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

It doesn't appear to me that you have looked at what effect mexilitine has on the individuals.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Myotonia is so rare, please let the individuals have the best drug's available to relieve their symptoms. There is no cure but to know they won't suffer on a daily basic, or make a fool of themselves by tripping....no cost can be put on that. Taking mexilitine has improved the mental health of my daughter as she can lead a near normal life now.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

It is a discrimination against the disabled to take away the drugs that allow them to lead a normal life

recommendations

1 Recommendations

In the experience I have with my daughter, being prescribed mexilitine allowed her to live a near normal life again. For a 16 year old to find out that her body doesn't work like everybody else's is devastating. To not be able to walk upstairs without tripping, play sport without your body freezing up would put even the strongest teenager into a spin. mexilitine change all that for her.
Please don't withdraw it.

Name	[redacted]
Organisation	The British Myology Society
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, please see my detailed comment below

Are the recommendations sound and a suitable basis for guidance to the NHS?

no, please see my more detailed response in final comment below
Lamotrigine not considered first line treatment by experts in the field
Carbamazepine and phenytoin considered ineffective

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Comments

As [redacted] of the British Myology Society Council (BMS), I have been asked by the members to comment on the recommendations of this NICE appraisal.
The BMS council members do not consider Lamotrigine to be first line treatment for non-dystrophic myotonia because it may take many months to be effective and there is a risk of serious side-effects. Other drugs mentioned in this report: Carbamazepine and Phenytoin were not deemed to be clinically effective, which is why there have not been trials comparing these agents with Mexiletine. From a clinical perspective, Mexiletine is tolerated well and is without doubt, the most effective treatment. It substantially improves symptoms and quality of life of patients.
Some members reported that supply of the generic version of Mexiletine is erratic, and sometimes may not be available for weeks or months. Thus, patients taking this form of Mexiletine may sometimes have to interrupt treatment. Suddenly stopping treatment worsens their symptoms. Thus colleagues, particularly from the larger centres, expressed concern that this decision by NICE would impact significantly upon patient quality of life.
They also raised concern that the Namuscla preparation is the only licensed treatment for non-dystrophic myotonia and thought it would be a somewhat odd situation for them not to be able to prescribe it. They also raised concern that those patients already taking this product would have their treatment withdrawn.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

I think the available evidence has been scrutinised

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I believe the INQOL and other outcome measures in the MYOMEX study are entirely appropriate for this population, albeit short term. I do not think the ERG has given enough credit to these clear-cut outcome measures and positive effect sizes of Namuscla treatment. These cannot be compared with other RCTs.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I hope disability from a rare disorder has been appropriately addressed

Comments

Please acknowledge my comments below and in particular to the statement:
Are the recommendations sound and a suitable basis for guidance to the NHS?
I do not believe this recommendation allows appropriate optimal care for patients with NDM who I treat in my tertiary muscle clinic. Although the cost-effectiveness estimates for Namuscla need to be appropriately scrutinised the current appraisal does not reflect routine clinical practice where Mexiletine is used as first line treatment for NDM and that the trials do in fact reflect doses used in clinical practice. The availability of other sodium channel blocking agents with lamotrigine having the highest level of evidence (RCT placebo-controlled) cannot be compared to Namuscla due to study capture outcome measures and therefore the standardised effect sizes cannot be compared. The neuromuscular outcome measures captured in the Myomex trial where much more comprehensive and reflective of this population, albeit being a short-term trial.
I believe If Namuscla cannot be recommended by NICE as first line treatment for patients with NDM this would have a significantly adverse effect on the quality of life and potentially occupational productivity of these, generally young, patients in full time employment. It severely restrict therapeutic options for NDM and I do hope that the rarity of this disorder has not had an indirect effect on this provisional ACD outcome.

Many thanks

[redacted]

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

recommendations

As a partner of somebody diagnosed with Paramyotonia Congenita I cannot agree with this recommendation, especially 3.13 ‘The reduction in quality of life for carers of people with NDM should be removed as an assumption’. Since starting mexiletine there has been a ‘night & day’ change to my partner’s life but also my own. Not having the stress and worry of my partner falling over when her legs lock and potentially causing further bodily harm (and potential further costs to the NHS through hospital visits) by hitting her head, or cutting her hand if she was carrying a glass for instance, both of these scenarios have already been played out before mexiletine.

If funding for mexiletine is withdrawn, then I am faced with a lifetime of care, helping my partner get up from a chair, or move about the house for fear of falling. This could lead to me having to give up my job to be a full time carer for my partner, I may have to claim benefits, yet another cost to funding.

We have together a much much better quality of life with mexiletine in our lives, of course with lockdown we have been limited, but even going out for walks together or doing exercise regimes has greatly helped our fitness and weight, and just as importantly our mindfulness and wellbeing, all of this is lost without mexiletine. The disease will progress at the quick rate it was before the appropriate treatment and cause a significant life long impact on daily life for my partner and those close.

Yes, this disease may not affect many people in the UK, but the net of people this does affect is much larger than the patient themselves and those potential associated costs, especially mentally.

So as a partner of somebody diagnosed with Paramyotonia Congenita, I urge NICE, no beg NICE to reconsider their recommendation.

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the ACD:	

Dear colleagues

I use the product for patients with non dystrophic channelopathies. We have an internal MDT and if approved prescribe this product.

We have used fora few patients and with good response and indeed been revolutionary for at least one. It is well tolerated. Hopefully an agreement will be reached moving forward.

Bw
[redacted]

[redacted]
Consultant Neurologist

Name	[redacted]
Organisation	The Walton Centre NHS Foundation Trust
Conflict	N/A
Comments on the ACD:	

Dear [redacted],

Apologies for missing the deadline for comment for recent NICE consultation ID1488. It may be too late, but I wished to register my concern that most of the patients on mexiletine at our neuromuscular centre have already tried and failed other sodium channel blockers. The reason for refusing mexiletine seems to be that it was not compared with cheaper alternatives – most of us are mindful of this and will try other sodium channel blocker first. Could not mexiletine be approved for those with symptomatic myotonia that impacts day-to-day life who have already tried other sodium channel blockers? Thanks,

[redacted]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders

ADDENDUM: Critique of the company's response to ACD

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. Company's response to the Appraisal Consultation Document

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 Appraisal Consultation Document (ACD).

In their response to the ACD, the company provided the following supporting data, which can be found in the Appendices to the company's response:

- Appendix 1: Clinical Elicitation for utility comparisons and comparators
- Appendix 2a: Utility valuation analysis
- Appendix 2b: Updated company deterministic base case and scenario analyses

In addition, the company presented the following nine comments:

1. Usage of special mexiletine

The company argues that special unlicensed mexiletine is very rarely used alone or instead of NaMuscla to treat myotonia symptoms in adults with non-dystrophic myotonic disorders and that the Company is very concerned for patient welfare in the event of a negative recommendation for NaMuscla as special unlicensed mexiletine would not be a suitable alternative.

ERG comment: The ERG has no opinion on this matter.

2. Sodium channel blockers as a comparator

The company argues that:

a. Lamotrigine should not be considered a comparator as it is not in established clinical practice to treat NDM patients.
b. There is no quality evidence to support the safety or efficacy of the other sodium channel blockers carbamazepine, acetazolamide, flecainide and phenytoin in NDM treatment.
c. A comparison to sodium channel blockers is not appropriate or possible due to the lack of data.

ERG comment: The ERG agrees with the committee that the most appropriate comparator is what people currently taking mexiletine would have if mexiletine was not available. Therefore comparators include, as outlined in the NICE scope: "Established clinical management without mexiletine, including but not limited to: lamotrigine and best support care".[1] The company does not present any new evidence; therefore, the ERG refers to the discussion of comparators in the original ERG report.[2]

3. Longer term Dosing

The company reiterate arguments that evidence from clinical experts, Suetterlin et al. and MYOMEX follow-up suggests that the mean dosage of mexiletine in clinical practice over the long term will be on average around 400mg per day.[3-7] They report that although all trials were relatively short in duration, evidence does exist for the effectiveness of mexiletine over the long-term with lower doses than seen in MYOMEX, including:

• In the 63 patients from the Suetterlin et al. observational study (mean duration 4.8 years - the study conducted at the main treating centre Queen Square (HSS)) doses were titrated "until symptoms resolved" on an average dose of 416.7 mg mexiletine hydrochloride.[4] The company state that some patients will have been on higher doses of 600mg mexiletine hydrochloride, and therefore many

patients on lower doses will receive the same clinical benefit. They state that the mean dose of 416.7mg 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 describes the patient dosing in the study as the "Mean Effective Dose".

• In August 2020, the senior clinicians from the main treating centre Queen Square (HSS), confirmed that the dosing they currently use (approximately on average 300mg to 400mg of mexiletine hydrochloride) is "usually sufficient to improve quality of life to normal".[5]

• The MYOMEX study supports current practice, with the EMA noting that some patients had already significant reduction of stiffness score on day four (200 mg mexiletine hydrochloride once a day).[8] and the long-term follow up (mean 48 months) data from MYOMEX which shows at least maintained efficacy response to treatment at a mean dose of two capsules per day (400mg mexiletine hydrochloride).[6]

ERG comment: The ERG has nothing to add here. If the committee prefers to use the 600mg dose, to be consistent with the dosage given in the MYOMEX trial, on which the model efficacy is based, then this is their prerogative.

4. Dose titration

The company acknowledges that some patients will be titrated using 100mg special import mexiletine hydrochloride, but report that they understand that the majority of clinicians now titrate using NaMuscla.[3, 7] The company has modelled the rate of titration from the NaMuscla SmPC and the dosing using the costs of NaMuscla, which might capture the costs conservatively. However, the company acknowledges that some patients will be titrated at a more cautious rate.

To investigate the effect on the cost-effectiveness of mexiletine of using a more cautious dose titration in clinical practice, the company has added functionality for a scenario in the model, which allows two extra phases of titration, allowing the user to select up to 4 different titration doses before the final maintenance dose.[3] Although NaMuscla is not currently available in other doses, the scenario costs these other doses on a per NaMuscla capsule cost basis, assuming a linear pricing strategy for any other capsule/pack sizes. However, the company report that, should a cheaper 100mg mexiletine hydrochloride special import be used to titrate for some patients, the cost-effectiveness results for this scenario would be conservative.

The ICERs for scenarios between the fastest and slowest dosing titration are provided below:

• The new company base case in Appendix 2 (titration as per MYOMEX, up to 15 capsules per week, no disease progression, Hybrid model 1 to inform utilities and new PAS): [redacted]

• 200mg (mexiletine hydrochloride) for 4 weeks, 300mg for 4 weeks, 400mg for 4 weeks, 429mg maintenance: [redacted]

ERG comment: The ERG notes that the above scenario for more cautious titration uses the cost of NaMuscula rather than the price of imported mexiletine and therefore will not reflect the true current cost of more cautious titration in 100mg steps. However, if the the cost of imported mexiletine would be lower, this would lower the ICER further.

5. Suitability of utilities derived from SF36 from the Statland et al trial

The company noted that Section 3.10 of the ACD states that the committee "*concluded that the generic SF-36 data from the Statland et al. trial could be included in its considerations*". The company reiterated that the ERG noted extensive limitations associated with its crude mapping of the SF-36 values from Statland et al. to EQ-5D-3L utilities.[3] The company noted limitations associated with:

- The availability of only mean scores from Statland rather than patient level data.
- The mapping algorithm was not designed or validated in NDM patients.
- The fact that the mapping algorithm was found by its authors to underestimate the burden of severe health states (giving higher than expected EQ-5D values to such states). The company believe that utility scores for the BSC patients calculated using this methodology (mean [redacted]) could be higher than expected, which may be why they do not align with the TTO/vignette or revised Hybrid scenarios.
- The mapped utilities for mexiletine treatment are between [redacted] and [redacted] (average [redacted]). The company consider these 'on-treatment' utility scores to be extremely low, given that the senior clinicians at the main treatment centre Queen Square expect patient quality of life to improve "to normal" when treated with mexiletine.[5]
- The committee's suggestion that that the muscle locking function would be difficult to capture. The company report that this is in line with findings of Sansone et al, where the SF36 domains of Role physical and Physical functioning had a very weak correlation of -0.22 and -0.20 respectively with the Locking domain of INQoL[9] and the Delphi panel which identified muscle locking as the most impactful INQoL domain to NDM patients QoL.[7]
- The literature suggests that the use of the SF-36 is not supported in NDM, as supported by the ABN technical engagement response: "*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*."[10-13]
- Concerns regarding how the SF36 data was collected in the Statland trial. In the vast majority of SF36 questions, respondents are asked to review aspects of their health "During the past 4 weeks", whilst in another question the respondent is to consider a year. Given that 22% of patients were being treated with Mexiletine prior to the trial, it is not clear how the SF36 could show an accurate difference in HRQoL between treatments.

ERG comment: The ERG outlined the limitations of their mapping scenario within the ERG addendum and has nothing further to add to these. Given the limitations of this analysis, the ERG did not (and continue not to) use these values in their base-case.

The ERG would like to note that the quote from the ABN submission that the SF-36 is commonly used, although it seems to have a less clear correlation in NDM than other more systemic conditions is not evidence that the SF-36 is not valid in NDM. A less strong correlation does not mean it is not sufficiently correlated to capture changes in health.

6. Valuation methodologies and derived Clinical benefit

Arguments that DCE and TTO valuation studies confirm each other

The company argue the quality of both valuation studies (DCE and vignette/TTO) stating that valuation methodologies were independently reviewed by three experts, none of whom suggested that the valuation exercises or results were highly uncertain.[3] The company report specific comments from the experts including, "confidence in the general validity and supportiveness for both approaches", and "the overall approach is sound", referring to the TTO.

In their response the company reiterate their argument for the similarity in the results of the two methods, when anchoring them to the same range (incremental utility from the TTO results of [redacted] is very similar to the incremental utility obtained from the DCE results when assuming the same upper and lower anchors as the TTO of [redacted]), stating that when anchored to the same range, the utilities produced correlate very highly (R^2=0.96), and that this finding validates and gives confidence and credence to the two datasets and methodologies, as supported by the comments of the expert reviewers.[3]

The company report that another expert, who carried out the new hybrid analysis of the TTO and DCE data, considered that the TTO appeared to undervalue the muscle locking dimension, confirming the findings of the existing expert reviewers.[3] The company repeat that in the TTO study participants were provided with less description of the disease dimensions than in the DCE study, which may have had an effect on the results of muscle locking/ myotonia, as it is such a specific disease symptom. From the TTO study results the muscle locking utility weights were valued at zero for all levels except the highest level "an extreme amount", and for this level description it was scored the lowest of all of the 8 items of the INQoL dimension chosen in the valuation exercise. The Company believes this is important because, as previously stated, muscle locking was identified by the specialist NDM clinicians in the Delphi panel as the most impactful to NDM patients' quality of life.[7] Therefore, the TTO study may underestimate the anchoring range, and thus the incremental utilities that inform the economic model.

ERG Comment: The company report several quotes selected from the expert validation reports which suggest that both methods were considered positively and not considered uncertain. The ERG feels this gives a fairly one-sided view of the experts' comments and would like to reiterate some of their concerns including "The DCE and TTO approaches give very different results The DCE and TTO methods are very different and I would not expect them to produce the same values." Louise Longworth[14] "Some of the remarks regarding the DCE study also apply to the vignette study, for instance, as previously noted in the review of the DCE, non-dystrophic myotonic disorders (NMD) are not inherently life-limiting. It is therefore a little puzzling why this option was presented to participants or alternatively why participants interpreted some health states as worse than death (suggesting perhaps a misunderstanding of the task on their part?)" Adam Smith [15]

Again, the ERG reiterate that it is inherent that when anchored to the same range, values will be more similar, but this does not mean that the two methodologies, applied as in the model according to their individual respective ranges, give similar results. For example, if cm and inches are anchored on the same scale, the results will be the same, but this does not mean that 10cm=10inches.

The company continue to repeat the argument that the TTO should not be used as it undervalued muscle locking, which was considered the most important issue to patients. The ERG would like to note that it is

not patients' preferences that are being measured, but general population preferences. If they felt that only extreme muscle locking would impair their daily lives, then that is a valid preference. This feature may also be a result of considering it separate to the other physical functioning symptom and a lesser issue compared to that symptom. This is a reason for not including very similar dimensions within one descriptive system for valuation.

Addressing Limitations of the valuation studies

The company state that quality control checks for the DCE task are described in clarification response B7. The DCE was hosted online by Global Perspectives, an organisation that specialises in this type of survey.[3] It was assumed that the subscribing respondents would likely have some experience in completing similar surveys of this kind. Nevertheless, the respondents were provided contact details to contact the facilitators to ask questions to support their understanding of the task at any time. Quality checks such as checking that no respondent always answered A or B were performed, whilst other potential quality control checks were deemed not necessary.[16]

The company acknowledges a series of limitations of its valuation studies, including: sample size (limited by practicality), an unadjusted DCE, non-monotonicity, interpolation between levels, and the muscle locking valuation from the TTO. The company also acknowledge that the literature suggests that an individual can only process between five and nine pieces of information at a time,[17] and therefore their descriptive system of 8 dimensions would be at the higher end of that range.

In order to rectify some of these limitations, the company requested a new analysis of the valuation data, as reported in Appendix 2a, described in the next section.

ERG Comment: The ERG would argue that you cannot assume that possible prior experience of completing DCEs means that participants understood the company's DCE, gave it their full attention, did not take heuristic shortcuts or that they provided consistent high-quality results. This is why quality control checks are of the utmost importance. If participants are completing many such tasks for financial renumeration, it could be argued that their attention to each task may be reduced, hence why it is important to keep the presented DCE profiles simple and small.

New hybrid analysis of DCE and TTO data

The conduct of the hybrid modelling, which combined data from the DCE and vignette TTO studies into a single model was described extensively in Appendix 2a of the company's ACD response.[18]

The health state utility values which result from the hybrid models examined, as well as all the other valuation study options available, are shown in Table 1.1.

Table 1.1: 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) [19]
Original Company Valuation studies				
DCE (33333)	[redacted]	[redacted]	[redacted]	0.8896
DCE (23223)	[redacted]	[redacted]	[redacted]	

DCE (23333)	[redacted]	[redacted]	[redacted]	
Vignette/TTO	[redacted]	[redacted]	[redacted]	
Statland mapping				
Period 1	0.67	0.54	0.13	
Period 2	0.61	0.53	0.08	
Averaged periods	0.64	0.54	0.10	
Hybrid DCE TTO modelling				
Hybrid 1	[redacted]	[redacted]	[redacted]	
Hybrid 2	[redacted]	[redacted]	[redacted]	
Source: Lupin response to ACD and ERG Report.[2, 3] BSC = best supportive care; DCE = discrete choice experiment				

ERG comment: The ERG consider that the hybrid modelling analysis was well conducted and that the analysts have done their best to limit the impact of the limitations in the data of the original studies. For example, the analysis controlled for left-right order in the DCE and non-monotonicity was prevented using box constraints, such that the incremental disutility of moving to a worse level along any INQoL dimension had a lower bound of 0. Linking the data from the two studies also resolves the anchoring issues for the DCE.

However, the reanalysis of data derived from a DCE study with design issues will not resolve those design issues or improve the quality of the data on which results are based. Concerns surrounding the complexity of the task with 8 simultaneously varying domains and the lack of clear monotonicity in response options and the impact these issues had on the understanding and attention of the respondents and the quality of the data remain. Therefore, the ERG still prefers to use the utility values produced by the vignette/TTO study to avoid the use of the DCE data. Scenario analyses using the other utility approaches are included in Section 3.

BSC health state utility score validation

To validate the BSC utility scores produced, the company conducted a clinical elicitation exercise, where they asked NDM clinicians to estimate where an average untreated adult NDM patient with symptoms severe enough for treatment with mexiletine might sit on the MS Expanded Disability Status Scale (EDSS).[20] The results of this exercise, provided in Appendix 1, suggest that the total range would be between an EDSS score of 3-7.5 (very rarely), but more frequently predicted between a score of 3-6. Four of the six clinicians, who could make the proxy comparison, stated a specific usual mean score of 5.0 (one said 5.0+).[21] An EDSS patient with a score of 5.0 is described as "*Disability severe enough to impair activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m*". EDSS patients with a score of 3.0 have no mobility issues, but three or four mild or one moderate functional system impairment. A patient with an EDSS score of 6.0 would require a walking aid, and is able to walk 100m with or without resting. With an EDSS score of 7.5, which is described in Appendix 1 as very rare (which is aligned with the clinical expert's experience in section 3.13 of the ACD), the patient can only take a few steps and would require a wheelchair.

The company reported various pieces of evidence on the functional ability of patients in MYOMEX as well as information available from patient experts, the MDUK submission and the literature.[3]

Two large UK cohort studies compared EDSS scores to EQ-5D scores.[22, 23] These studies estimated mean EQ-5D scores for patients scoring 5 on the ESSD of 0.531 or 0.518 for all MS patients or 0.438 for relapse/remitting patients. The company state that they believe this evidence provides some validation of the mean utility scores of the new hybrid models (with BSC utilities of [redacted] and [redacted])

ERG comment: The proxy utility scores identified from the studies comparing the EQ-5D to the ESSD in MS patients range from 0.531-0.438. This could provide support to the majority of BSC utilities produced by the various valuation methods, with the only value substantially outside of this range being the [redacted] predicted by the DCE with bottom anchor 33333. Therefore, if the company believe this to validate the BSC values produced by the hybrid models, they also believe that the value produced by the vignette/TTO method is valid, as this value sits between the two Hybrid values. However, given the fact that these scores are obtained from a different patient population, and the ESSD score=5 is only an estimate, this range provides an uncertain estimate of the BSC utility in NDM patients.

Treatment health state utility score validation

Again, the company select quotes from patient statements, clinician statements, the MDUK submission and the MyoPath survey regarding improvements in symptoms with mexiletine treatment[3], such as:

- "With Mexiletine, the situation improved considerably"
- "Patient expert explained that using mexiletine addressed most of the symptoms of NDM with near normal muscle function".
- Clinicians confirmed a greater than 0.3 utility gain, supportive of the significantly positive impact mexiletine can have on an NDM patients' quality of life
- "A wonder drug"
- "I wouldn't have a proper life without it"
- Senior clinicians from the main treating centre Queen Square (HSS), have confirmed that it is usual for mexiletine "to improve quality of life to normal"

Given this evidence the company believes that there is validity for the results of the mexiletine utility values produced by the hybrid models.

ERG comment: None of these quotes provide evidence for or against any of the alternative mexilietine values available. Again (as discussed in the ERG addendum following technical engagement), 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. The company submission includes statements from patients such as: "In late 30's, started medication which helped. Symptoms receded - 70% improvement"[24] 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, and actually provides support for the vignette/TTO value of [redacted].[25] Another expert stated that we would expect utility values of [redacted] for patients on mexiletine and of

approximately [redacted] in patients not receiving treatment. Only the values produced by the hybrid and vignette/TTO methods fall within these predicted ranges for both treatments.

7. Caregiver disutilities

The company report that they had planned to present results from a caregiver survey to provide further data to demonstrate the impact of NDM on carers to support the inclusion of a carer disutility within the cost-effectiveness model. However, due to ethical approval delays, the survey remains on-going.[26] The company agrees with the ACD that NDM can affect the QoL of both patients and caregivers and provides quotes from caregivers from the Patient Organisation submission.

The company reported that in technical engagement, scenarios were presented based on caregiver studies for both DMD and MS.[3] The ACD suggested that the disutilities assumed from caring for DMD were inappropriate for this appraisal, given that this disutility represents carers of non-ambulatory patients, who are very rare in NDM. However the company note that they had incorrectly reported this in the technical engagement response, as the primary source does not differentiate between ambulatory and non-ambulatory patients for this carer disutility (both ambulatory [56%] and non-ambulatory [44%] DMD patients were included in the study).[27] The company applied a conservative [redacted] as the input for the proportion of patients who required sufficient care to represent a DMD caregiver disutility, based on feedback from the clinical advisory board.[28]

The company conducted further scenarios regarding carer disutilities, using a study by Acaster et al. which examined carer disutilities for carers of MS patients against patient determined disease scores (PDSS).[29, 30] EDSS and PDSS scores have been shown to be highly correlated, and a score of 4.0 or 5.0 on the EDSS scale could be interpreted as approximate to a score of 2.0 to 3.0 on the Patient determined disease steps (PDSS) scale.[31] The more severe PDSS score of 3.0 is described as "*Gait Disability: MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually doesn't need a cane or other assistance to walk, but I might need some assistance during an attack*." The company believes it is plausible that this score could be justified as a proxy for an NDM patient receiving BSC. From the Acaster et al study the estimated disutility of a caregiver of an MS patient with a PDSS score of 2.0 to 3.0 was found to be -0.045. This value is greater than those investigated by the company at technical engagement, and suggests that the Company base case value used previously (an average of -0.022 per patient) may even be conservative. No base-case change was made.

ERG comment: It is unclear whether the assumption that all patients with NDM would score 2 or 3 on the PDSS is appropriate, or whether some patients would also score 1, described as "*The person that I care for has some noticeable symptoms from his/her MS but they are minor and have only a small effect on his/her lifestyle*." If this is the case, the disutility for carers of patients at this level would be -0.002 and therefore the company's assumed disutility of -0.045 would be overestimated. The ERG notes that the DMD disutility of -0.11 does indeed include the carers of both ambulatory and non-ambulatory patients. However, this disutility is still more severe than the NMD population given that the clinical expert in the committee meeting stated that non-ambulatory NDM patients are very rare, given that they had only ever seen 1 patient who needed to use a wheelchair.[32] It is unclear whether the application of this overestimated disutility to [redacted] of the NMD population is appropriate. On balance the ERG still considers that there would be an impact on carers, but it is unclear what disutility would apply, to what proportion of patients. Given the committee's

preference to remove this, in light of these substantial uncertainties and given that these uncertainties remain unresolved, the ERG will remove this disutility from their updated base-case.

8. Clinical trial/ unblinding – Trial design

The company argues that this evidence was required by and accepted by the EMA in order for NaMuscla to receive its licence. The potential carry over effect and unintentional blinding were not evidenced in the MYOMEX trial, and no risk of bias has been found. The Company therefore does not believe that relevant evidence provided above has been taken into account.

ERG comment: The ERG agrees with the committee the potential for unblinding and carry-over effects, short trial duration and few patients contribute substantial uncertainty to the MYOMEX results as outlined in our original ERG report.[2]

9. Resource use

The company clarified that the questions used in the Delphi study to elicit the resource use multiplier were clear in asking the percentage of patients who would use each type of resource and *of those patients who use the resource*, how often would they use it per year.

ERG comment: In the ACD, the committee highlighted the uncertainties related to this multiplier and the likelihood that it was overestimated given that patients not receiving mexiletine would likely be receiving an alternative treatment.[32] Therefore, the committee considered the ERGs amendments were likely to be appropriate for comparison with BSC, but would not reflect what happened in clinical practice. Given the limited impact of the assumed resource use multiplier (of 1, [redacted] or [redacted]) on the ICER, shown in Table 3.7 of the ERG's addendum following technical engagement, no ERG base-case change will be made.[33]

10. Other comments

Disease Progression - Given the uncertainty of the natural history of the disease, the Company has removed any disease progression assumptions from its base and scenario economic cases.

ERG Comment: The ERG agrees with this choice.

Statland trial - The ERG agrees with the company that 59 patients were randomised in the Statland trial.

NDM patients over 65 – The company noted that in section 3.5 of the ACD it states: "*The Company noted that most people over 65 with NDM are on treatment with mexiletine*".[32] The Company doesn't believe it has noted this in the evidence.

ERG Comment: The ERG has nothing to add here.

Mexiletine formulation – Section 3.7 of the ADC states: "*NaMuscla is a new formulation of mexiletine that uses different dose measurements to previous off-label use (a 167 mg capsule of NaMuscla formulation [mexiletine base] is equivalent to 200 mg of imported mexiletine [mexiletine hydrochloride]). However, all*

the clinical evidence uses the imported formulation of mexiletine." The company wanted to clarify that NaMuscla contains mexiletine hydrochloride, and 200 mg mexiletine hydrochloride corresponds to 167 mg of mexiletine.

ERG comment: The ERG has nothing to add.

Adverse events – The company noted that in section 3.7 of the ACD it says "*The committee considered that because of the short duration of the MYOMEX trial, some adverse events might not have been reported. In clinical practice, such adverse events could take much longer than the MYOMEX trial duration to emerge*."[32] In their response to technical engagement, the company noted that it believed 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.[4] The company amended its base case because the MYOMEX study and the Suetterlin et al study have relatively similar AE rates, and AEs are not a large driver of the cost-effectiveness results, and to align with the Technical teams assumption of the MYOMEX AE input in the base case. The company provided a scenario based on its updated base-case (using Hybrid Model 1 utilities), which showed that the ICER using the MYOMEX AEs is [redacted] and the ICER with Suetterlin et al. AEs is [redacted].

ERG Comment: The scenario provided shows that this choice has a very minor impact on results and is not a key issue.

MYOMEX and Suetterlin responders – In section 3.8 of the ACD it states: "*The committee also noted that not everyone in clinical practice would be expected to respond to treatment with mexiletine; MYOMEX and the Suetterlin et al. study selected patients that would be more likely to respond* (see section 3.6)."

For the company's revised base case (see Appendix 2b), the model does not assume every patient responds. The discontinuation applied to the revised base case the Company believes is conservatively applied (8% from Myomex trial is higher than others reported from Statland et al, Stunnenberg et al or Suetterlin et al). There are a number of patients (3) who didn't respond with lower utility values on mexiletine than on placebo in the revised base case (see Economic model patient level data).

Additionally, the company feel that it isn't clear in section 3.6 why the MYOMEX or the Suetterlin et al. would have selected patients that would be more likely to respond, as Suetterlin et al is a retrospective study of clinical practice, whereas for the MYOMEX study the Company evidenced that any previous treatment with mexiletine did not influence the expectations of the patients with respect to treatment effect (see section 8).

ERG Comment: The ERG has nothing to add here.

EQ-5D-3L – The company comment that section 3.10 of the ACD states: "*The Company considered that generic quality-of-life measurement tools such as the Short Form 36 (SF-36) or EuroQoL 5 dimensions (EQ-5D-3L) are unable to effectively capture the quality-of-life implications of muscle locking in NDM*". The company doesn't believe it has stated in the evidence that the EQ-5D-3L is unable to effectively capture the quality-of-life implications of muscle locking in NDM in the evidence. From a review of the literature,

the EQ-5D has never been used in this disease area, and therefore the suitability of this tool in capturing quality of life in this patient population is unknown.[3]

ERG Comment: The ERG considers that if there is no evidence that the EQ-5D does not perform well in this population, then it should have been used by the company all along. Additionally, if the EQ-5D had not been collected in the patient population, the company could have performed a mapping study (as preferred by NICE when no EQ-5D utilities are available) from the INQoL to the EQ-5D which would have removed the need for the conceptual mapping and reduction of INQOL and the DCE and TTO studies and the uncertainties introduced into the HRQoL analysis by these elements.

Mobility – The company noted that in section 3.13 of the ACD it states, "*no patients in MYOMEX needed to use wheelchairs or walking aids*." Company is only aware that no patients in the MYOMEX trial needed a wheelchair or walking aid to complete a walking test of 3 to 5 meters.

ERG Comment: The ERG thanks the company for this clarification. The ERG also notes that the clinical expert in the committee meeting reported that they had only ever seen one patient who used a wheelchair and therefore non-ambulatory patients were rare.

467mg mean effective dose – The company report that there is an error in the ERG's calculation of the mean effective dose of 467mg estimated from Suetterlin et al, which relies on 40 patients with a chloride channel mutation requiring a mean dose of 550mg mexiletine hydrochloride.[4] The company report that this is incorrect as from the Suetterlin et al study, only 10 patients are reported to be on this dose.

ERG Comment: Given the committee preference for using the maintenance dose of 600mg, this mean effective dose is no longer used in the ERG base-case or scenarios and therefore this issue is no longer relevant.

MS Patient utility – The company noted that in the lead team slides it states that "*the company compares utility of NDM to multiple sclerosis. Reference EQ-5D utility value for an ambulatory but relatively severely disabled multiple sclerosis patient – and provides a utility value of 0.59*." The Company does not believe it has compared the utility of NDM to a multiple sclerosis patient with a utility value of 0.59.

ERG Comment: The ERG has nothing to add here.

2. Company's updated cost effectiveness results

In their ACD response, the company propose an increased discount in the price per pack from [redacted] to [redacted] (from an original price of [redacted]) and this new PAS is included in their updated cost effectiveness analyses.

Based on ACD, the company has made the following changes to their post-technical engagement base-case:

- Removal of disease progression
- Use of utilities estimated from Hybrid 1 model

The committee and company preferred base-cases still differ on the following aspects:

- Preferred mexiletine maintenance dose (416.7 mg of mexiletine hydrochloride in the company base-case and 600mg in the committee preferred base-case)
- Inclusion a carer disutility (-0.11 for [redacted] of patients off-mexiletine in the company base-case, not included in the committee preferred base-case)
- Resource use based on the Delphi Panel (multiplier of [redacted] in company base-case, multiplier of [redacted] in the committee preferred base-case)
- Source of utility values (Hybrid DCE and TTO model in company base-case, TTO study in committee preferred base-case)

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]	-	-	-	-

Source: Table 2 of the company response to the Appraisal Consultation Document.[3]
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]	-	-	-	-

Source: Table 2 of the company response to the Appraisal Consultation Document.[3]
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

[redacted]

Source: Figure 1 of the company response to the Appraisal Consultation Document.[3]
PSA = probabilistic sensitivity analysis; QALYs quality-adjusted life years, WTP = willingness to pay.

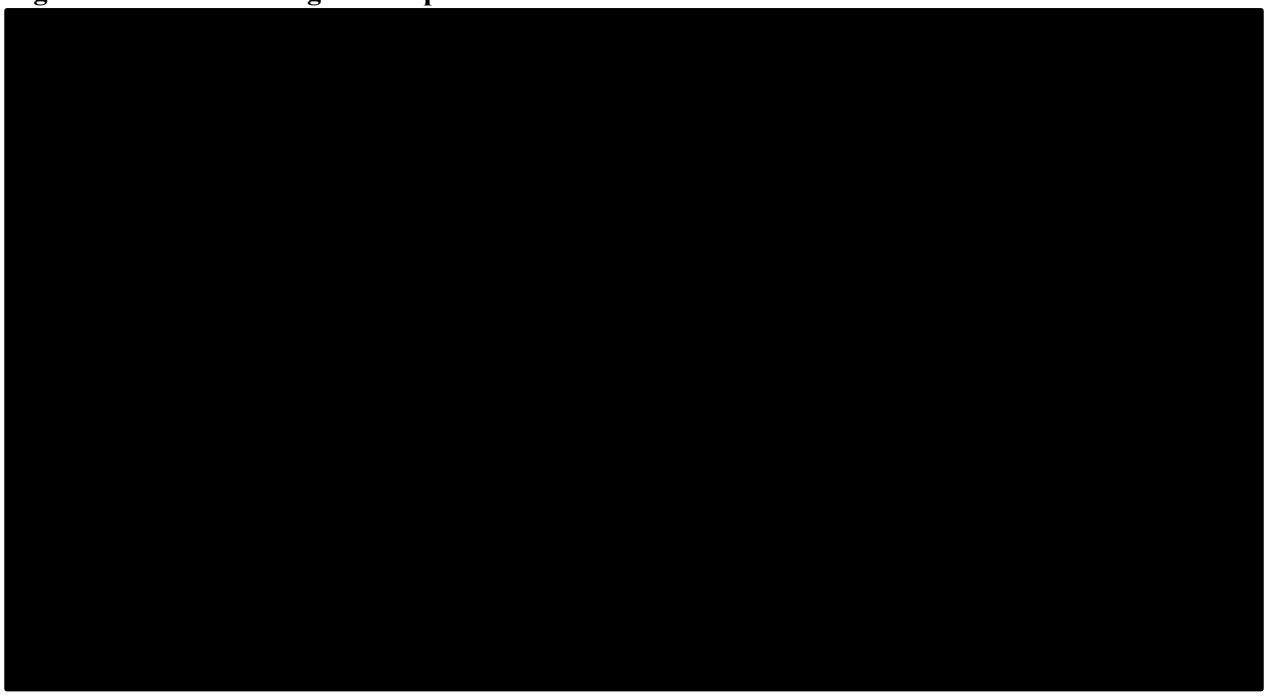
Figure 2.2: Company's updated CEAC

Source: Figure 2 of the company response to the Appraisal Consultation Document.[3]
CEAC = cost effectiveness acceptability curve.

2.2.2 Deterministic sensitivity analysis

Figure 2.3 shows that the parameters with the largest impact on the ICER were the assumed maintenance dose of mexiletine, the compliance rate and the assumed utility values for each treatment. These parameters closely reflect the key issues remaining in this appraisal.

Figure 2.3: Tornado diagram: impact on ICER



Source: Figure 3 of the company response to the Appraisal Consultation Document.[3]
ICER = incremental cost effectiveness ratio.

2.2.3 Scenario analyses

The company conducted a limited number of scenarios on their updated base-case, as shown in Table 2.3. The scenarios all had a fairly small impact on the ICER, with the most impactful scenario being that which assumed a carer disutility of 0.045 for all patients receiving BSC, which decreased the ICER by approximately £1,500. All four scenarios resulted in ICERs below £30,000 per QALY gained.

Table 2.3: Company scenario analyses (New PAS, discounted)

Scenario	Mexiletine		BSC		Incr. cost	Incr. QALYs	ICER £/QALY
	Costs	QALYs	Costs	QALYs			
Updated Company BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario using slower mexiletine titration*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario using Hybrid 2 model for utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario using a carer disutilities of 0.045 for all placebo patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Mexiletine		BSC		Incr. cost	Incr. QALYs	ICER £/QALY
	Costs	QALYs	Costs	QALYs			
Updated Company BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
and patients off mexiletine							
Scenario using Suetterlin et al (2015) AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*4 weeks at 200mg, 4 weeks at 300mg, 4 weeks at 400mg, 4 weeks at 500mg, 429mg maintenance dose
Based on company model submitted alongside their Response to the Appraisal Consultation Document.[3]
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:

- Maintenance dose 600mg
- The vignette/TTO HRQoL valuation approach was used instead of the company's preferred Hybrid approach
- Exclusion of carer disutility due to uncertainties in severity of population in relation to disutility sources
- The ERGs preferred resource use multiplier of [redacted] was used to replace the company's preferred multiplier of [redacted].

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, approximately double the ICER from 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 company model submitted alongside their Response to the Appraisal Consultation Document.[3] 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. The changes which had the largest impact on the ICER were increasing the maintenance dose to 600mg and switching from the Hybrid model utilities to the vignette/TTO utilities.

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 ACD	2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 1 – Maintenance dose 600mg		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG change 2 – Vignette/TTO valuation approach used instead of Hybrid		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 3 – Carer disutility removed		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 4 - Resource use multiplier [redacted] instead of [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on company model submitted alongside their Response to the Appraisal Consultation Document.[3]
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 company model submitted alongside their Response to the Appraisal Consultation Document.[3]
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 the Appraisal Consultation Document.[3]
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 the Appraisal Consultation Document.[3]
CEAC = cost effectiveness acceptability curve.

The DSA run on the ERG's updated base-case shows that the assumed maintenance 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 the Appraisal Consultation Document.[3]
ICER = incremental cost effectiveness ratio.

3.1 Additional scenarios conducted by the ERG

3.1.1 Scenario set 1: Mexiletine dosage

As shown in Table 3.4, assuming the company preferred 429mg maintenance dose of mexiletine reduces the ICER to [redacted], which represents a decrease of approximately [redacted] from the ICER based on the 600mg dose.

Table 3.4: ERG mexiletine dosage scenarios

Mexiletine dosage	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Trial dose 600 mg (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Suetterlin dose 429 mg (Company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on company model submitted alongside their Response to the Appraisal Consultation Document.[3]
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 Hybrid 1 model, while the ERG prefer to use the vignette/TTO approach. Using the company's preferred hybrid model 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. These both increase the ICER substantially but should be interpreted with caution given the substantial limitations to this crude analysis.

Given the 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. The ERG explored scenarios with carer disutilities applied as per the company base-case and a reduced carer disutility of 0.06, to account for the possibility that the carer disutility of 0.11 assumed from ambulatory and non-ambulatory Duchenne patients was too large for a severe NDM population. Assuming the disutility of 0.11 for [redacted] of patients not receiving mexiletine decreased the ICER by approximately [redacted], while the smaller disutility of 0.06 reduced the ICER by approximately [redacted]. These scenarios show that while assumptions surrounding carer disutilities do have some impact on the ICER, the far more impactful issue is the HRQoL valuation approach chosen.

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette/TTO approach (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid 1 (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid 2	[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 [redacted] of NDM placebo patients and patients off	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility values	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
mexiletine (company BC)							
Carer disutility of 0.06 applied to [redacted] of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No carer disutility (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on company model submitted alongside their Response to the Appraisal Consultation Document.[3]
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.

4. ERG conclusions

Several key issues remain in the cost effectiveness analysis, which represent the differences in the company and ERG/committee preferred ICERs. The issues which have the largest impact on the ICER are the valuation approach used to determine the health state utility values and the assumed maintenance dose of mexiletine. Two other issues which have a smaller impact on results are assumptions surrounding carer disutilities and the assumed resource use multiplier.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders

ADDENDUM: ERG results following updated PAS, July 2021

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. Company's updated results

The company submitted an updated patient access scheme (PAS) of [redacted] (previously [redacted]) which lowered the price per pack of Namuscla (mexiletine) to [redacted].[1]

1. Updated company base-case results

The company's base-case deterministic and probabilistic results including their updated PAS are presented below in Table 1.1. The deterministic analysis resulted in an incremental cost of £[redacted] and an incremental QALY gain of [redacted], which equates to an ICER of £[redacted] per QALY gained. Incremental costs were lower in the probabilistic analysis, but incremental QALY gains were higher, resulting in a probabilistic ICER of £[redacted], which is closely aligned to the deterministic ICER.

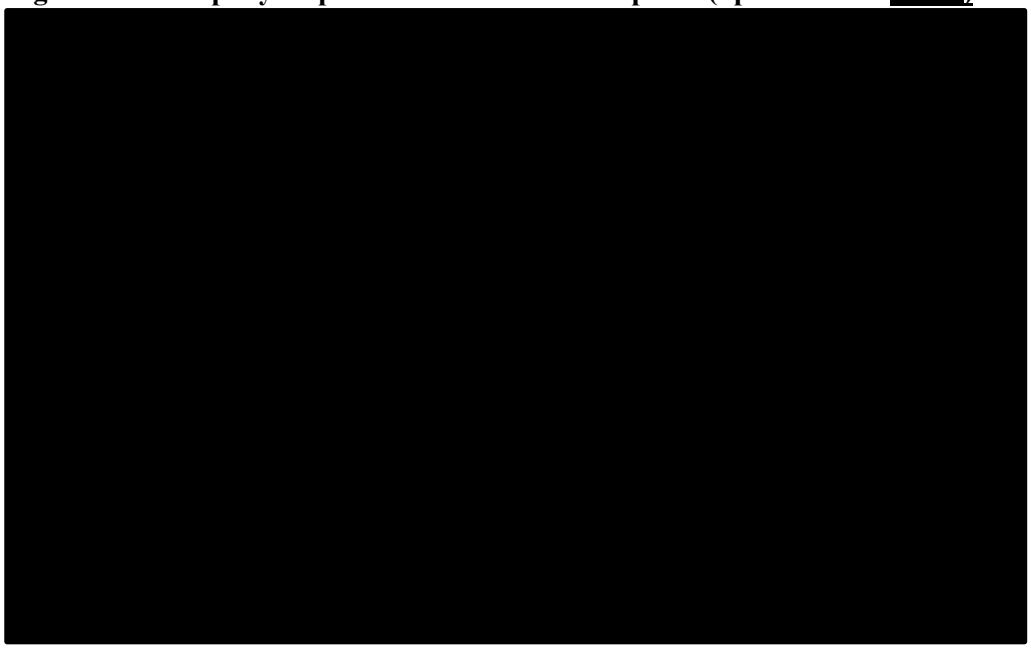
Table 1.1: Company updated base-case cost effectiveness results (Updated PAS [redacted], discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Deterministic							
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]	-	-	-	-
Probabilistic							
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]	-	-	-	-

Source: Table 2 of the company's updated evidence.[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.

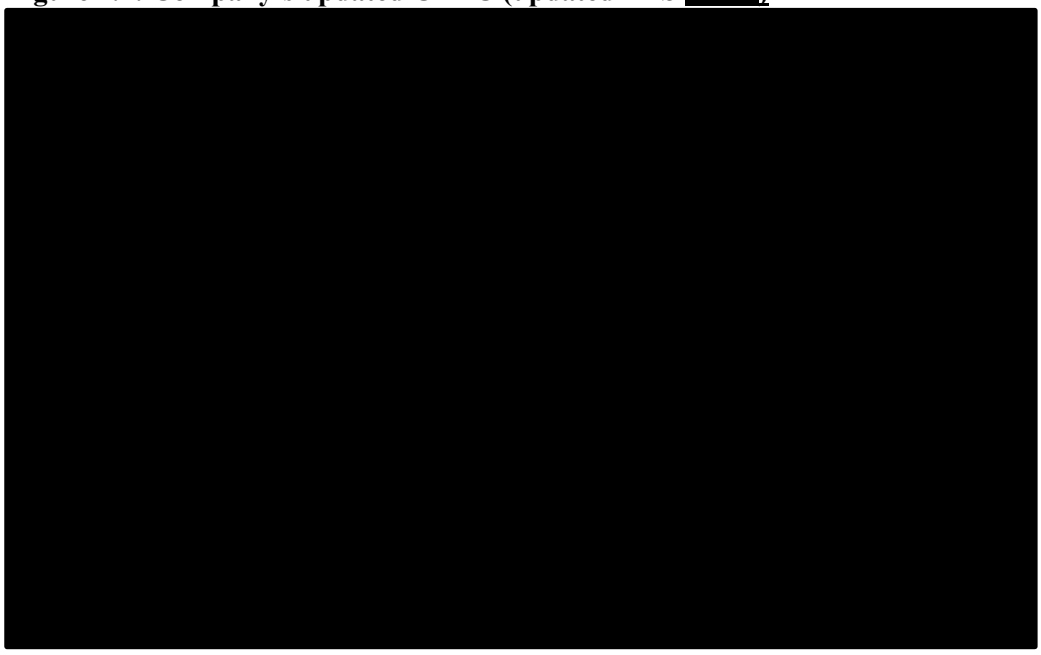
The updated cost effectiveness plane and cost effectiveness acceptability curve (CEAC) are shown in Figures 1.1 and 1.2 respectively. These results show that at thresholds of £20,000 and £30,000, mexiletine has probabilities of [redacted]% and [redacted]% of being cost effective respectively.

Figure 1.1: Company's updated cost effectiveness plane (updated PAS [redacted])



Source: Figure 1 of the company's updated evidence.[1]
PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years; WTP = willingness to pay.

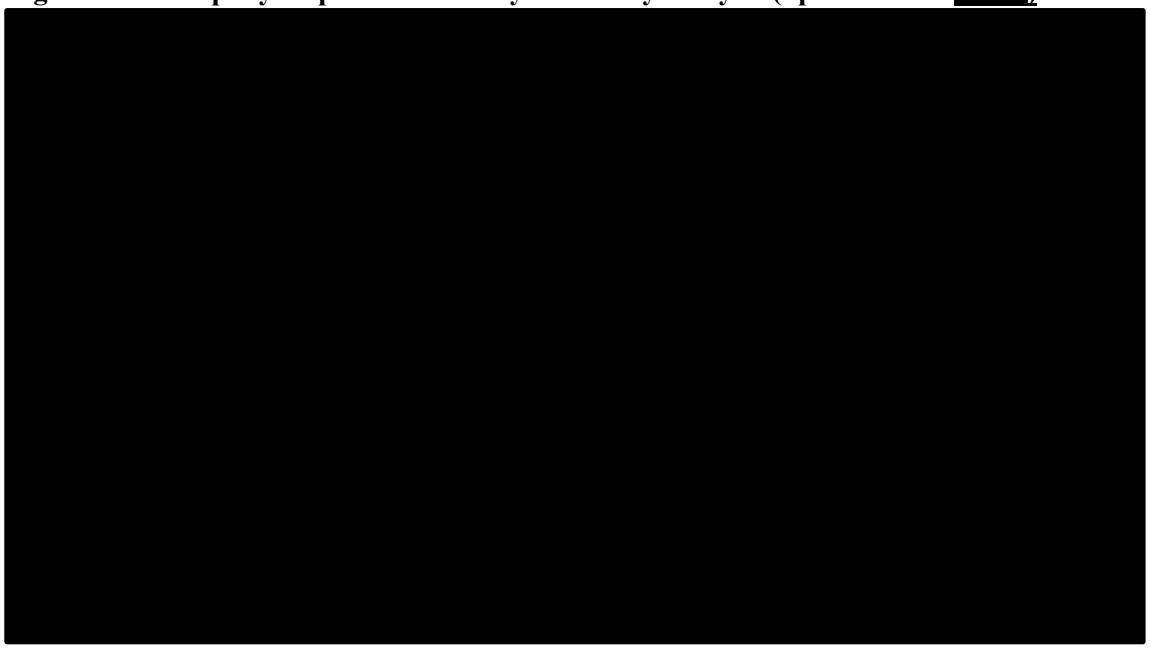
Figure 1.2: Company's updated CEAC (updated PAS [redacted])



Source: Figure 2 of the company's updated evidence.[1]
CEAC = cost effectiveness acceptability curve.

The updated one-way sensitivity analysis displayed in Figure 1.3 shows that the mexiletine maintenance dose, compliance rate and utility values remain the key drivers of model results.

Figure 1.3: Company's updated One-way sensitivity analysis (updated PAS [redacted])



Source: Figure 3 of the company's updated evidence.[1]
ICER = incremental cost effectiveness ratio

The company also report that the updated budget impact analysis suggests that the net budget impact for this medicine in Year 3 at the updated PAS is circa [redacted], which they report represents a medicine already established in clinical practice.[1]

ERG comment: The ERG can confirm that updated deterministic and probabilistic results are consistent with previous assumptions and models and only reflect the change due to the updated PAS.

2. Updated company scenario analyses

The company provided results for a number of scenarios conducted on the company and ERG base-cases, according to both the Appraisal Consultation Document (ACD) PAS and the updated PAS. Results of these scenarios are shown in Table 1.2 below.

Table 1.2: Updated company scenario results

	ICER	
	ACD PAS [redacted]	**Updated PAS [redacted]**
Updated company base case	[redacted]	[redacted]
Scenario using Hybrid 2 for utilities	[redacted]	[redacted]
Scenario using a carer disutilities of 0.045 for all placebo patients and patients off mexilitine	[redacted]	[redacted]
Scenario with no carer disutility for all placebo patients and patients off mexilitine	[redacted]	[redacted]
Scenario using 21 doses	[redacted]	[redacted]

ERG base case*	[redacted]	[redacted]
ERG base case with carer disutilities of 0.045 for all placebo patients and patients off mexilitine	[redacted]	[redacted]
ERG base case with no carer disutility for all placebo patients and patients off mexilitine	[redacted]	[redacted]

Note: *ERG base case is the company base case with the following amendments:
- TTO data for utilities
- Multiplier for healthcare resource use for no treatment of [redacted] (company base case uses a multiplier of [redacted])

Source: Table 1 of the company's updated evidence.[1]
ACD = appraisal consultation document; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; PAS = patient access scheme

ERG comment: The ERG was able to verify the results of the scenarios performed on the company base-case. However, the updated ERG base-case results and scenarios presented do not reflect the most recent ERG base-case, which was amended in the ERG addendum following the ACD.[2] The notes in Table 1.2 above show that the company assumed that the ERG base-case differed from theirs in only two elements: utility values estimated using vignette/TTO data (company base-case uses Hybrid 1 model) and assuming a multiplier for healthcare resource use for no treatment of [redacted] (company base case uses a multiplier of [redacted]). However the ERG's updated base-case post ACD (as outlined in their addendum post-ACD[2]) differs from the company base-case in these two assumptions, as well as assuming a mexiletine maintenance dose of 600mg (429mg in the company base-case) and no disutility due to caring (-0.11 for [redacted] of patients off-mexiletine in the company base-case). Therefore the ERG base-case results and scenarios presented in the company's document and Table 1.2 above are inaccurate and updated results will be presented below.

3. Updated ERG base-case results

The ERG's base-case deterministic and probabilistic results including the updated PAS are presented below in Table 1.3. The deterministic analysis results in an incremental cost of £[redacted] and an incremental QALY gain of [redacted], which equates to an ICER of £[redacted] per QALY gained. The probabilistic results were well aligned with the probabilistic results, resulting in a probabilistic ICER of £[redacted].

Table 1.3: Company updated base-case cost effectiveness results (Updated PAS [redacted], discounted)

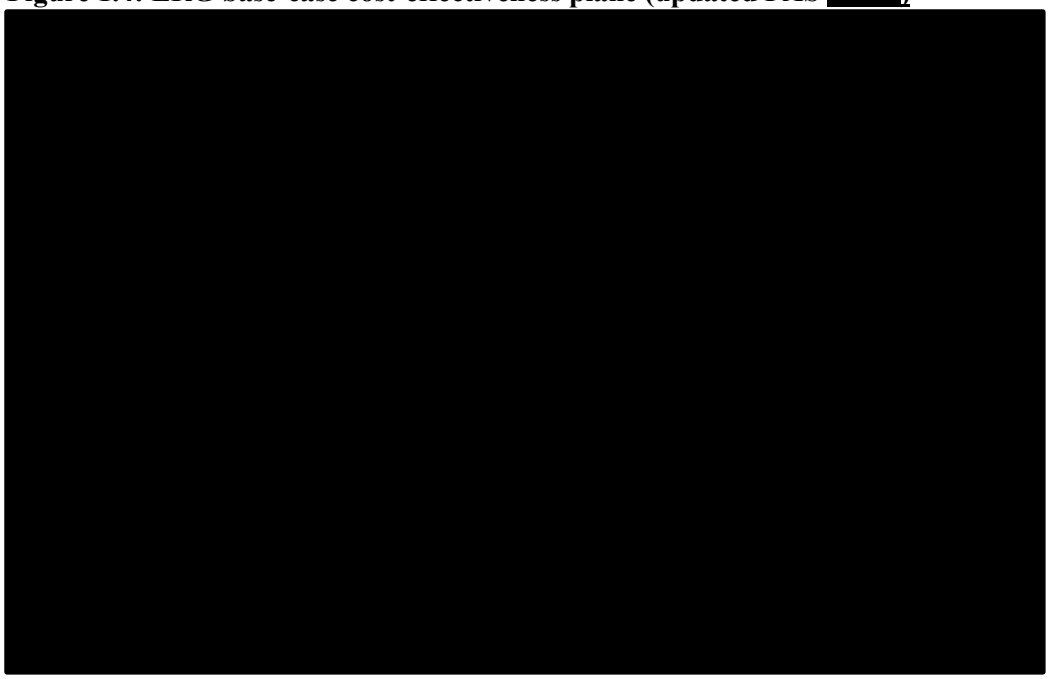
Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Deterministic							
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]	-	-	-	-
Probabilistic							
Mexiletine	[redacted]	37.99	[redacted]	[redacted]	0	[redacted]	[redacted]
BSC	[redacted]	37.99	[redacted]	-	-	-	-

Based on the model accompanying the company's updated evidence.[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.

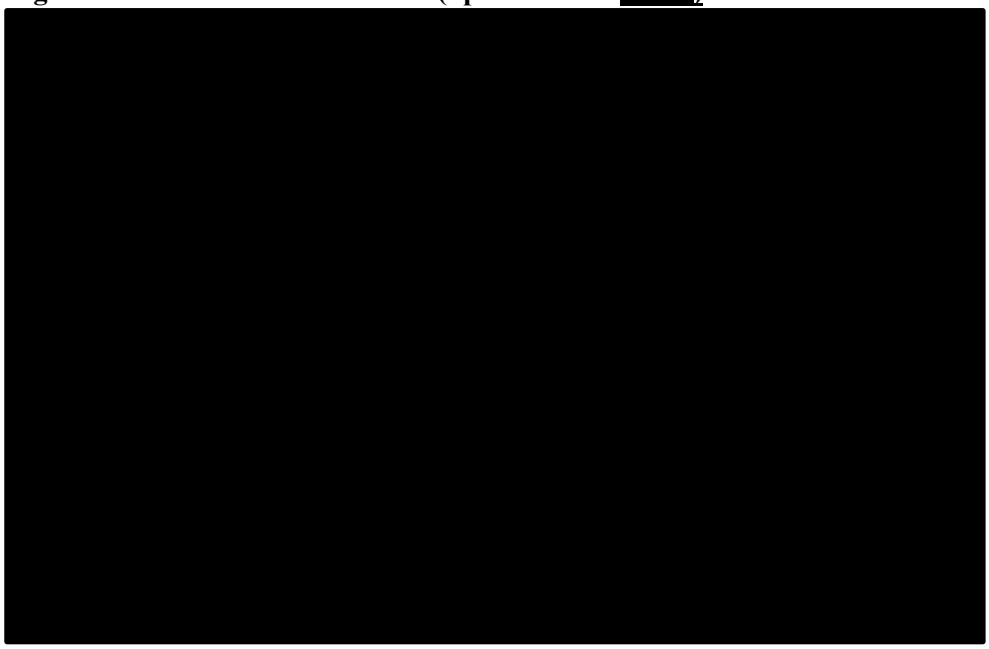
The updated cost effectiveness plane and cost effectiveness acceptability curve are shown in Figures 1.4 and 1.5 respectively. These results show that at thresholds of £20,000 and £30,000, mexiletine has probabilities of [redacted]% and [redacted]% of being cost effective respectively.

Figure 1.4: ERG base-case cost-effectiveness plane (updated PAS [redacted])



Based on the model accompanying the company's updated evidence.[1]
PSA = probabilistic sensitivity analysis; QALYs quality-adjusted life years, WTP = willingness to pay.

Figure 1.5: ERG base-case CEAC (updated PAS [redacted])



Based on the model accompanying the company's updated evidence.[1]
CEAC = cost effectiveness acceptability curve.

Table 1.4 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. The changes which had the largest impact on the ICER were increasing the maintenance dose to 600mg and switching from the Hybrid model utilities to the vignette/TTO utilities.

Table 1.4: ERG step-by-step assumptions and cumulative impact on ICER (updated PAS [redacted])

Preferred assumption (combined with previous lines)	Mexiletine		BSC		Inc. Costs (£)	Inc. QALYs	Cumulative ICER
	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company updated base-case after ACD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 1 – Maintenance dose 600mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 2 – Vignette/TTO utilities instead of Hybrid 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG change 3 – No carer disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG change 4 - Resource use multiplier [redacted] instead of [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on the model accompanying the company's updated evidence.[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 one-way sensitivity analysis run on the ERG's updated base-case shows that the assumed maintenance dose, compliance rate and utility values have the largest impact on results as shown in Figure 1.6.

Figure 1.6: ERG base-case DSA tornado diagram (updated PAS [redacted])

[redacted]

Based on the model accompanying the company's updated evidence.[1]
ICER = incremental cost effectiveness ratio.

3.1 Additional scenarios conducted by the ERG

3.1.1 Scenario set 1: Mexiletine dosage

As shown in Table 3.4, assuming the company preferred 429mg maintenance dose of mexiletine reduces the ICER to [redacted], which represents a decrease of approximately [redacted] from the ICER based on the 600mg dose.

Table 1.5: ERG mexiletine dosage scenarios (updated PAS [redacted])

Mexiletine dosage	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Trial dose 600 mg (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company preferred dose 429 mg (Company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on the model accompanying the company's updated evidence.[1]
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 1.6. The ERG and company still disagree on which HRQoL valuation approach to use in the base-case, with the company preferring the Hybrid 1 model, while the ERG prefer to use the vignette/TTO approach. Using the company's preferred hybrid model 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. These both increase the ICER substantially, but should be interpreted with caution given the substantial limitations to this crude analysis.

Given the 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. The ERG explored scenarios with carer disutilities applied as per the company base-case and a reduced carer disutility of 0.06, to account for the possibility that the carer disutility of 0.11 assumed from ambulatory and non-ambulatory Duchenne patients was too large for a severe NDM population. A scenario whereby a caring disutility of 0.045 was applied to all patients not on mexiletine was also included to provide a correct ICER for the company's scenario in Table 1.2. Assuming the disutility of 0.11 for [redacted] of patients not receiving mexiletine decreased the ICER by approximately [redacted], while the smaller disutility of 0.06 reduced the ICER by approximately [redacted]. Applying a disutility of 0.045 to all patients off mexiletine reduces the ICER by approximately [redacted]. These scenarios show that while assumptions surrounding carer disutilities do have some impact on the ICER, the far more impactful issue is the HRQoL valuation approach chosen.

Table 1.6: ERG utility value scenarios (updated PAS [redacted])

Utility values	Mexiletine		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs			
HRQoL valuation approach							
DCE approach anchored to 33333 and 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vignette/TTO approach (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid 1 (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid 2	[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 [redacted] of NDM placebo patients and patients off mexiletine (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutility of 0.06 applied to [redacted] of NDM placebo patients and patients off mexiletine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carer disutilities of 0.045 for all placebo patients and patients off mexilitine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No carer disutility (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on the model accompanying the company's updated evidence.[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.

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Mexiletine for treating the symptoms of myotonia in non-dystrophic myotonic disorders

Extra model calculations after Technical engagement – updated PAS

Authors: Hannah Penton and Maiwenn Al (ESHPM, in collaboration with KSR)

Date: 10 September 2021

Updated scenario ERG after TE (PAS [redacted])

Scenario set 3: lamotrigine as a comparator

No direct head-to-head evidence assessing the effectiveness of mexiletine compared to lamotrigine was identified. In order to still get an indication of the balance between costs and effects for mexiletine versus lamotrigine we had to make a few assumptions.

First, given that the impact of treatment on HRQoL is the only unit of effectiveness in the model, the current scenario investigates different utility values for lamotrigine, relative to those observed for BSC and mexiletine. This provides a range of scenarios regarding the potential cost effectiveness of mexiletine compared to lamotrigine, dependent on the utility value assumed for lamotrigine.

Additionally, we assumed that patients would receive lamotrigine at 300 mg per day. The price of lamotrigine was identified from the BNF (access data 25 February). Based on a price for lamotrigine 100mg 56 tablet of 2.98, lamotrigine 200mg 56 tablet = 3.07, we arrive at an annual cost of £43.67.

Next, 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]

Furthermore, we assumed that the probability of treatment discontinuation would be the same for mexiletine and lamotrigine, at 8% annually and that the carer disutility would only apply after discontinuing treatment with lamotrigine.[3]In addition, we disabled the disutility for gastro-intestinal adverse events for mexiletine, as we have also not incorporated a disutility due to SJS.

Finally, 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 of mexiletine (real world use) and [redacted] when using the higher dosage (as per the RCT). It should be remarked here that in a full incremental comparison including BSC as well, lamotrigine would be dominated by BSC, assuming a utility equal to that of BSC.

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[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

[3] It might be considered more reasonable to have this discontinuation rate and carer disutility vary between the mexiletine value and the BSC value in line with the utility for lamotrigine. This more elaborate change to the model was not feasible in the time available, but is likely to be of small effect on the ICERs.

Table 1: Scenario 3 Results - 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: Scenario 3 Results - lamotrigine as a comparator (Dosage mexiletine as in MYOMEX)

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; RW = real world.