



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 August 2013

Submission of comments on 'Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy' (EMA/CHMP/236981/2011)

Comments from:

TREAT-NMD Alliance

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).



1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>The TREAT-NMD Alliance, in collaboration with stakeholders in the neuromuscular field, welcomes the opportunity to comment on these draft guidelines. A TREAT-NMD workshop hosted by the EMA, on September 25th 2009, discussed the development of antisense oligonucleotide therapies for DMD, and a workshop report was published in 2010 (Muntoni et al., 2010). This workshop included discussions regarding outcome measures for clinical trials in DMD, and over the last 2-3 years substantial data has been gathered and published in regard to the 6MWT and other outcome measures in DMD. This work has included substantial input from various patient organisations, which have helped to contribute to the current knowledge of these measures and the clinical meaningfulness of their use in clinical studies with a number of different therapeutic strategies.</p> <p>Duchenne MD patient organizations have contributed to a more efficient drug development process, becoming partners in care, research and drug development; willing to shoulder responsibility and contribute towards advancing treatments and a cure. Some organizations have started their own research institutes, and others have invested in extramural research, clinical centres and industry to develop viable treatments. Collaboration</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>with patient organisations at all stages of the therapeutic development process has led to a speedier transfer of promising technology from the laboratory into clinical trials and will in future ensure that approval of and access to effective treatments will be addressed with the utmost urgency warranted by the severity of the condition.</p> <p>Duchenne Muscular Dystrophy is a progressive disorder where patients lose muscle fibres, causing muscle breakdown every single day and at all ages. This muscle breakdown leads to progressive loss of function, one function after another. In general, one could state that <u>slowing down or stopping the progression</u> of the disease is the most meaningful to patients because it preserves their quality of life, delaying by months or years the next loss of function.</p> <p>For the younger patients, being able to walk, to stand, to be able to get up from the floor after a fall or to fall less; to have enough arm strength to open a door or to lift one's arms to reach for an object; simple tasks, but activities of daily living that are important to preserve as long as possible. Maintaining the ability to walk is a priority which seems quite obvious but it is important to recognize that when it becomes impossible to walk up or down one or more steps, the individual will also be</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>unable to step off a curb, walk across the street and enter buildings with even a small threshold. If unable to get up from the floor, significant independence is lost as it then becomes unsafe for the individual to be alone, without assistance. The loss of these abilities impacts the school experience, increases the risk as well as the fear of falling.</p> <p>Losing the ability to stand further compromises the quality of life. It means the loss of the ability to transfer from chair to the toilet, from the bed to the chair, from chair to the car. With the loss of ambulation, stability of the trunk and arm function becomes very important to maintain. Arm function impacts the ability to manoeuvre the chair, to eat, to comb hair, to brush one's teeth, to take care of the simple tasks of everyday life. Hand function is a bridge to prevent the social isolation that accompanies progressive, debilitating diseases.</p> <p>Preserving the ability to turn over while in bed is important as this has a major impact on the entire family. Losing this ability necessitates a member of the family to wake several times each night, often between 6 and 10 times, to reposition the individual which leads to a great deal of lost sleep and increased stress for both the patient and the parent.</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>In adolescents and adults, coughing is essential to clear the airway and to maintain respiratory function. The inability to cough indicates increased weakening of the muscles of respiration. As a result, significant complications and death may result from infection and pulmonary complications. Finally, muscles become too weak to properly ventilate the lungs; night time ventilation is required and will ultimately be needed around the clock.</p> <p>The lack of dystrophin has a negative impact on the heart as cardiomyocytes are replaced by fibrous tissue and fat, which leads to rhythm abnormalities and right sided heart failure.</p> <p>In progressive debilitating diseases such as DMD, the loss of function ripples throughout the family as primary caregivers and other family members accommodate for the loss. The result is social isolation of the family as well as financial distress, as families struggle to cover expenses due to loss of income as a family member will necessarily be needed to provide the required comprehensive care.</p> <p>Individuals with DMD want and need to be productive members of society. It is important to realize that small changes, stabilization of disease no matter the age or</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>degree of function would make a meaningful difference in the lives of these patients and their patients, dramatically impacting the way these individuals feel, function and survive.</p> <p>The Duchenne community fears drugs currently in the pipeline, when showing safety and positive results, will only be allowed for a narrow label; that is, limited to the subset of patients tested during the trial. Young children and non-ambulant boys and men may have to wait many more years if a full dataset is required through a phase 3 clinical trial. Drugs are approved on data and not on emotions but <i>high medical need seems to counterweigh uncertainties about the scientific evidence in the benefit-risk assessment of OMPs (Putzeist, 2012)*</i></p> <p>The Duchenne Community believes it is essential to underline the high medical need as well as the risk of doing nothing. In rare, progressive, debilitating, life limiting conditions, there are very few or no options. Patients lose muscle fibres every day from birth on (young children already having CK levels above 20.000 IU/L, normal range is generally up to 250 U/L, showing massive muscle breakdown, is typical) which results in loss of function. Opportunities to slow or halt disease progression are severely limited or non-existent. Older boys and men with DMD still consider their lives as</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>very valuable. In adults, with little remaining muscle and severely limited function, it does not mean it is not important to treat them. On the contrary, for them, maintaining the ability to use their hands is crucial. To use a joystick as well as their computers, gives them the opportunity to work and communicate. Here is what some patients have to say:</p> <p>Robert (age 28) "Keeping as much functionality in my hands as possible is vital to me, it is really the only part of my body that has any strength left in it. It means I still have a little bit of independence left, because they enable me to still drive my chair with ease meaning I can go out with friends and family without having to rely on someone pushing me. I also participate in powerchair football, which is the only physically active sport that I am able to play and it is a good chance to socialise, but if my hands became too weak to drive my chair I would be unable to participate in this sport.</p> <p>I can still clean my teeth, I can still text my friends, and once I have been set up at my computer I can surf the Internet, chat with friends, send emails and play my favourite games all without any assistance, meaning I feel a sense of independence. Being able to go on the internet and chat with my friends is vital for helping me</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>socialise, particularly in the cold winters when I am unable to get out the house so often and this would increase my isolation further still. I then would be 100% dependent on others for every single little thing and I would be very isolated from the outside world, and this would be very hard to deal with.”</p> <p>Mark (age 43) “Keeping what limited hand movement I have, particularly in my right hand is extremely essential in maintaining independence. Whilst it may not be one of the life threatening aspects of my condition it is vital to many of the activities I carry out every day. The hand movement I have allows me the freedom to control my chair and operate my computer, thus keeping what little independence without assistance I have. When you need assistance with almost everything it’s very liberating to do a few things yourself. However, when my hand is cold I completely lose all function which is very frustrating and extremely debilitating. Anything which could avoid losing hand movement would obviously be hugely beneficial to myself and many others.”</p> <p>Jon (age 31) “Improved hand strength has a huge impact on the ability to people with DMD to maintain a degree of</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>independence and carry out activities of daily living. The ability to control a wheelchair independently is greatly enhanced by improved hand strength, without which individuals can lose the ability to get out and about, particular in cold weather, and may be isolated in their homes. Improved hand strength also vastly improves an individual's ability to use a computer, which is often a window to the world for people who may be isolated and is a social lifeline. The ability to use a mouse or keyboard can enable individuals to engage in gaming, one of the few interactive leisure opportunities available to adults with DMD which can have a huge impact on wellbeing."</p> <p>Extrapolation of data gathered in other groups of patients should be considered as an important opportunity for the Duchenne community. We are also encouraged by the on-going discussions about 'adaptive approaches' to clinical research, including extrapolation of data and hope the DMD patients can benefit from new recommendations in the very near future (please refer to de Jong et al., Nature Reviews Drug Discovery, Vol 12, September 2013, pp 647-648).</p> <p>* <u>Drug Discov Today</u>. 2012 Apr;17(7-8):352-8. doi: 10.1016/j.drudis.2011.10.027. Epub 2011 Nov 7.</p> <p>Determinants for successful marketing</p>	

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>authorization of orphan medicinal products in the EU.</p> <p>Putzeist M, Heemstra HE, Garcia JL, Mantel-Teeuwisse AK, Gispén-De Wied CC, Hoes AW, Leufkens HG.</p> <p>Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, The Netherlands.</p>	

2. Specific comments on text

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
Line 54		Comment: All cases of DMD have an onset in early childhood.	
Line 68		Comment: symptomatic girls are exceedingly rare.	
Line 74		Comment: a third of the patients with DMD do show cognitive or behavioural abnormalities, but these abnormalities don't deteriorate.	
Line 77		Comment: BMD is <u>always</u> milder than DMD	
Lines 78-79		<p>Comment: mentions quadriceps weakness can be the only BMD symptom - this sentence is obsolete. Either describe the variation from very mild to very severe or do not give any examples (patients with only elevated CK are known as well – this seems to be just a random phenotype that is included)</p> <p>Proposed change (if any): we suggest to delete this sentence and describe the variability of the disease (based on the following references: Comi et al., 1994; Angelini et al., 1994; McDonald et al., 1995; Aartsma-Rus et al., 2006)</p>	
Lines 79-82		Comment: We suggest to replace this sentence with that below.	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		Proposed change (if any): Patients remain ambulatory for a variable period of their life and the majority are not wheelchair dependant. Most patients develop at some point in time dilated cardiomyopathy that is the most common cause of death. Mean age of death is in the mid-60s, and life expectancy is likely to improve further with improved cardiac surveillance.	
Lines 81-82		<p>Comment: guideline states the mean age of death of BMD patients is mid-forties: This is not what is found in the Dutch BMD cohort – the average age of death is 51 years (range 34-89 years).</p> <p>Proposed change (if any): the estimated mean age of survival of BMD patients (based on a Kaplan-Meier analysis of the Dutch cohort) is 64 years.</p>	
Line 86		Comment: dystrophin is part of the dystrophin glycoprotein complex (DGC) that serves to link the muscle fibre cytoskeleton to the cell membrane and further to the extracellular matrix. (The sarcoglycan complex is part of the larger dystrophin glycoprotein complex).	
Lines 91-95		<p>Comment: Please insert the following sentence at the end of this paragraph.</p> <p>Proposed change (if any): It is nevertheless important to</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		realise that a genetic diagnosis in isolation and without the additional confirmation of dystrophin expression on muscle biopsy has a predictive accuracy of ~88% (Kesari et al., 2008).	
Line 97-98		Comment: we suggest to delete the sentence about other diagnostic methods, as the methods listed are either unspecific (CK, imaging) or explained further down in the text (biopsy).	
Line 102		<p>Comment: Please insert the following sentence at the end of this paragraph.</p> <p>Proposed change (if any): However the possibility of a 10-12% misdiagnosis based on genetic prediction alone should be born in mind (Kesari et al., 2008).</p>	
Lines 105-106		<p>Comment: states that corticosteroids are not approved for treatment of DMD patients and their use is limited due to significant side effects: we do not agree with this – corticosteroid use is in the standards of care for DMD and the majority of patients in the Western World are on steroids. Steroids have been shown to influence the natural history of the disease by prolonging lifespan, and delaying the onset of cardiac and respiratory complications, as well as delaying the time to loss of ambulation.</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		Proposed change (if any): <u>This statement is not correct – please replace with the following sentence.</u> Corticosteroids are recommended treatments and are NICE approved, and when using the two most commonly used steroid regimens, prolongation of ambulation has been achieved (Ricotti et al., 2013).	
Lines 169-172		<p>Comment: This sentence is not correct at least as far as steroids are concerned, and the sentence should be corrected. There are many different studies that have shown major prolongation of ambulation in DMD treated patients, for a recent reference that summarises the effect of the two most commonly used regimens please refer to Ricotti et al., 2013 (PMID 23250964).</p> <p>Proposed change (if any): Please amend sentence to include the following: `when applying standards of care for DMD, including the two most commonly used steroid regimens, prolongation of ambulation has been achieved (Ref. 6&11: Bushby et al, 2010; Ricotti et al., 2013).</p>	
Lines 175-176		<p>Comment: The use of the term `delay disease onset' is not correct as the disease onset is from birth. The `spread of disease' is also misleading, as this implies this is an infectious disease.</p> <p>Proposed change (if any): We suggest amending this sentence</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		as follows: 'This includes the delay of symptoms of weakness (or loss of function) in certain muscle groups as well as the delay in time to milestone events'.	
Lines 191-193		<p>Comment: We propose to change the end of this sentence as below.</p> <p>Proposed change (if any): A muscle biopsy could provide complementary information, and improve the diagnostic accuracy.</p>	
Lines 212-217		<p>Comment: The comment that studies should start in older children with a step-down approach should be amended. Therapies that specifically target muscle would only demonstrate a positive outcome in patients who still have muscle. As the disease progresses and muscle is lost this would indicate that younger patients would show greater benefit from these therapies than older patients. However, therapies that target fibrosis may have a clear benefit in older patients who have already lost most if not all their muscle, which at that stage will have been replaced by fibrotic tissue.</p>	
Lines 226-227		<p>Comment: we suggest deleting the last sentence of the paragraph, as many of the proposed assessment tools for muscle function have been validated and published over the last couple of years, as was presented at the TREAT-NMD workshop in London (http://www.treat-</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		nmd.eu/industry/regulatory-affairs/dmd-workshop-2013/ .	
Lines 230-231		<p>Comment: This might depend on the nature of a study. In a phase 1a or 1b study in which function is not an issue, why would one exclude a child started with steroids 4 months earlier?</p> <p>Proposed change (if any): This sentence should be specified 'for efficacy assessment'.</p>	
Lines 237-238		<p>Comment: This should be for treatments that are not mutation-specific.</p> <p>Proposed change (if any): subjects without a confirmed mutation in the dystrophin gene or a muscle biopsy confirming DMD; subjects with another neuromuscular disease.</p>	
Lines 251-253		<p>Comment: Evidence for a clinically relevant effect should be demonstrated in strength and translated into parameters of function, and vice versa. We do not agree.</p> <p>As demonstrated in recent publications and reported at the TREAT-NMD workshop in London, there is no linear correlation between muscle strength and function in boys with DMD (McDonald et al., Muscle & Nerve, pp357-368, 2013). It therefore seems to be unreasonable to always ask for evidence that there is a clear correlation between strength</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		and function. Please also see the comment below.	
Lines 254-256		<p>Comment: mentions that co-primary endpoints of strength and function should be used for clinical trials. We do not agree. Strength and function are both important outcomes but are not linearly related. A co-primary would dilute the power of the most relevant measure and would also increase the number of patients required to power a trial. Functional ability measured by motor performance is the most appropriate primary endpoint with other measures which may include strength and timed tests as secondary endpoints (this is based on discussions at a recent ENMC workshop on exon skipping – Aartsma-Rus et al, Neuromuscular Disorders, 2013). The primary endpoint may vary according to the stage of the disease. For example in ambulant boys 6MWT or North Star Ambulatory Assessment (NSAA) may be most appropriate whereas in older non-ambulant boys and men one of a variety of respiratory function tests or upper limb performance may be more appropriate. In infants development scales may be suitable.</p> <p>It has been demonstrated in mouse models that express low dystrophin levels that muscle pathology and motor function is improved and suggest that in patients low levels of dystrophin may benefit functionally, while strength is not improved (van Putten et al., 2013; van Putten et al., 2012).</p> <p>Furthermore, extensive data is now available showing that the correlation between strength and function is not linear in</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		<p>ambulant patients (McDonald et al., Muscle & Nerve, pp357-368, 2013). In fact, at early stages, patients lose a lot of strength, while decline in function is slow. By contrast at late stages patients lose a little strength and function declines rapidly. Finally, in studies restoring dystrophin, it is unlikely to improve strength, as dystrophin does not make muscle fibres stronger, but protects them from damage during contraction. Thus it is anticipated for compounds restoring dystrophin that the decline in strength will be slower, but not that muscles will become stronger.</p> <p>Taken together, asking for co-primary endpoints will dilute the effect, requiring larger groups of patients to find significance for both endpoints and given the non-linear correlation between strength and function it is unlikely that significant findings will be found for both.</p> <p>Proposed change (if any): Replace the suggestion of co-primary outcomes by a primary endpoint for muscle function, backed up by secondary endpoints for additional muscle function tests and/or strength (depending on the age group and the compound tested).</p>	
Lines 277-283		<p>Comment: This paragraph should be amended to reflect the good correlative nature of various outcome measures (such as 6MWT) with later outcomes, on one hand, and also the good correlation between many of these outcome measures, such as 6MWT and NSAA (Mazzone et al., 2011; Mazzone et al.,</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		2013). Proposed change (if any):	
Lines 282-283		<p>Comment: It states that it is not clear how timed activities correlate with quality of life, time to death and other life-changing events (e.g. time to wheelchair). This is not true – there are studies reporting a correlation between timed items and loss of ambulation (McDonald et al, Muscle & Nerve, pp343-356, 2013). In a recent study (Mazzone et al, 2013) the value of the North Star and the 6MWT in predicting loss of ambulation within 2 years has also been reported.</p> <p>Proposed change (if any): Revise text based on these new publications.</p>	
Lines 291-294		<p>Comment: We propose to change the text of this paragraph – see below.</p> <p>Proposed change (if any): “Generic scales with such a wide scope will include items that are not specific to the disease and severity of a target population so may not be sensitive or specific enough for use in a clinical trial. However the MFM could be appropriate for studies which have a wide range of diseases and different severities.”</p>	
Lines 295-297		Comment: We propose to change the text of this paragraph –	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		<p>see below.</p> <p>Proposed change (if any): "The NSAA is disease and stage specific to ambulatory DMD and has replaced the HMAS in both clinical and trial settings. NSAA offers a robust linearized score which is meaningfully related to activities of daily life for DMD. Responsiveness has been demonstrated in relationship to steroid regime and a minimal important difference (MID) has been published (Mayhew et al., 2013). A positive correlation exists between the NSAA and the 6MWT (Mazzone et al., 2012) and NSAA has been adopted as a secondary outcome measure in several therapeutic trials."</p> <p>Please refer to the following relevant references: Mazzone (PMID 19553120), Mazzone (PMID 20634072), Mayhew (PMID 21410696), Mazzone (PMID 21734183), Scott (PMID 21954141), Ergul (PMID 22404693), Mazzone (PMID 23326337)</p> <p>Detecting meaningful change in North Star Ambulatory Assessment in Duchenne Muscular Dystrophy. Anna G. Mayhew, Stefan J. Cano, Elaine Scott, Michelle Eagle, Kate Bushby, Adnan Manzur, Francesco Muntoni, ON BEHALF OF THE NORTH STAR CLINICAL NETWORK FOR PAEDIATRIC NEUROMUSCULAR DISEASE. DMCN, 2013</p>	
Lines 305-307		Comment: Recent studies have shown that there is no	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		<p>relevant learning effect associated with the 6MWT and have shown minimal clinically important differences (McDonald et al., Muscle & Nerve, pp343-356, 2013; McDonald et al., Muscle & Nerve, pp357-368, 2013).</p> <p>Proposed change (if any): We recommend the data and conclusions from the above references are included in the guideline to support the use of 6MWT as an outcome measure in ambulatory DMD trials.</p>	
Lines 308-314		<p>Comment: We propose to change the text of this paragraph – see below.</p> <p>Proposed change (if any): “Timed function tests continue to be used clinically and in trials because they provide relevant and meaningful linear data. By incorporating such activities into standardised functional rating scales (e.g. NSAA includes timed rise from floor and timed 10m run) and using appropriate calibrated timing devices confidence in the accuracy of these tests is high. Improved collaboration between international groups and standardised training procedures, including quality control by video review of assessments ensures accuracy.”</p>	
Line 315		<p>Comment: We propose to expand the text of this sentence – see below.</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		<p>Propose change (if any): "Measures for non-ambulant patients have been recently developed with the aim of providing data on clinically meaningful change. For example the performance of upper limb scale (PUL) and associated PROM (Mayhew, Eagle, Mazzone 2013). The recent development of these scales has been a collaboration between patients their advocacy groups and a multi-disciplinary international team of experts. This has ensured a clear link between measured performance and meaningful activities. Functional ability over the long term is measured with the validated Egen Klassifikation scale (EK)."</p> <p>Reference: Development of the Performance of the Upper Limb (PUL) module for Duchenne muscular dystrophy. Anna Mayhew, Elena Mazzone, Michelle Eagle, Tina Duong, Maria Ash, Valerie Decostre, Marlene Vandenhauwe, Julaine Florence, Marion Main, Flaviana Bianco, Erik Henrikson, Laurent Servais, Giles Champion, Elizabeth Vroom, Valeria Ricotti, Natalie Goemans, Craig McDonald, Eugenio Mercuri, on behalf of the PUL working group. DMCN, 2013</p>	
Lines 316-321		<p>Comment: These issues are being addressed particularly in assessment of ambulant patients. The NSAA combines clinically relevant functional performance with two timed tests.</p> <p>Proposed change (if any): "Recent publication of a linearised</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		scale generated by modern psychometric analysis (Rasch) for use in ambulant DMD has addressed issued raised by sum scores and has provided a definition of MID (Mayhew 2013 – in press). The techniques employed for this functional rating scale are currently being employed in other functional rating scales, e.g. Performance of the Upper Limb (Mayhew et al., 2013). Long term data are being systematically collected internationally for NSAA, 6MWT, timed tests.”	
Lines 334-339		<p>Comment: There is limited experience of these in the DMD population, while on the contrary there is recent and convincing data on the PODCI and its correlation with functional activities (Henricson et al., 2013).</p> <p>Proposed change (if any):</p>	
Lines 340-345		<p>Comment: This should not be limited to tracheostomy only. What about the requirement for ventilation for at least part of the day, in addition to night ventilation? Other criteria could include coughing or incidence of pneumonias.</p> <p>Proposed change (if any):</p>	
Lines 353-356		Comment: Cardiac MRI should be included in this section.	
Lines 357-360		Comment: Further research is needed to see if the PedsQL is sensitive to detect changes in DMD patients during a clinical	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		trial. Data will soon be available on the use of the Kidscreen.	
Lines 361-363		<p>Comment: Cognitive deficits in DMD are not progressive. This would only be relevant for those drugs that cross the blood brain barrier. Also, behavioural changes could also be influenced by positive effects or changes that make them feel better or have more energy.</p> <p>Proposed change (if any): delete 'or lack of deterioration in' from lines 362-363. This should now read: improvement of cognitive function might be a relevant clinical achievement.</p>	
Lines 389-391		<p>Comment: states that exon skipping will likely restore dystrophin irrespective of disease state: we disagree. Exon skipping targets dystrophin transcripts which are produced by muscle tissue. Thus exon skipping is anticipated to have more impact in younger children than older children with DMD.</p> <p>Proposed change (if any): Therapies that make use of dystrophin transcripts rely on muscle quality as only muscle produces dystrophin transcripts.</p>	
Lines 399-406		<p>Comment: This paragraph is very conservative. There is good evidence from the DMD/IMD and BMD population that any dystrophin is better than none and that it is associated with a functional benefit (with the exceptional exceptions of in-frame deletions completely lacking the actin binding domain or the</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		<p>beta DG binding domain). Therefore, we would hope that whenever appropriate we would use dystrophin as a pharmacodynamics marker of response, but that large studies will not be necessary to demonstrate efficacy when testing novel compounds such as novel antisense compounds, for which there will not be a large population to test.</p> <p>Proposed change (if any):</p>	
Lines 407-411		<p>Comment: states that the mdx model is a poor model for DMD phenotype and the predictive value of GRMD is not known. We agree, but would like to add that both models have been pivotal to gain insight into the pathology and that the mdx model has been very useful to develop many therapeutic approaches, in spite of its limitations. In particular it is well suitable for genetic approaches that are mainly discussed in the document. The reason the GRMD is of limited predictive value is that the phenotype varies a lot and usually only a few dogs are included in tests. TREAT-NMD has produced a number of standard operating procedures for enhancing predictability of drug testing in the mdx mouse model and these are increasingly used worldwide (Nagaraju et al., 2009; van Putten et al., 2010; van Putten et al., 2012). We would like to add that properly conducted mouse studies, along with a closer collaboration between pre-clinical and clinical scientists, help to prioritize best candidates or best approaches for clinical trials and likely reduce the risk of</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		<p>failure during translation. Many papers are now available to outline how to properly use the mdx mouse (Grounds et al., 2008; Willmann et al., 2012) and evidence are being produced in favour of a better matching of data set in mice and patients (Heemskerk et al., 2009; Heemskerk et al., 2010; Tanganyika-de Winter et al., 2012)</p> <p>Proposed change (if any): We suggest modifying lines 408-410 as follows: The proposed mechanism of action of a new product should be described and discussed in relation to possible testing in available animal models. The widely used mdx mouse and the golden retriever muscular dystrophy dog are of value for pathology studies and for pre-clinical tests of therapeutics. Adoption of standard operating procedures (such as those developed by TREAT-NMD) and of controlled experimental settings is highly recommended to minimise the known limitations of both models and enhance predictability of data (www.treat-nmd.eu/research/preclinical/dmd-sops/; Nagaraju et al., 2009; Willmann et al., 2009).</p>	
Lines 470-471		<p>Comment: We agree with this statement, but at the same time we propose the value of available datasets of current natural history cohorts, with essentially identical data on disease progression measures from the USA, Belgium, UK and Italy, as an example, given that they have been treated under the same standards of care as patients in clinical trials.</p>	

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		Proposed change (if any): To include the following statement: The use of natural history data will likely make the use of historic data a valuable means to contextualise the data seen in treated patients, particularly in long-term treatments where one can't utilise placebo. In that setting it is crucial to be able to use these data as the best means available to contextualise the findings.	
Line 554		<p>Comment: Another reason cardiac function may be more impaired after treatment is that muscle function improves so the strain on the heart becomes higher. It is also important to highlight and acknowledge that we do have mainstream therapies for cardiomyopathy and these are quite effective.</p> <p>Proposed change (if any): Add the comment "this is also discussed in Aartsma-Rus et al, Neuromuscular Disorders, 2013"</p>	

Please add more rows if needed.