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EMA/178057/2019
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments on 'Stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device' (EMA/532515/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Name of organisation or individual
Duchenne Community Advisory Board (CAB)
Representatives from the Critical Path for Parkinson's, Duchenne Regulatory Science Consortium, Critical Path for Alzheimer's Disease, Patient Reported Outcome Consortium, and the Quantitative Medicine Group on behalf of the Critical Path Institute, Ltd.
Pfizer Ltd
Duchenne Parent Project Belgium
Action Duchenne
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1. General comments

Please note that line reference numbers apply to the draft opinion.

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular_en.pdf

Stakeholder number	General comments	Agency Response /Outcome
1 (CAB)	The Duchenne CAB supports the use of suitable wearable devices as a measurement of outcomes in clinical trials for the following reasons: 1. The suitable wearable device is more patient relevant than and possibly superior to the 6MWT because: a. The 6MWT is subject to bias from the assessor and the family since the patient can be incentivised to do well by verbal encouragement or the promise of a reward. This is a concern and almost certainly influences outcomes; b. Patient compliance, mood, time of day, fatigue from travelling to the hospital inevitably impact the results of the 6MWT undertaken in a hospital setting; 2. Data collected continuously over a much longer period of time and in a natural setting, whether at home, school or work, would be far more reliable, objective and accurate than several 6MWTs taken in a hospital weeks or even months apart, which can only provide snapshots; 3. The use of data from a suitable wearable device is more relevant to clinical benefit as it tracks an individual's regular physical	Applicant plans to further develop usage of the device (waterproofing) and the importance of non-ambulant upper limb variable. No changes required.

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	activities throughout the day/week/weekend/month, thus eliminating variability; 4. It would increase patient outreach since it could be used to collect evidence of functional benefit in patients shortly before loss of ambulation who would probably not be accepted into a clinical trial using the 6MWT as an outcome measure, thus enabling and encouraging the participation of this as well as the non-ambulant population in clinical trials; 5. A suitable wearable device would lessen the burden of clinical trial procedures for patients and their families since less hospital visits would be required; 6. It would also be an additional measure for trials in the non-ambulant population groups to measure upper limb function in a natural setting i.e. home, school and work; 7. The amount of data collected by a suitable wearable device could significantly reduce the duration of clinical trials. In order to make the data collected by a suitable wearable device even more reliable and valuable, we strongly recommend the use of a (digital) patient diary to account for daily variation (physio; swimming; gym class; school and other holidays; illnesses etc. We also recommend that the next development in suitable wearable devices should be waterproofing them in order to additionally capture swimming exercise; waterproofing would hopefully also eliminate compliance issues due to patients forgetting to put the device back on after swimming, showering or bathing (increased compliance).	

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	In summary, the Duchenne CAB's opinion is that a suitable wearable device should be accepted as a secondary outcome measure in clinical trials as it has value for patients, sponsors and regulatory authorities in that it can more clearly prove the functional benefit of a treatment.	
2. CPath	Stride velocity 95th centile (SV95C), measured by the proposed ankle/wrist device, appears to be a potential equivalent, but not superior, measure to the six-minute walking test (6MWT) and the North Star Ambulation Assessment (NSAA). The SV95C may also reduce travel burden to individuals participating in clinical trials. Taken together, we agree a qualification opinion recommending SV95C as a secondary endpoint seems appropriate. However, given the limitations of the data presented, the ultimate impact of the qualification opinion, that is, how a drug sponsor could use this measure as a part of a clinical trial, is unclear. Many of the SAWP/CHMP's list of requested clarifications align with key recommendations from the Critical Path Institute's Electronic Patient-Reported Outcome Consortium's publication "Selection of and evidentiary considerations for wearable devices and their measurements for use in regulatory decision making: Recommendations from the ePRO". (Byrom 2018) Specific examples of these issues include test/retest data (gait variables), evolution of the device through validation studies, validation in healthy controls, compliance and patient burden concerns, impact of small numbers and concern for bias, measures to ensure data quality specific to continuous monitoring, data privacy and protection, influence of compliance on measurement variability, and how changes in the concept of interest (stride velocity) are linked to clinically relevant effects.	

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	Despite these limitations, a significant amount of work covering many aspects of disease progression is presented. We believe addressing the following issues in the final qualification opinion will help to optimize its utility and impact in encouraging both drug development in Duchenne Muscular Dystrophy (DMD) and the advancement of existing and novel wearable devices for medical applications. 1. It is unclear if the device itself, as purchased, generates the endpoint, or if a separate computer system is required for analysis. Further, no details of the algorithm used to process the raw sensor data to generate the SV95C are given. Many questions regarding data traceability, reliability, and provenance are therefore left unanswered. 2. The document refers to measurement using a “valid and suitable” wearable device, noting “the device should be able to detect all strides at all paces (slow to fast and turning strides)”, but does not specify how other devices would demonstrate the acceptability and accuracy of their stride length and velocity measurements. If other devices are capable of measuring SV95C to an acceptable regulatory degree, it should be clearly stated. 3. There is a single published citation highlighting the use of the ActiMyo1 Device in DMD. (Le Moing 2016) In that paper, the device was reported as an innovative device that uses magneto-inertial sensors to record angular velocities and linear accelerations that can be used over long periods of time in the home environment. This study included a severely limited sample size of seven DMD patients in a non-ambulatory setting for the initial validation work. In order to demonstrate the broader generalizability of the device’s use, it is	1. The focus of the qualification is the clinical measure. Details on methods & algorithms were already included in line 682 to 722 from the dossier. Further explanations are provided in the patent WO2017060660. The code themselves are part of Sysnav confidential information and will not be made public. 2. Other devices demonstrating the same or better performance as the ActiMyo could be accepted similarly. Additional text has been added to Introduction section of the opinion. 3. See QO appendix for details of the specifications and tests undergone by ActiMyo.

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	recommended the submitter publish the more extensive data (included in the qualification opinion) in a peer reviewed journal to enhance the scientific acceptance of this platform. 4. A second technical publication describing the comprehensive analysis methodology in sufficient detail to be replicated by others should be pursued and cited. A patent is cited in the current qualification opinion, but it is unclear whether or not this provides a comprehensive description of the device's analysis. 5. Validation of the device's measurements in patients of different ages, stages of disease, and variances in gait pattern is important to ensure the measure remains valid and can be applied in broader trials. 6. In the recently issued EMA qualification opinion of the Parkinson's Imaging Biomarker, the final opinion included a section on technical recommendations and methodologies for appropriate use in clinical trials.[3] A similar section would be helpful in the current opinion to ensure proper use in ongoing and prospective trials. We believe addressing these topics in the final qualification opinion will help provide sponsors a more defined roadmap for including this technology in future clinical trials. Given that additional data are requested to support its expanded use, we believe encouraging sponsors to include SV95C as an exploratory or secondary endpoint, possibly through a letter of support or similar mechanism, would be beneficial.	4. The performance observed in validation tests is also presented in detail in the dossier. There is no unique set of algorithms to compute the proposed endpoint. It is only critical to have a method which ensures at least a similar level of performance in validation tests. 5. Please see the current QO COU which details in which patients the SV95C is deemed acceptable as a SEP Ambulant DMD patients 5 years of age and above 6. A section on best practice in clinical trials has been added to the QO Appendix 3. .
Pfizer Ltd	<u>Overall impression:</u> We welcome the consideration of developing a digital endpoint to be a	The SV95C was most robust in comparison to cumulative (number of steps, duration of walk episodes …) or qualitative

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	secondary endpoint in DMD clinical trials. The data presented is innovative and interesting, and the need to develop alternative tools that can reliably, objectively, and quantitatively measure changes in disease progression in real-world settings is highly desired. However, we are concerned that the narrow focus on one specific gait parameter (95PSV) may be premature at this point, considering that the use of digital endpoints in DMD is still a matter of speculation. Further research is still needed before sufficient validation can be fully determined and firm conclusions can be drawn. Until then, we recommend the Agency to caution against overreliance on this validation.	(stride length, stride speed …) outcomes and turned out to be the most relevant and stable parameter. However, this does not exclude collecting data on other variables. Furthermore SV95C was considered relevant as a submaximal parameter, and less effected by age and height over time. No change required.
Pfizer Lid	<u>Recommendation for taking a device agnostic approach:</u> The clinical validity of the 95th percentile stride velocity seems to rely on the use of “valid and suitable device”. However, the accuracy of this endpoint and the generalizability of the findings are highly dependent on the system used for activity monitoring, and therefore, a more detailed definition of what constitutes a “suitable and valid wearable device” is warranted, especially with regards to the algorithms used to derive the endpoints from the raw data, comparison with gold standard measures, and test-retest reliability assessments. The generalizability of these findings and the reproducibility of the proposed endpoint in studies that utilize other wearable devices and that have been published in peer-reviewed journals should be considered. We recommend to the Agency that the future development of this endpoint for clinical trials in DMD should be based on scientific evidence and clinical relevance that are independent of the device used.	See CPath comments 1 and 2 above
Duchenne Parent Project	As parents of boys affected by DMD, we are very positive towards an objective measurement of the potential progresses generated by a new	No changes.

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Belgium	drug during CT. The 6MWT is really cruel and NSAA when captured occasionally at the hospital is not enough reliable given the little number of boys in DMD CT's	
Action Duchenne	• A wearable device has the potential to capture data on a consistent, long term basis in a real-world setting. • This has the potential to capture far more data points than a 6MWT conducted every few months, as well as measuring a far more natural for of activity. • This activity should be less liable to external influence such as a particularly encouraging assessor or attending legal guardian (ie parent). • Given how few data points a sporadic 6MWT delivers, they are particularly vulnerable to the patient's mood, demeanour, state-of-mind, experience (a long journey, pre-test anxiety, time of day/year etc) that day. • It would help reduce the burden on families of taking part in clinical trials - we know many families who regularly travel across the UK to participate. The 6MWT creates are a very high threshold of ambulation; as the condition progresses there will be many who can walk significant distances (sufficient to move around their homes or get into the car) but who won't be able to complete the 6MWT, thereby excluding them from tje vast majority of clinical trials into Duchenne	No changes.

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Clinical Specialist Neuromuscular Physiotherapist	Thank you for the opportunity to comment on the above proposal. At the John Walton Muscular Dystrophy Research Centre in Newcastle, we assisted the applicant in piloting these devices with our children with DMD. We have concerns at the application of this device and its utility as a secondary endpoint for clinical trials and contribution to regulatory decision making. Our experience with the devices is different to that reported in the EMA application and we suggest further work is undertaken by the applicant prior to a final decision being made by CHMP/EMA. Experience with the device We had poor compliance from the children, with 50% initially refusing to wear the device and then at follow up, 100% refusal from even those boys who had consistently worn the devices daily for many months. This is in stark comparison to the 90% compliance noted on line 157 of the report. Our patients and their families voiced several concerns - The length of the recording periods that initially were required to wear. This was daily for a year. - The size of the device worn at the wrist- large, bulky - Device is unattractive, conspicuous and their child was teased for wearing it- “it looks like you’ve been tagged” i.e. wearing an anti- social behaviour device - That there is no visual or auditory feedback possible to be given to the child, no interaction when using the device - It is not water or shower proof and the main form of exercise for the boy was swimming so as an activity monitor it lacks the ability to capture the boys when they are exercising and at their	At the time of inclusions, centers did not record to which patients they offered the ActiMyo and which ones refused. In the dossier, the compliance for the patients who were equipped during the first month was computed. For new studies, an improved process is in place, in which all inclusions will be followed, use standardized training for the physiotherapists in charge of proposing the ActiMyo, and track and improve compliance for each patient. To complement the data from the dossier and have statistics on larger pool of patients, confidential data on compliance and acceptability for the largest recent study, and another study on controls with 91 subjects have been gathered and shared with EMA. These data on user acceptance and compliance are reassuring. High level data are summarised in the responses of the applicant following the consultation annexed to the opinion.

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	most active Our main concern with this device was safety after one family narrowly avoided a fire in the home after their **docking station device started smoking** and was close to catching fire.	Device conformance is out of EMA scope. See CPath comment 2 above. According to Sysnav the battery management issue resulted in the previous version heating up during charging. A partial redesign has been done and solved entirely the issue with heating. All margins regarding the battery management have been increased compared to the manufacturer recommendations. Despite the battery heating up, the old devices were safe. In parallel with the recall, extensive stress tests were performed including burning and drilling of devices batteries. Even in these very extreme test condition, none of the test devices presented a risk to the user. See applicant's statement annexed to this document. (appendix 1)
	Data protection and privacy issues The data from the device is required to be uploaded each evening. In our experience, there were significant issues with data upload issue. The size of the data files meant that families were exceeding the daily fair usage policies of their internet providers. An alternative was to routinely post the USB devices to France. This required the families visiting the centre in order for the Physiotherapists to remove and replace the USB and organise a courier. Although data is not identifiable by name, the posting of patient data is not an efficient or best method.	The size of the internet data uploaded in a day (less to 500MB) is the same order of magnitude as the size of a movie and should not be a general problem. The back-up process is used only in restricted situations. It was designed to ensure the highest standard on data protection & privacy issues (e.g. data are encrypted, a proprietary format only readable by company is used, there is

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		no identifiable information which would permit to link the data to a patient). If the patient does not want their station to upload the data, upload of that station is deactivated.
	Proposed Gait variables There are 5 proposed ambulation variables - 95th percentile of the stride velocity measured at the ankle - Median stride velocity measured at the ankle - 95th percentile of the stride length measured at the ankle - Median stride length measured at the ankle - Distance walked/recorded hour The main limitation is that the endpoint is no longer possible when the patients become non-ambulant. Stating its potential use for ambulant and non-ambulant or population with the potential lost of ambulation is therefore unapplicable. Activity monitors are proposed to give a continuous, long term recording of the child's function, based around normal activity in the home environment. It is interesting that the proposed endpoint, found to be most useful by the applicant is gait velocity, rather than a more global measure of steps taken or distance walked over the recording period. The stride velocity 95th centile (SV95C) is being proposed as a secondary endpoint. That being, the fastest walking/running speed a child demonstrates whilst wearing the device. The stride velocity or gait speed is routinely collected during the 10m walk/run test as part of the North Star Ambulatory assessment (NSAA) or as part of the 100 meter	This qualification concerns ambulant patients. Research on non-ambulant patients to propose a relevant outcome for qualification is continued. This is mentioned in the opinion. Overall no changes required.

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	test (Alfano et al, 2017).	
Clinical Specialist Neuromuscular Physiotherapist	**Other commercial devices** There are currently several commercial devices, that are less costly than this device, more attractive and also have 3axis-accelerometers. There have been numerous publications looking at the utility and validity of devices such as the Actigraph, Apple Watch 4, and Fit-Bit. Several of these are currently under investigation for their utility in DMD. Each of these devices has beneficial features not seen in the ActiMyo such as appearance, size, change length, waterproof case, simple data capture. Until the results of those research trials are completed, the consideration of the utility of an activity monitor as a secondary endpoint should not be finalised. **Alternative measures of gait velocity and stride length** Other measures of gait velocity that do not require constant wearing of a device include the 100m run/walk test and 10m walk/run. Normative data for this is already available and the test-re-test reliability of the test established (Alfano et al, 2017). The test is sensitive to change over time and correlates well to existing measures, particularly the NSAA (Miller et al, 2017). In addition, basic technology can be used to minimize interrater reliability in timed tests (Photoelectric cells, force platforms, Glatthorn et al, 2011, Vicente-Rodriguez et al 2011) despite being proved that trained evaluators can be a valid method to get quality data. **Summary** The SV95C as a proposed endpoint requires significant further	See CPath comments 1 and 2 above Fitbit trackers and similar devices are affected by significant systematic errors. (Feehan 2018, Collins 2019) Not accepted. No changes required. See Pfizer comment above

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	investigation against current measures of gait velocity in this population that are already in use in standard of care assessments and clinical trials. It is surprising given that that applicant has compared to NSAA, that this work has not yet been undertaken. If fastest gait velocity is most useful measure from this device, then a simple and cost-effective test may have better utility than a device that is worn for prolonged periods and has not demonstrated good compliance outside of a local study group. The clinical utility of this device and other activity monitors in DMD require further investigation. Numerous studies are running concurrently to look at the commercially available devices and their role in activity monitoring in DMD. This include the Actigraph, the Fit-Bit and Apple Watch 4. Prior to a final decision being made to the use of the proposed end-point, the data from these trials should be examined to determine the role and specific outcome measures that an activity monitor in DMD would be provide.	
Neurologist - Pediatric neurologist	The applicant provides a solid rationale and extensive background for a new endpoint to be used in clinical trials of Duchenne muscular dystrophy (DMD). In this disease, the field is facing many ongoing and planned clinical trials, and there is a need for better endpoints than the ones currently used. All major aspects regarding validity, reproducibility and compliance of the stride velocity 95th centile are discussed in the qualification, and the endpoint is considered to be applicable as secondary endpoint by EMA. The use of the stride velocity 95th centile applies to the ambulant phase of the disease. The applicant does indicate the use of the device in non-ambulant patients by carrying an additional sensor on the wrist in case a patient loses ambulation. At this point it is not completely clear how the	SV95C context of use as qualified is as intended and as a secondary endpoint. SV95C is not qualified as a Primary endpoint given remaining uncertainties and need for further data collection. Loss of ambulation will be captured with other measures also. It is agreed that patients incur a non-linear decline in

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	endpoint itself will be brought into statistical analyses in case of loss of ambulation, and this could potentially strengthen the application. On the other hand, a non-linear decline towards the loss of ambulation has also not been considered is the approval of previous endpoints in DMD.	ambulation. It is agreed that loss of ambulation can be defined when the patient does not walk more than 10m straight in the final phase. It is recognised that multiple factors impact on loss of ambulation. The definition of ambulation using ActiMyo probably encompasses more patients than if using the clinical definition since patients may use an assistance. It is agreed that being able to walk, either with an assisting device, is important for patients quality of life, and quantifying the ultimate part of ambulation decline decrease the floor effect of a more strict definition of ambulation. The statistical handling of SV95C has to be determined in the context of other measures in a given trial, multiplicity hierarchy and missing data strategy. Further longitudinal data building on the current data (Table 6, 7 and 8) will support modelling. The current proposal examines % change in SV95C at set points but other parameterisations could be proposed in specific contexts.
	The recruitment of patients is described briefly, presumably due to confidentiality, and the fact that the studies from which patients have been recruited have not been not published until now. It is therefore difficult to tell from the current document if selection could have affected the applicability of the endpoint in the general ambulant DMD population.	Whether selection could have affected the applicability and generalisabilty: the limited numbers are acknowledged and further longitudinal data in DMD are needed as already identified. Broad risk categories are covered by age and 6MWTD groups. Data collection in other conditions will also be helpful.
	Although it is clear that a balance has been found between the requirement of longer quantification of ambulatory performance in the	It is agreed that the current recommendation is to record during 30 days to ensure 180 hours of adequate recording. Recording period is suitable to determine capacity without

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	home setting, and the need to avoid decline during that quantification, the reasoning in lines 141 and 881 seems not completely consistent. Although disease progression may not be expected within 180 hours, it should be taken into account that the proposed methodology requires 30 days to obtain those 180 hours. A minor point is that correlation analysis between 95th percentile stride velocity and 6MWT (Figure 2 on line 244, and Figure 28 on line 1474) seems to be based on the combination of the two cohorts, i.e. Duchenne patients and healthy controls. Potentially this should be done for the two groups separately as the clear differences in performance will influence linear statistics. The main issue remains if the 95th percentile of velocity could not be used as primary endpoint. Limitations are appreciated and discussed in sufficient detail. However, the acceptance of 6MWT and other motor endpoints currently used do not seem to have been based on more solid data than the endpoint in this dossier. EMA may be able to substantiate the rationale for the use as secondary endpoint only in more detail, and may also be able to provide more extensive guidance as to what additional information is required. This is particularly important in view of the significant amount of time this may take while multiple clinical trials for DMD will be planned using the currently approved endpoints with their known limitations.	disease progression. This has been done, and the correlations provided in the document only apply to DMD patients. See data presented and annexed to the opinion. Data collected for other indications are appended to the opinion, however the Context of Use agreed for SV95C is in DMD patients. Any qualification for other indications would entail a qualification procedure directed at that indication.
World Duchenne Organization -	The World Duchenne Organization - UPPMD - is in favour of using suitable wearable devices as a secondary endpoint in clinical trials in Duchenne Muscular Dystrophy.	No changes required.

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UPPMD	It is our opinion that a suitable wearable device is more patient-relevant than and superior to the 6MWT because the data obtained from the device are less subject to bias from assessor and/or family. Bias can have a huge impact on trial results. In addition, the patient's mood, the time of day, fatigue can all influence the performance of a 6MWT in a hospital setting. A wearable device collects continuous data over a much longer time span in a natural setting, whether at home, school or work. This data is far more reliable, objective and accurate than several 6MWTs taken in a hospital weeks or even months apart, which can only provide snapshots. The use of data from a suitable wearable device tracks an individual's regular physical activities throughout the day/week/weekend/month and is thus more relevant to clinical benefit and eliminates variability It could increase patient outreach as it can be used to collect evidence of functional benefit in patients shortly before loss of ambulation. These patients are frequently denied participation in clinical trials using the 6MWT as one of the inclusion criteria and/or as a primary or secondary endpoint, so using a wearable device might enable and encourage their participation in clinical trials. A suitable wearable device is also usable to measure functional benefit such as upper limb function in the non-ambulant Duchenne population, where it is often difficult to determine appropriate endpoints. In addition, the use of a suitable wearable device could effectively lessen the burden of clinical trial procedures for patients and their families, since less hospital visits would be required in order to collect a sufficient amount of data.	

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	The amount of data collected by a suitable wearable device might contribute significantly to reducing the duration of clinical trials and with this to limiting the burden since the device collects far more data over a much shorter period of time. In turn, this would make for more efficient and more economical trials with more reliable results. To render the data collected by a suitable wearable device even more reliable and valuable, a patient diary, either in paper form digital or even recorded, might be an advisable addition to account for daily variation (physio; swimming; gym class; school and other holidays; illnesses, etc.). We strongly recommend waterproofing the device so as to capture swimming exercises, for example; in addition, waterproofing would help eliminate compliance issues due to patients forgetting to put the device back on after swimming, showering or bathing (increased compliance). In the event of more such devices being developed in the future, the data should preferably be collected in an open source system, so that all the data collected in Duchenne Muscular Dystrophy patients can be compared. To summarize, the World Duchenne Organization - UPPMD - is of the opinion that a suitable wearable device should be accepted as a secondary outcome measure in clinical trials for DMD as it has value for patients, sponsors and regulatory authorities alike as well as payers, since it can more clearly demonstrate the functional benefit of a treatment.	See above CAB comment

2. Specific comments on text*

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
Line 50	CPath	**Comment:** A generic description of the device is given but is insufficient to inform what specific device is able to collect the data in the qualification or how a suitable device must process the raw data for use. **Proposed change:** A more detailed description of the device and analytics could be provided in the body of the text, with consideration for the minimum system performance characteristics.	Is included.. The CE certificate of the device used is annexed to the opinion.
Line 65-66	CPath	**Comment:** Longitudinal studies have only been performed on ambulant patients able to walk <450m on a 6MWT test. In this population, walking declines most rapidly and 6MWT is known to change more quickly.[4] The rate of change in this group may not be able to be generalized to the greater ambulant population of patients, especially those as young as 5, who may still be gaining strength, and therefore distance, due to development. **Proposed change:** This outcome measure may only be appropriate for a	The comment is not correct. Patients walking more than 450 m in the 6MWT have been also recorded and analysed. The subpopulation (>6yo and <450m) was considered because it is a common inclusion criterion for DMD clinical studies and to benchmark with 6MWT data. A significant difference was also observed on the entire population of ambulant DMD. QO is limited for 5 years and above and ambulant

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		limited population of Duchenne patients, based on the data presented. Further analysis of a broader population is needed to determine if sensitivity is greater than existing measures.	
Lines 157-159	CPath	**Comment:** The compliance within the studied population was noted. However, it would be useful to state a minimal level of compliance at which such data might be useful, both in terms of days of data measured and proportion of those days in which the device was worn.	Experimental variability of the variables as a function of the recorded duration are presented. Periods with less than 50 hours of data were discarded. No change required.
Line 187	CPath	**Comment:** Table 2 shows that SV95C correlates with patient height and age. This needs to be considered when looking at velocities longitudinally, as patients in this population are expected to grow over the course of a year.	Correlation is rather low. SV95C was considered relevant as a submaximal parameter, and less effected by age and height over time. See Pfizer general comment above. No change required.
Lines 192-195	CPath	**Comment:** A one month measuring period every 3 months would require patients to be recording data over 1/3 of the study duration, potentially resulting in non-compliance greater than that seen in the preliminary study.	Confidential data from an ongoing trial were provided. These data on user acceptance and compliance are reassuring. See comment to physiotherapist in part 1 above. No change required.
Line 570	CPath	**Comment:** It remains unclear if the device is CE marked as a medical	The device used to gather data for the current qualification of SV95C is CE marked as a class 1 medical device (hardware

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		device. **Proposed change:** The addition of language to clarify if the device is CE marked as a medical device, and if so (a) what the indications and intended use are, (b) what class the device is marked as, and (c) if other suitable devices must also be CE marked as a medical device.	and software). See QO" The latest device which was redesigned for cosmetic purpose is CE marked." The certificate is annexed to the opinion. No additional wording required.
Line 576-577	CPath	**Comment:** It is possible for a cosmetic change to affect the performance of the device, depending on the nature of the cosmetic change being made. For example, it is well documented that a change in adhesiveness can change accelerometer measurements. Bridging data may therefore be necessary. **Proposed change:** Inclusion of the specific acceptable cosmetic changes are recommended to ensure bridging data is not necessary.	Agreed; there is a need for bridging data using a sensitive methods reaching a pre-specified and justified level of accuracy and precision if there are major changes to sensors.
Line 576	CPath	**Comment:** It could be useful if the qualification document explained how bridging between devices should be performed if the device is more significantly upgraded in the future. The qualification also suggests other devices could be used to gather data, thus, understanding the process for showing	Sensitive methods reaching a pre-specified and justified level of accuracy and precision should be used if there are major changes.

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		equivalence between two devices would be useful.	
Line 707-709; and Line 50	CPath	**Comment:** It is stated that magnetic measurements are not explicitly used, however the device description in Line 50's footnote and the patent mentioned in Line 703 seem to indicate the use of magnets and magnetometers. **Proposed change:** Clarification regarding the presence and usage of magnets in the device would be helpful. If magnets/magnetometers are only used for certain measurements, this should be clearly stated.	The method used to compute ankle trajectories and gait variables and described in the patent WO2017060660 does not require magnetic measurements. QO states states: "Also, because magnetic measurements are not explicitly used in this technique, the trajectory and the gait parameters deduced are not impacted by magnetic disturbances in the vicinity of the device." Change to: "Magnetic measurements are used for the identification of phases of immobility and to estimate gyroscope bias. "
Line 1560	CPath	**Comment:** Data from the two patients who initiated steroids during the study do not strongly support this measure's ability to demonstrate disease modification with treatment. Two anecdotal cases are insufficient, and a greater sample size would be needed to make meaningful claims of the device's utility in assessing treatments that present rapid effects.	More patients have been recorded since last year so it will be possible to release new data for the qualification as primary outcome. Since this is not the goal now this is not essential. No change required.
Line 83	Pfizer Ltd	Given that the wearable device is equipped with a built-in gyroscope, investigating additional measures of gait patterns, such as balance, sway, turns, stair climb, and falls would especially important and may be highly relevant to quality of life measures of DMD patients. The system	These data are in development. No change required.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		presented here seems to be well equipped to render this information. If such data is available it should be shared.	
Line 86-87 and Table 1, Line 150	Pfizer Ltd	The wearable device described in the document consists of two sensors: one on the wrist and one on the ankle. It is unclear what the wrist sensor is used for, given that all the endpoints described in Table 1 are measured by the ankle sensor. What measurements are being collected by the wrist sensor? Is the wrist sensor necessary for studies in ambulatory patients with DMD? It would be useful to understand this further from both cost and compliance perspectives, in terms of patient burden and implementation in trials. If both sensors are used to derive certain endpoints, what steps are taken to ensure temporal synchronization of the data from both sensors? How does the device compensate for clock drifts over time between the two sensors?	During the discussion meeting with the applicant, it was clarified that in patients who could transition to non-ambulant as it is the case in the population of interest, ankle/wrist recording is better than ankle/ankle recording as it offers the opportunity of a continuous measure across loss of ambulation. Further data are in development. See the Best practice guide; Appendix 3. No change required.
Line 128	Pfizer Ltd	It seems that the validation against optical motion capture system was performed only with 8 healthy controls. Given that the gait patterns of Duchenne boys are very different that those with typically developing children (Gaudreaul et al, 2019), it would be crucial to perform this validation also in DMD patients. In the absence of this data, the accuracy and validation of the proposed device is still questionable.	See Figures 4 and 6 Patient data are available. See:"Correlations between the proposed gait variables obtained on 180 hours of recording and usual outcome measures in ambulant DMD patients have been studied on 45 patients who wore the wearable device for over 180 hours in

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			the first 2 months." No change required.
Line 150; Table 1, Line 132, Line 162	Pfizer Ltd	It is unclear how many patients were included in data analysis: N=28 (Line 150; Table 1), N=23 (line 132), N=48 (Line 162). What is the reason for this inconsistency? What selection criteria were used to determine which patients are included for the different analyses? How missing data was handled? What was the cut-off of inclusion partial days?	Patients were issued from several studies with different study protocols. Some studies used the 6MWT, some other no. The same applies for other outcomes like NSAA. In some studies, patients had to wear the device continuously but not in others. For all sub analysis, all data available at the time of data cut off were used. The number of patients that could be included for each statistic therefore varied depending on the criteria needed for the statistics (reference data availability for correlations, minimum compliance for variability analysis and week days comparison…). No change required
Line 157-161	Pfizer Ltd	"Compliance rates of 90% were observed amongst patients who agreed to use the system over a period of 1 month". What was the percentage of patients/families who did not agree to use the wearable device as part of the study? This would be useful information to report in order to evaluate the potential feasibility and scalability of using wearable devices in DMD trials.	See general comments above and C-Path comment to lines 192-195. These confidential data on user acceptance and compliance are reassuring.
	Pfizer Ltd	It is unclear how compliance rates were computed. "Compliance rates went down to 79% after 6 months i.e.	

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		31 of 39 patients had more than 50 hours of recording". This statement may be misleading because compliance rate should be calculated based on the difference between the expected wear time vs. the actual wear time. In this case, patients were expected to wear the device for 180 hours. However, in practice, only 31 patients had a wear time of > 50 hours. The compliance rate is therefore 27% ([50/180]*100) and not 79% as stated in the document. This low compliance rate should be fully acknowledged as a possible limitation.	
Line 170-173	Pfizer Ltd	The possibility of the device being worn by someone else is mentioned as a possible limitation. However, considering the claimed accuracy of the device in reliably detecting stride length and stride velocity, this possible limitation might be mitigated simply by detecting a significant difference in gait parameters when a non-DMD patient is wearing the device, which can be used to notify the study team of a potential problem. Is that something currently under development or consideration?	The data processing software issues warnings and comments on the data to indicate when there is an abnormal low number of steps or a failure in the sensors. A low number or an absence of steps usually indicate that wrist and ankle sensors have been swapped. The logs are read to detect issues in the data, in case of suspicion of ankle/wrist swap, the algorithm is rerun on the wrist sensor to confirm that steps are detected on that recording. The sensor being worn by someone else than the patient would be difficult to detect if done on a single day but if it is done continuously, it would be detected as a sudden change in the level of the variables. No change required.

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Table 2, Line 187	Pfizer Ltd	Does the correlation of stride velocity metrics with the 6MWT, NSAA and 4SC still hold true after correcting for Age and Height?	See above. Correlation with age and height is rather low. SV95C was considered relevant as a submaximal parameter, and less effected by age and height over time. See Pfizer general comment above and CPath comment to line 187. No change required.
Figure 1, Line 542	Pfizer Ltd	It would be useful to provide more information about the device used, especially what makes it “a suitable device”? The wrist and ankle sensors seem quite large and unfashionable, at least from the picture. Is there any indication that this may affect compliance, especially when worn by kids at school, especially in trials of long duration? Are these sensors waterproof? Would patients have to take them off when washing hands or during swimming therapy?	Compliance was acceptable. The aim of this procedure is to qualify the measurement and not the device. No change required.
Line 927-935 ; Table 5	Pfizer Ltd	In addition, the data presented in Table 5 is based on 10 patients, whereas the dataset used for examining the impact of daily fluctuations consisted of 45 patients (Line 935). However, since this analysis was done on an n of 10. What was the rationale for excluding 35 patients from Table 5?	The statistics was calculated on study with 10 very compliant patients which is the most sensitive population. Issue clarified. No change required.
Line 927-935; Table 5	Pfizer Ltd	According to Table 5, The 95th percentile stride velocity is significantly lower on weekends vs. weekdays (~7% difference), with a particularly high variability of over 9%). This high variability raises critical questions as whether the	Averaging the signal over a 2 weeks period allows to completely avoid this pitfall. Even if the patient present a 8% slower SV95C during the week-end, the overall SV95C will not or very minimally change since this concerns the 5% most

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		current data presented in this document provides sufficient validation for the 95th percentile stride velocity as a potential secondary endpoint. How do seasonal variations affect the data (snow days vs. summer days)? To what degree potential bias may influence efficacy trials over 6-12 months, when comparing recordings from school days vs. holidays? If stride velocity is a pure measure of physical capacity due to disease state (rather than a matter personal preference), it should not be influenced by the day of the week (weekday vs. weekend) or changes in the patient's environment (i.e., school vs. home). It would therefore be important to test the generalizability of these findings in larger datasets and across different real-world settings before any firm conclusions can be made with regard to endpoint validation.	rapid strides, whenever they happen. No change required.
Line 1033	Pfizer Ltd	Sample size calculation for the 95% percentile stride velocity is requires further clarification. What was the rationale for a sample size increase from N=14 (Table 9) to N=30 (Line 1033) per arm? What was the statistical computation underlying doubling the sample size? It is reasonable to expect a moderate inflation of the estimated power to account for possible data heterogeneity and poor compliance rates. However, wasn't compliance as high as 79% at 6 months (Line 913)?	New confidential data on user acceptance and compliance are reassuring.

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Figure 18, Line 911, Line 1238	Pfizer Ltd	Figure 18 warrants further explanations with regard to the outliers and number of patients included. Number of subjects: There have been 39 patients who have reached the 6th months of study with the wearable device (Line 911). However, Fig 18 contains data for only 15 patients. What is the reason for this discrepancy? Outliers: Two patients showed a significant change in 6MWT but minimal change in 95th percentile stride velocity Was there anything different in the characteristics of these patients? This information would be useful in determining whether the 95th percentile stride velocity is more applicable to a particular class of patients (age, disease state, steroid regimen etc.)?	In the graph (figure 18 in the dossier) on average the group of patients appears to clearly decrease on the SV95C while no direction can be deduced from the 6MWT at 6 months. If the patients with extreme values are removed from the graph, the difference between SV95C and 6MWT is still clear visually. No change required
Line 1332	Pfizer Ltd	The generation of normative data is highly desired. However, what is the rationale and clinical relevance to DMD for collecting normative data from healthy controls between the age of 40-84 y.o., including females?	Controls of all age and sex were recruited but the majority were boys with age between 6 and 18 years old therefore matching the DMD population. Since the device is currently under validation process in several other diseases, including adult diseases, data were collected in adults and in females also. But as illustrated on the figures, data of DMD patients were compared with age-matched male controls. No change required.
Line 799, Figure 6	Pfizer Ltd	Figure 6 shows data from the 6MWT collected by the wearable device. Clarification is needed if the device is intended for in-clinic use (e.g. during 6MWT) or only at	This figure is given to illustrate the precision of the strides trajectory by comparing with 6MWT performed by DMD. In the scope of the EMA dossier, ActiMyo is intended for home based

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		home-based settings?	settings. Issue clarified. No change required.
	Clinical Specialist Neuromuscular Physiotherapist	The applicant has related the device outcomes to the NSAA total score but not specifically the 10m run or the 10 metre test. It is essential to understand the relationship between simple clinical measures of speed, where the child is asked to run as fast as possible. If the data are similar the device may be redundant and the child not required to wear it for many weeks to obtain the same data provided in a quick and inexpensive 10m or 100m run test. As the applicant has noted, the 95% percentiles are more sensitive to change than the medians over 6 and 12 months (line 206). The NSAA has the strongest correlation (line 187) between the proposed gait variables at baseline.	SV95C has been compared with three different outcomes used as primary endpoint in different trials, like the 6MWT, the 4SC and the NSAA. No comparison to 95CSV with MFM32 (total, or D1, or D1+D2), Brooke/Whalton score, Handgrip strength, pinch strength, vital capacity, MMT, 1MWT, 2MWT, 100m WT, 10 MWT, NeuropedsQL, Promis, Time to rise from floor, Reachable working space, and several other outcomes not only for obvious practical reasons, but also that performing many measures on the same subject finally change the measure itself, because of fatigue and demotivation. This is acceptable. No change required.
	Clinical Specialist Neuromuscular Physiotherapist	The statement on relation to motivation (Line 125)“The applicant wishes to concentrate on the 95 th percentile stride velocity measured at the ankle, which is another way of measuring top velocity, but is not dependent upon motivation as the 6MWT.” Suggests that the use of the proposed endpoint is not dependent in motivation. The reality is that it is dependent in motivation but its effect on the variable can not be captured like it is in the 6MWT.	Influence of motivation on the 6MWT has been demonstrated by the group of Mendell, using a 50 USD incentive. (Alfano 2015) It is more unlikely that motivation can affect patients condition over a long period of time. No change required.

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	Clinical Specialist Neuromuscular Physiotherapist	**Content validity** The validation of the device using the gold standard Three dimensional gait analysis (3DGA) has only been taken in 8 healthy controls. We see no report for subjects with DMD who have significant gait variation undertaking 3DGA testing and their 3DGA results compared to the device. In other neuromuscular conditions, different reliability of the device was noted between healthy controls and patients with Myotonic Dystrophy (Jimenez-Moreno et al, 2018) **Clinical relevance and MCID** The applicant examined relationship between device and NSAA MCID (line 250). It would be extremely information to correlate the SV95C to the NSAA Item 17- 10m run time velocity or the 100 metre test.	See comment above. No change required.
	Clinical Specialist Neuromuscular Physiotherapist	**Concern at variability of assessment** In the proposal summary, line 381, the applicant suggests the device has significant advantage over current gold standard measures. There is insufficient evidence to support this claim. The tool may be objective, but it still is dependent on the patients' performance, level of motivation to ambulate. One obvious concern is the impact on season on maximum speed. It is highly likely that there is a significant difference in maximum gait speed in season with suitable weather for outdoor play. Also, there is no relation of the device output to function and so the device clinical	SV95C is less likely to be affected by external factors than the overall number of strides. See comment above. No change required.

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		meaning compared to a scale such as the NSAA. In addition, the application suggests the device would decrease the variability of assessment, and overcome variations in practice which impact significantly on clinical trials (This is unlikely, as most clinical trials in Neuromuscular disease incorporate standardised training and manuals and assessments (James et al, 2012, Glanzman et al 2018) and more frequently, reliability testing of all clinical evaluators is completed with video quality checks of assessments through the studies.	
16-19 24-25	F. Hoffmann-La Roche Ltd	Comment: The proposed context of use adopted by the CHMP for the SV95C is for 'ambulant DMD patients 5 years of age and above'. This endpoint quantifying a patient's ambulation ability could be of value to utilize in other neuromuscular diseases. It is therefore proposed to broaden the context of use to assess ambulation in DMD and other diseases. Proposed change (if any): This report provides a final agreed draft Context of Use for public consultation (…) as an appropriate endpoint in studies to support regulatory decision making on medicines for the treatment of Duchenne muscular dystrophy (DMD) and other diseases… CHMP considers that for ambulant Duchenne muscular dystrophy (DMD) patients 5 years of age and above with	Data are also being gathered in other NMD, such as SMA3, FSHD, DNM2 but are not subject to this qualification procedure. No change required.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		Duchenne muscular dystrophy (DMD) or other diseases: (…)	
47-51	F. Hoffmann-La Roche Ltd	Comment: Specifics on the wearable device used to collect SV95C data to support validation and qualification of the endpoint are included (e.g., lines 87-90, 167-173). As technology will change over time, it is suggested that the footnote 1 in the opinion is clearly presented as a description of the device used for the validation of the endpoint, rather than a strict description of what would be expected of a 'valid and suitable wearable device and system" to collect 95SVC data. Proposed change (if any): This distinction means that the clinical measure is the focus of the opinion and the measuring device/system used is assumed to be valid and referred to as a "suitable and valid wearable device'. See footnote 1* for a description of the wearable decide/system used for validation of the SV95C endpoint. The proposed gait variables measure with a valid and suitable wearable device and system 1* quantifies a patient's ambulation ability in a continuous manner across five different variables	As the technology evolves, the precision of the sensors will improve allowing for new variables or alternative methods. No change required now.
63-64	F. Hoffmann-La	Comment:	Agreed.

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
	Roche Ltd	Proposal to rephrase poor compliance to the influence of 'missing data'. Proposed change (if any): Measurement of the variability of gait variables and studying the influence of poor compliance missing data to generate recommended minimal use.	Change- to Measurement of the variability of gait variables and studying the influence of poor compliance and missing data to generate recommended minimal use.
111-117	F. Hoffmann-La Roche Ltd	Comment: Although motivation and distance travelled are factors which may limit performance on outcomes in clinic, there are many positive aspects of standardized in clinic (or at-home) assessments in DMD trials. This particular digital monitoring COA would be better considered as complementary data to standardized in-clinic assessments. Proposed change (if any): All these assessments (6MWT, NSAA or 4SC) are episodic, and provide a snapshot overview of the supposed maximal patient's functional ability. While providing relevant and clinically meaningful insights into patient functioning, these outcome measures can be affected by They have specific limitations related to patient motivation	One of the key benefits of the SV95C is that it allows a completely objective measurements which could lead to reducing the burden of travels. Currently this is assessed as a secondary endpoint. Can be accepted but needs to be modified: While providing relevant and clinically meaningful insights into patient functioning, these outcome measures can be affected by patient motivation at the time of assessment which the proposed system intends to overcome.

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		at the time of assessment which the proposed system intends to overcome. All existing Completion of these measures in clinic requires patients to travel to specialist neuromuscular centers, often some considerable distance away. This, alone, can causes major stress and disruption to patients and family. In addition, motivation is known to play an important factor in the 6MWT; experiences have shown that a child can increase significantly the distance walked if offered an incentive to perform better.	
120-123	F. Hoffmann-La Roche Ltd	Comment: SV95C could be considered to fall within observer or performance clinical outcome categories. The classification of this as a digital biomarker/biometric data on the basis that no active participation is required is in contrast to the FDA draft Patient Focused Drug Development guidance where it seems such a measure could still be considered a clinical outcome assessment (COA), albeit measured passively ("Digital monitoring sensors can be used for clinical outcome assessment (e.g., step counts collected via actigraphy"). Proposed change (if any): During the Discussion meeting, it was clarified that the method was considered as a digital biomarker / biometric data and not as a "patient reported outcome", since no	Agreed. Line 163: This is agreed and should be considered a digital

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		active participation from the patient is requested. The system captures data passively when worn. This is agreed and should be considered a digital clinical outcome assessment.	clinical outcome assessment.
127-134	F. Hoffmann-La Roche Ltd	Comment: There is little description in this section “content validity, accuracy’ about the qualified COA content validity, i.e. relevance and importance to patients. It would be useful to summarise in the qualification opinion why SV95C was selected as targeting a relevant concept from a patient perspective over other gait parameters or instead of a composite of various parameters captured with the wearable device.	From the parent perspective involved in the qualification procedure, maximal speed is avitally important measure and represents a solid outcome.
228-233	F. Hoffmann-La Roche Ltd	Comment: Regarding the clinical relevance / MCID, can the agency provide additional information on why use of patients with 50+ hours was an acceptable population to conduct these analyses? Patients appear to have been mandated to wear 180 hrs of recording.	The variability with 50 hours is higher than with 180 hours of data but is considered still acceptable. Most of the patients achieve to record more than 180 hours. Issue clarified. No change required.
237-243	F. Hoffmann-La Roche Ltd	Comment: The McDonald paper is focused on distribution based methods (SEM: SD X SQ ROOT (1-R)). The formula should be provided.	Agreed.

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		A key missing section of text relates to how this estimate will be applied, i.e. to evaluate a between-groups MCID or to evaluate within-patient score change. It is assumed that this is referring to a between groups MCID. Proposed change (if any): There are several ways of estimating a between-groups MCID. The applicant used the distribution based methods (SEM: SD X SQ ROOT (1-R)) applied by Craig Mc Donald et al. (2010) when they estimated an MCID of 30 meters for the 6MWT.	Line 238: The applicant used the distribution based methods (SEM: SD X SQ ROOT (1-R)) applied by Craig Mc Donald et al. (2010) when they estimated an MCID of 30 meters for the 6MWT.
250-254	F. Hoffmann-La Roche Ltd	Comment: NSAA total score (0-34) would be clearer here. The linearized NSAA MCID is 10 points. The Mayhew paper states “mean MID was 6.9 and 8.8” (depending on steroid regimen), therefore seven points is the lower MCID boundary. Proposed change (if any): Upon further request the applicant also presented data on the MCID comparison for the NSAA. The correlation slope between 95th percentile stride speed and non-lineralized NSAA (scored on 34 total score (0-34)) is 0.04295 m/s per 1-point NSAA. It means that 0,1m/s on the 95th percentile stride speed is correlated with 2,32	Agreed. Changes The correlation slope between 95th percentile stride speed and non-lineralized NSAA (scored on 34 total score (0-34)) is 0.04295 m/s per 1-point NSAA. It means that 0,1m/s on the 95th percentile stride speed is correlated with 2,32 points on the ~~non linearized~~ NSAA total score non linearized North Star, which corresponds approximatively to 7 points in the linearized North Star. ~~This is considered as the MCID for NSAA (Mayhew et al. 2013)~~ This is considered within the range of

Line number(s)	Stakeholder	Comment and rationale; proposed changes	Outcome
		points on the NSAA total score non linearized North Star, which corresponds approximatively to 7 points in the linearized North Star. This is considered within the range of published MCID estimates for NSAA (Mayhew et al. 2013).	published MCID estimates for NSAA (Mayhew et al. 2013).
264-267	F. Hoffmann-La Roche Ltd	Comment: SV95C should be recognised as complementary secondary endpoint to other clinical assessments currently used in DMD trials. Proposed change (if any): Other gait variables It is agreed that currently used endpoints in DMD trials such as the 6MWT, NSAA and 4SC have limitations to capture the full disease experience deficiencies as described above and that the proposed variables measured by a suitable and valid wearable device are promising would be complementary in collecting efficacy evidence of an investigational product.	Not fully agreed: It is agreed that currently used endpoints in DMD trials such as the 6MWT, NSAA and 4SC have deficiencies as described above and that the proposed variables measured by a suitable and valid wearable device are promising and would be complementary as a secondary endpoint in collecting efficacy evidence of an investigational product.

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Appendix 1

Feedback to the EMA request related to a comment regarding a prototype of ActiMyo

The current version of ActiMyo, commercialized by Sysnav, is a CE marked medical device. It is designed to fulfil home monitoring constraints and is tested in lab and in a home setting.

During its development, several prototyped versions were manufactured. One of the prototyped versions could heat up in its docking station and may result in the battery to inflate after several weeks of charging cycles. This known phenomenon for this type of medical batteries induces reduced battery life. These prototyped devices are still safe. The current product which is qualified as CE marked medical device corrects this limitation.

This public statement gives the ActiMyo team the opportunity to re-iterate the importance to raise any concern or adverse event and to remind that it is particularly important to use ActiMyo as instructed. Any concern or adverse event is worth mentioning and can be reported at contact@actimyo.com.