Supplementary Material

Evidentiary basis of the first regulatory qualification of a digital primary efficacy endpoint

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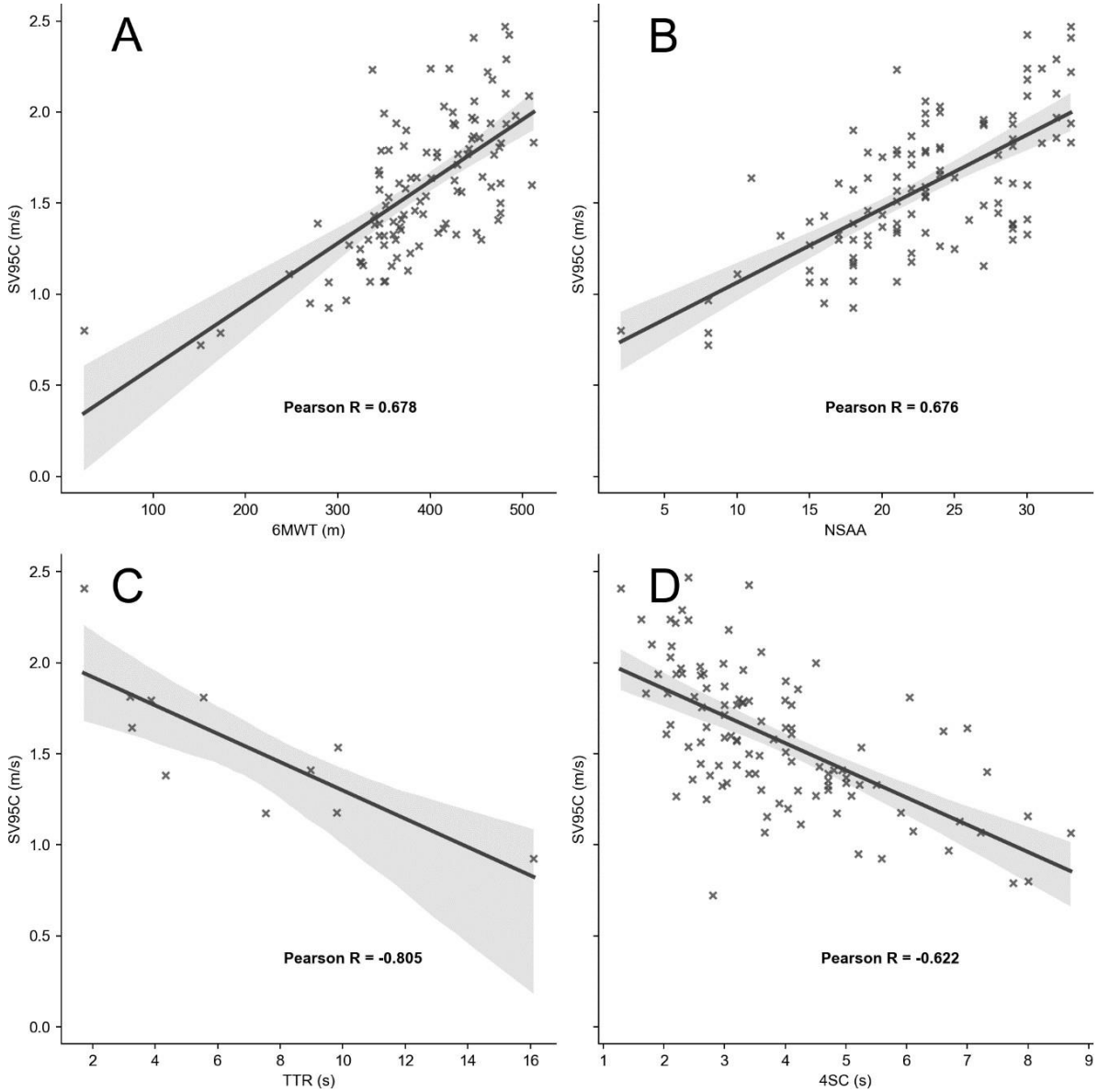
Supplementary Figure 1. Baseline correlations of SV95C with other outcomes: 6MWD (A), NSAA (B), TTR (C), and 4SC (D)



4SC 4-stair Climb, *6MWD* 6-minute Walk Distance, *6MWT* 6-minute Walk Test, *NSAA* North Star Ambulatory Assessment, *SV95C* stride velocity 95th centile, *TTR* Time to Rise.

Supplementary Table 1. Correlations between SV95C and other clinical outcome assessments

COA	Correlation coefficient	Baseline (N = 107)[a]	Month 3 (N = 43)	Month 6 (N = 20)	Month 9 (N = 24)	Month 12 (N = 15)
6MWD	Spearman's	0.657***	0.761***	0.524*	0.691***	0.835***
	Pearson's	0.678***	0.761***	0.507*	0.698***	0.821***
NSAA	Spearman's	0.644***	0.575***	0.396[ns]	0.677***	0.753***
	Pearson's	0.676***	0.599***	0.547*	0.658***	0.758***
TTR (N = 11)	Spearman's	−0.782**	N/A	N/A	N/A	N/A
	Pearson's	−0.805**				
4SC	Spearman's	−0.634***	−0.603***	−0.536*	−0.651***	−0.749***
	Pearson's	−0.622***	−0.587***	−0.486*	−0.647***	−0.625*

4SC 4-stair Climb, *6MWD* 6-minute Walk Distance, *COA* clinical outcome assessment, *N/A* not applicable, *ns* non-significant *p*-value (> 0.05), *NSAA* North Star Ambulatory Assessment, *SV95C* stride velocity 95th centile, *TTR* Time to Rise. Source: Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies © European Medicines Agency, 2022.

* $p < 0.05$.

** $p < 0.01$.

*** $p \leq 0.001$.

[a]N = 107 for 6MWD, NSAA, and 4SC. N = 11 for TTR.

Supplementary Table 2. Within-group meaningful change for SV95C at week 48

Instrument	Patients	Mean change in SV95C over 48 weeks (m/s)	Median change in SV95C over 48 weeks (m/s)
CGI-C			
Improved	N = 4 (4 minimally improved, 0 much improved, and 0 very much improved)	−0.175	−0.025
Stable/no change	N = 5	−0.302	−0.210
Worsened	N = 3 (0 minimally worse, 3 much worse, 0 very much worse)	−0.370	−0.280
PODCI			
Improved (≥ 10% gain)	N = 0	N/A	N/A
Stable/no change	N = 9	−0.221	−0.100
Worsened (≥ 10% loss)	N = 6	−0.293	−0.245

CGI-C Clinical Global Impression of Change, *N/A* not applicable, *PODCI* Pediatrics Outcomes Data Collection Instrument, *SV95C* stride velocity 95th centile. Source: Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies © European Medicines Agency, 2022.

Supplementary Table 3. SV95C MCID and MDC in patients with DMD and in controls

	Patients with DMD			**Controls**		
	5−14 years N = 103	**5−7 years n = 43**	**8−14 years n = 60**	**6−14 years N = 55**	**6−7 years n = 17**	**8−14 years n = 38**
ICC[a]	0.962	0.956	0.957	0.851	0.814	0.862
95% CI	0.943−0.974	0.918−0.976	0.928−0.974	0.744−0.913	0.500−0.932	0.735−0.928
SV95C-RP1 mean (m/s)	1.467	1.609	1.365	2.383	2.266	2.435
SV95C-RP1 SD	0.360	0.338	0.342	0.404	0.321	0.429
Standard error of measurement[b] (m/s)	**0.070**	**0.071**	**0.071**	**0.156**	**0.139**	**0.159**
Standard error of measurement relative to RP1 (%)	4.780	4.412	5.193	6.539	6.113	6.545
MDC80% (m/s)	**0.127**	**0.129**	**0.129**	**0.282**	**0.251**	**0.289**
MDC90% (m/s)	0.163	0.165	0.165	0.362	0.322	0.371
MDC95% (m/s)	0.194	0.197	0.197	0.432	0.384	0.442

CI confidence interval, *DMD* Duchenne muscular dystrophy, *ICC* intraclass correlation coefficient, *MCID* minimal clinically important difference, *MDC* minimal detectable change, *MDC80%/90%/95%* minimal detectable change at the 80%/90%/95% confidence level, *RP* recording period, *SD* standard deviation, *SV95C* stride velocity 95th centile. Source: Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies © European Medicines Agency, 2022.

[a]Two-way random effect model, absolute agreement, average measure.

[b]SEM = SD*SQR(1-ICC).

Supplementary Table 4. Characteristics of DMD (patient and patient caregiver) respondents (n = 92) to online survey

Age of patient (in years)	Mean (SD)	15.5 (9.47)
	Median	13.0
	Min−Max	1−57
	Q1, Q3	9.0, 21.0
Age symptoms first appeared (in years)	Mean (SD)	3.4 (2.48)
	Median	3.0
	Min−Max	0−12
	Q1, Q3	2.0, 4.0
	Missing	8
Ambulant[a]	Yes	49 (53.2%)
	No	43 (46.7%)
Relationship to patient	Caregiver	2 (2.6%)
	Father	14 (18.2%)
	Mother	56 (72.7%)
	Grandparents	4 (5.2%)
	Legal guardian	1 (1.3%)
	Missing[b]	15
Country	Belgium	1
	Germany	1
	United States	90

DMD Duchenne muscular dystrophy, *Max* maximum, *Min* minimum, *n* number, *Q1* first quartile (25th percentile), *Q3* third quartile (75th percentile), *SD* standard deviation. Source: Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies © European Medicines Agency, 2022.

[a]Defined as ability to walk 10 meters (25 feet) without help, based on survey response.

[b]Question not answered by patient respondents, only by caregiver respondents.

Supplementary Table 5. Patient survey questions

Survey question	Response options
In which country do you live?	Open-ended
How old are you (in years)?	Open-ended
What is the disease you are living with?	▪ Duchenne muscular dystrophy (DMD) ▪ Spinal muscular atrophy (SMA) ▪ Facioscapulohumeral muscular dystrophy (FSHD) ▪ Centronuclear and myotubular myopathy (CNM / MTM) ▪ Myotonic dystrophy (MD) ▪ Limb girdle muscular dystrophy (LGMD) ▪ I prefer not to respond ▪ Other (please specify)
List the first symptoms at the beginning of the disease	▪ Symptom #1 (open-ended) ▪ Symptom #2 (open-ended) ▪ Symptom #3 (open-ended)
What age did the symptoms first appear (in years)? (for from birth, please enter "0")	Open-ended
Are you able to walk 10 meters (25 feet) without help?	▪ Yes ▪ No ▪ I prefer not to respond
Have you previously participated in or are you currently enrolled in a clinical trial?	▪ Yes ▪ No ▪ I prefer not to respond
What does Mobility mean to you?	Open-ended
How does the disease impact your mobility?	Open-ended
How does the disease impact family activities?	Open-ended
How important are the following aspects of ambulation (i.e., ability to move around) for you? • Walking ability • Jumping ability • Climbing stairs ability • Running ability • Fatigue • Limiting falls • Being able to self-transfer	Answered separately for each aspect of ambulation: ▪ Very important ▪ Quite important ▪ Few Important ▪ Not important ▪ Add other very important aspects if needed (open-ended)
Regarding upper-limb movement, how important are the following aspects for you? • Ability to dress independently • Ability to brush teeth / hair • Ability to feed yourself • Ability to play sports that involve upper limb movements • Ability to reach face with hand • Ability to type / write / draw, and use tablet • Ability to use joystick • Fatigue	Answered separately for each aspect of upper-limb movement: ▪ Very important ▪ Quite important ▪ Few Important ▪ Not important ▪ Add other very important aspects if needed (open-ended)
What effect(s) on your symptoms do you expect from a treatment?	Open-ended
What is most important to you when deciding to participate in a clinical trial? Please rank the following answers from 1 (most important) to 4	▪ Improve your own health ▪ Improve health of others ▪ Get access to better care

(least important)	▪ Get access to information about drug development program
What are the 3 functions you would like to see maintained, improved, or restored by a treatment?	▪ Maintained (open-ended) ▪ Improved (open-ended) ▪ Restored (open-ended)
Which reasons might you decline clinical trial participation involving a drug? • Distance to travel to trial site • Frequency and duration of the visit (could not get time off work / school) • Potential side effects • Possibility of getting placebo • Not feeling well enough to participate • Fear of invasive procedure • Waiting for a more promising trial • Not confident in how the treatment efficacy will be assessed	Answered separately for each reason: ▪ Likely ▪ Unlikely ▪ Add reason not included (open-ended)
ActiMyo as a wearable device – Your acceptance/tolerability The community is looking for more reliable, sensitive and objective endpoints to detect with high confidence small changes in mobility, which might be lacking in current endpoints. ActiMyo is a wearable device composed of 2 small watch-like sensors that you could wear around your wrist and your ankle, or around both ankles, or you could wear one sensor around your wrist and the second one on the wheelchair if you are non-ambulant (Figure 1). These sensors collect very precise information about your steps (their length, their speed) and other upper limb movement parameters in your real life, while being protective of your privacy (no GPS or other tracking), and is at the basis of a valid endpoint qualified by the European Medicines Agency (EMA). Figure 1: ActiMyo device  If you have the choice, how would you prefer that your mobility be assessed during a trial?	▪ I prefer mobility be assessed regularly in the clinic by a physiotherapist or a physician ▪ I prefer mobility be assessed by wearing a wearable device in the real-life setting ▪ Any comments? (open-ended)
Have you ever used the ActiMyo device?	▪ Yes ▪ No ▪ I prefer not to respond
Do you think such a device would make participating in a clinical trial more attractive?	▪ Yes ▪ No ▪ I prefer not to respond
Would you be willing to use the ActiMyo	▪ Yes

device to measure your mobility / to evaluate your movements?	▪ No ▪ I don't know ▪ I prefer not to respond
If yes, how long would you accept wearing ActiMyo continuously?	▪ As long as the trial lasts ▪ Never ▪ Two weeks ▪ One month ▪ Six months ▪ One year or more ▪ I don't know ▪ I prefer not to respond
If no, please explain why?	Open-ended
What could be the most important limitation to wearing ActiMyo?	▪ The appearance of the device ▪ The device is not waterproof ▪ Size or weight of the device ▪ Tolerability / Discomfort of wearing the device ▪ Duration of having to wear the device ▪ Looking different because you are wearing the device ▪ No limitation ▪ I prefer not to respond
The next section is related to ActiMyo outcomes which may characterize changes (improvement or decline) in ambulation. If you feel you are not concerned about ambulation outcomes and want to skip the next section and reach the section related to upper limb movements, please indicate below:	I am not concerned with ambulation outcomes (option to check box)
Usually, in clinical trials, ambulation (i.e., ability to move around) is assessed by the top performance achieved during standardized timed tests; for example: the maximal distance walked in 6 minutes, the minimal time spent to rise from the floor, climb and descend stairs, walk or run 10 meters. Each time, the clinical trial participant is asked to walk as fast as possible. From your point of view, among the following items, which best represents an ambulation improvement? (You may select up to 3 answers if some are equally important for you.)	▪ Ability to walk fast ▪ Distance walked before stop ▪ Distance walked per day ▪ Number of falls per day ▪ Time measured to climb stairs ▪ Ability to climb stairs ▪ Ease in climbing stairs (both feet on each step or one foot per step) ▪ Fatigue during ambulation ▪ I prefer not to respond ▪ Add other very important parameters if needed (open-ended)
ActiMyo can measure the maximal speed of your strides performed in a real-life setting and is already used as a clinical outcome assessment in several clinical trials. Do you think that measuring a change in the top speed while walking is representative of an ambulation improvement?	▪ Yes ▪ No ▪ I prefer not to respond
In a control population, we observed that people unaffected by a muscle condition walk around 600m // 2000 feet during the 6-minute walk test. In your estimation, how far can you	▪ 450 to 600 meters // 1500 to 2000 feet ▪ 300 to 450 meters // 1000 to 1500 feet ▪ 150 to 300 meters // 500 to 1000 feet ▪ less than 150 meters // 500 feet

walk in 6 minutes?	▪ It is too difficult for me to walk for 6 minutes ▪ I don't know ▪ I prefer not to respond
Given your estimation of how far you can walk in 6 minutes, how many meters/feet gained in the 6-minute walk test would you consider an improvement in ambulation? • 5 to 10 meters // 15 to 30 feet • 20 to 40 meters // 60 to 120 feet • 50 to 100 meters // 150 to 300 feet	Answered separately for each distance: ▪ Improvement ▪ Acceptable improvement ▪ Unacceptable improvement ▪ Not applicable
With ActiMyo, we can also study climbing stairs in a real-world setting and determine the maximal speed while climbing stairs. Would you consider it to be an improvement if you were able to: • Climb the stairs • Climb the stairs faster • Climb the stairs more safely • Climb more stairs • None of these	Answered separately for each option: ▪ Very important ▪ Quite important ▪ Few important ▪ Not important ▪ Other (please state) (open-ended)
In people unaffected by a muscle condition, climbing (i.e., ascending) a single flight of stairs (14 steps) takes less than 15 seconds. In your estimation, how many seconds does it take for you to climb a single flight of stairs (14 steps)?	▪ Under 10 seconds ▪ 11 to 20 seconds ▪ 21 to 30 seconds ▪ 31 to 40 seconds ▪ More than 60 seconds ▪ I cannot climb stairs ▪ I don't know ▪ I prefer not to respond
Given your estimation of how many seconds it takes for you to climb steps, how many seconds in total would you consider an improvement in ambulation?	▪ Maintaining the same amount of seconds ▪ 5 seconds faster ▪ 10 seconds faster ▪ 20 seconds faster ▪ I prefer not to respond ▪ Other (please specify) (open-ended)
With ActiMyo we can also detect falls in a real-world setting Do you think that a decrease in the number of falls per day is representative of an ambulation improvement?	▪ Yes ▪ No ▪ Not applicable to my condition ▪ I prefer not to respond
How many times a week do you fall?	▪ 0 ▪ 1 to 5 ▪ 6 to 10 ▪ 11 to 20 ▪ 21 to 30 ▪ More than 30 ▪ I don't know ▪ Not applicable to my condition ▪ I prefer not to respond ▪ Other (please specify) (open-ended)
A decrease of how many falls a week should be representative of an improvement in ambulation?	▪ 1 to 5 ▪ 6 to 10 ▪ 11 to 20 ▪ More than 20

	▪ I don't know ▪ I prefer not to respond
The next section is related to ActiMyo outcomes which may characterize changes (improvement or decline) in upper limb movements. If you feel you are not concerned about upper limb movement and want to skip the next section, please indicate below	I am not concerned with upper limb movement outcomes (option to check box)
Usually, in clinical trials, upper limb motor function is assessed by motor function scales such as Performance Upper Limb (PUL), Motor Function Measure (MFM), or Revised Upper Limb Function (RULM). Scales consist of a series of tasks to study if the participant succeeds in performing the task and how they achieve it. The total score computes the result observed for each task. Other assessments, like reachable capacity, are under development. From your point of view, among the following items, which would best represent an improvement in upper limb mobility? (You may select up to 3 answers if some are equally important for you.)	▪ An increase in your ability to reach for distant things ▪ Less effort to bring your hands to your face ▪ Less effort needed to reach your arms over your head ▪ Increase speed at which you perform a task with your arms / hands ▪ Decrease fatigue during movement ▪ Ease in ability to raise arms without compensation ▪ I prefer not to respond
With ActiMyo, wrist movements are detected, and horizontal and vertical movement accelerations are computed as well as the power engaged by the movements. Ways of measuring the reachable workspace with upper limbs, i.e., how far you can reach with your hands for daily activities, are currently under development. From your point of view, is a change in the workspace your hands can reach representative of an improvement in upper limb mobility?	▪ Yes ▪ No ▪ I prefer not to respond
What would you consider to be the lowest acceptable improvement in your upper limb mobility from treatment?	▪ Maintain the current arm mobility ▪ Being able to reach an object in a workspace increased by 10 centimeters // 4 inches around you ▪ Being able to reach an object in a workspace increased by 20 centimeters // 8 inches around you ▪ Being able to reach an object in a workspace increased by 50 centimeters // 20 inches around you ▪ Being able to reach your face for feeding, grooming, etc. ▪ I prefer not to respond

Supplementary Table 6. Healthcare professional survey questions

Survey question	Response options
What is your profession?	▪ Physiotherapist ▪ Study coordinator ▪ Physician ▪ I prefer not to respond ▪ Other (please specify) (open-ended)
In which country do you work?	Open-ended
How many patients with ActiMyo did you equip/follow?	▪ 0 ▪ < 5 ▪ 5–10 ▪ 10–20 ▪ > 20 ▪ I don't know ▪ I prefer not to respond
Do you have experience with other wearable devices?	▪ No ▪ Yes. Which one? (open-ended) ▪ I prefer not to respond
How were you trained for ActiMyo?	▪ Remotely ▪ During an onsite training ▪ During investigator meeting ▪ I prefer not to respond
Could you rank the following sections of the training from the most relevant (1) to the least relevant (3)?	▪ ActiMyo device, maximum speed analysis, and relevance for the patient ▪ How to train and equip the patient ▪ How to manage protocol and ActiMyo constraints to recover data (recording period, sensor configuration, assignment form)
From your experience, what is the more challenging task when training a patient?	▪ I don’t know, I have never equipped a patient ▪ Explain how to install bracelet or ankle band on the sensor (accessories) ▪ Explain where and how to install both sensors (configuration) ▪ Explain when using ActiMyo (recording periods) ▪ Explain daily routine of ActiMyo ▪ I prefer not to respond
The next page is dedicated to patient feedback. If you didn't equip or follow any patients with ActiMyo, please select "I didn't equip/follow any patients." Otherwise, click on the "Next" button at the end of this page.	I didn't equip/follow any patients (option to check box)
Which question(s) did patients or parents managing ActiMyo usually ask you after several days of ActiMyo use (or/and misuse(s) you observed)?	▪ #1 (open-ended) ▪ #2 (open-ended) ▪ #3 (open-ended)
List up to 3 main positive feedback comments from patients wearing ActiMyo or parents managing ActiMyo?	▪ Positive feedback #1 (open-ended) ▪ Positive feedback #2 (open-ended) ▪ Positive feedback #3 (open-ended)
What are the 3 main aspects noticed by patients wearing ActiMyo or parents managing ActiMyo on which ActiMyo could be improved?	▪ Expected improvement #1 (open-ended) ▪ Expected improvement #2 (open-ended) ▪ Expected improvement #3 (open-ended)
From your experience, how well did patients tolerate ActiMyo (1: not tolerated at all – 10: very well tolerated)?	(Sliding scale from 1–10)

From your experience, which group of participants faces the most difficulties using the ActiMyo device?	▪ I cannot answer, I have equipped/followed only one category of participants ▪ Patients with Duchenne muscular dystrophy ▪ Patients with spinal muscular atrophy ▪ Patients with centro-nuclear myopathy ▪ Patients with facio-scapulo-humeral dystrophy ▪ Patients living with Angelman Syndrome ▪ I prefer not to respond
From your experience, which group of participants faces the most difficulties using the ActiMyo device, next?	▪ Ambulant ▪ Non-Ambulant ▪ Whatever the ambulant status
What were the reasons for not wearing ActiMyo? • Technical issues • Breakage • Misuse • Complexity of the device • Weight of watch-like sensors • Discomfort / obstacle for upper limb movements • Discomfort / obstacle for lower limb movements • Mockery / accentuation of differentiation	Answered separately for each reason: ▪ Always ▪ Often ▪ Sometimes ▪ Never
Do you agree, partially agree, or disagree with the following statements? • A wearable device like ActiMyo is useful to detect changes (deterioration or improvement) in patients' walking abilities • A wearable device like ActiMyo is useful to detect changes (deterioration or improvement) in patients' upper limb movements • Measuring the maximal speed of a patient is important to assess changes (deterioration or improvement) in ability to walk • The SV95C, measured by ActiMyo and representing the highest speed of patients' strides over a specified period of time in a real-life setting, is more precise and meaningful than the 6MWT to measure the ability to walk of a patient • The gait speed fit with how patients assess their ability to walk • Regarding walking ability, a 0,1m/s change per year in the SV95C, corresponding to a 30m change in 6MWD, is clinically meaningful for patients living with a neuromuscular disease • Regarding walking ability, a change in stair-climbing time is clinically meaningful for patients living with a neuromuscular disease • For nonambulant patients living with a neuromuscular disease, a change in	Answered separately for each statement: ▪ Agree ▪ Partially agree ▪ Disagree

amplitude of upper-limb movements is clinically meaningful for the patients' upper-limb motor function	
Do you agree, partially agree, or disagree with the following statements? • ActiMyo device is easy to use • Patients' training is easy to perform • ActiMyo management at clinical sites is easy to perform	Answered separately for each statement: ▪ Agree ▪ Partially agree ▪ Disagree
How could we improve your experience with the device regarding the following points?	▪ Shipment & logistics: (open-ended) ▪ Equipping a patient: (open-ended) ▪ Support to patient: (open-ended) ▪ Support to clinical team: (open-ended) ▪ Data transfer & compliance: (open-ended)

6MWD 6-minute Walk Distance, *6MWT* 6-minute Walk Test, *SV95C* stride velocity 95th centile.

Supplementary Methods

A. CE-labeled medical device

The wearable is a CE-labeled medical device, indicating conformity with European standards of health, safety, and environmental protection. Supporting tests include the following: security (European Norms [EN] 60601-1:2007 for professional healthcare, EN 60601-1-11:2015 at home); electromagnetic compatibility (International Electrotechnical Commission [IEC] 60601-1-2:2014 for professional healthcare, IEC 60601-1-2:2014 at home); biocompatibility (International Organization for Standardization [ISO] 10993-1:2009); and usability (IEC 60601-1-6:2010, IEC 62366-1:2015). Software development complies with IEC 62304 testing standards. Stored data are encoded, and communication channels are encrypted. Only the researcher can access the patient identifier codes, and only the clinical center stores the link between patient identifier codes and personal patient details to protect patient privacy.

B. Meaningful change thresholds: Clinical Global Impression of Change (CGI-C) and Pediatrics Outcomes Data Collection Instrument (PODCI)

Clinicians completed the single-item CGI-C at the end of the double-blind period (week 48) to rate the degree of change they observed in a patient. The seven response options, coded from 1 to 7, include “very much improved,” “much improved,” “minimally improved,” “no change,” “minimally worse,” “much worse,” or “very much worse.” Responses were collapsed into categories based on any improvement, no change, or any worsening in the analysis of meaningful change. The mean SV95C change over the same period was calculated for each change category (improved, stable, or worsened).

The PODCI is an 83- to 86-question measure of physical functioning and health-related quality of life that includes five core scales (upper extremity and physical function, transfer and basic mobility, sports and physical functioning, pain/comfort, and happiness) and one global functioning scale. The PODCI was completed by the parents of pediatric patients. The transfers and basic mobility subscore, with a 10% change threshold, was used as an anchor of change. The mean change in SV95C over the same period was calculated.

C. Standard error of measurement and minimal detectable change (MDC)

The standard error of measurement threshold is an estimate of how repeated measures of a score are distributed around an individual’s “true” score, reflecting how much change can be attributed to measurement error. The standard error of measurement of SV95C (N = 103) was calculated as standard error of measurement = SD*SQR(1–ICC), with the intraclass correlation coefficient (ICC) calculated as outlined in the Methods section.

The MDC is the smallest amount of change in a measure that falls outside the measurement error. The MDC in SV95C (N = 103 patients) was measured based on the standard error of measurement at 95%, 90%, and 80% confidence levels, and by considering 0.2, 0.5, and 0.8 SDs.

D. Qualitative evidence

Qualitative data and insights were collected from an online survey (549 responders, including 92 patients with DMD or caregivers for patients with DMD; see Supplementary Table S4) developed in collaboration with a child neurologist and a physiotherapist, as well as American patient organizations (Parent Project Muscular Dystrophy and Myotubular Trust). The survey was distributed internationally through patient organizations between October 2020 and January 2021. Objectives of the survey were to identify ambulation-related factors that were most important to respondents and to determine the following: first

symptoms, disease impact on mobility and activities, functions patients and caregivers would most like treatments to impact, opinions about what constitutes a clinical improvement in ambulation, and openness to wearing a device at home to monitor walking abilities. Survey questions are shown in Supplementary Table S5.

Feedback on experiences with the wearable was collected through an online survey of healthcare professionals (see survey questions in Supplementary Table S6). Responses were gathered from 52 worldwide healthcare professionals, including physiotherapists (57%), study coordinators/nurses/managers (34%), and physicians (9%). The survey topics included wearable use, training experience, feedback from patients using the device, and potential uses of wearable device variables. The survey was sent to site staff who were trained to use the wearable, with data collected between June 11 and June 25, 2020.

Eight solicited letters of support were received from neurologists, pediatric neurologists, and physiotherapists. Additional comments were received from nonprofit organizations, industry representatives, and the broader scientific community during the European Medicines Agency qualification public consultation.

Finally, responses were collected from live polling conducted during the 2018 Parent Project Muscular Dystrophy annual congress, as well as support letters from the patient association. The respondents included caregivers (50%), industry professionals (16%), and healthcare professionals (11%). Most respondents (89%) were from the US.

Supplementary Results

A. Patient and caregiver perspectives: Duchenne Community Advisory Board (CAB) comments

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 6-minute Walk Test (6MWT) because:
    a) The 6MWT is subject to bias from the assessor and the family since the patient can be incentivized 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 traveling 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 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 fewer hospital visits would be required.
6. It would also be an additional measure for trials in the non-ambulant population 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.

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).

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.

B. Patient and caregiver perspectives: Duchenne Parent Project Belgium comments

As parents of boys affected by Duchenne muscular dystrophy (DMD), we are very positive about an objective measurement of the potential progresses generated by a new drug during clinical trials.

The 6MWT is really cruel, and the North Star Ambulatory Assessment, when captured occasionally at the hospital, is not reliable enough given the small number of boys in DMD clinical trials.

C. Patient and caregiver perspectives: Action Duchenne comments

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 form of activity.
- This activity should be less liable to external influence, such as a particularly encouraging assessor or attending legal guardian (i.e., parent).
- Given how few data points a sporadic 6MWT delivers, they are particularly vulnerable to the patient's mood, demeanor, state of mind, experience (a long journey, pre-test anxiety, time of day/year, etc.) that day.
- It would help to reduce the burden on families of those taking part in clinical trials; we know many families who regularly travel across the UK to participate.

The 6MWT creates 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 the vast majority of clinical trials into DMD.

D. Patient and caregiver perspectives: World Duchenne Organization comments

The World Duchenne Organization—United Parent Project Muscular Dystrophy—is in favor of using suitable wearable devices as a secondary endpoint in clinical trials in DMD.

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 the assessor and/or family. Bias can have a huge impact on trial results. In addition, the patient's mood, the time of day, and fatigue can all influence performance on 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. These data are far more reliable, objective, and accurate than several 6MWTs taken in a hospital setting 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 DMD 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 fewer hospital visits would be required to collect a sufficient amount of data.

The amount of data collected by a suitable wearable device might contribute significantly to reducing the duration of clinical trials, which reduces burden since the device collects much 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 or digital form or even recorded, might be an advisable addition to account for daily variation (physiology, swimming, gym class, school and other holidays, illnesses, etc.).

We strongly recommend waterproofing the device so as to capture, for example, swimming exercises; in addition, waterproofing would help to 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 from patients with DMD can be compared.

To summarize, the World Duchenne Organization—United Parent Project Muscular Dystrophy—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, as well as payers, since it can more clearly demonstrate the functional benefit of a treatment.