FOLLOW UP QUALIFICATION EMA/SA/0000083386

RESPONSES TO THE LIST OF ISSUES

Date :		28/06/2022	
Reference SYSNAV :		SV95C-EMA-PEP-LoIssuesResponses	
Edition	1	Review	1

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Responses to the List of Issues adopted by the SAWP during its 07-10 June 2022 meeting and issued on 15 June 2022.

An additional point for discussion was communicated on 20th and document was uploaded on the IRIS portal.

Applicants really appreciate having the opportunity to further discuss with EMA experts about the qualification of SV95C as a primary endpoint in clinical trials with Duchenne muscular dystrophy and its interest in other progressive neuromuscular diseases characterized by a proximal muscle weakness.

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Version: 1.1

Date: 28 June 2022

Content

Figure Index

Table Index

List of Abbreviations

4SC	4-stair climb test
6MWD	6-minute walking distance
6MWT	6-minute walk test
BMD	Becker muscular dystrophy
BL	Baseline
CGI-C	Clinical Global Impression of Change
COA	Clinical Outcome Assessment
CT	Clinical Trial
CTRL	Control
DMD	Duchenne Muscular Dystrophy
FSHD	FacioScapuloHumeral muscular Dystrophy
FU	Follow up
HCP	Healthcare Professional
MCT	Meaningful Change Threshold
MDC	Minimal Detectable Change
MFM	Motor Function Measure
NHS	Natural History Study
NMD	NeuroMuscular Disease
NSAA	North Star Ambulatory Assessment
PODCI	Pediatrics Outcomes Data Collection Instrument
PRO	Patient reported Outcome
Rho (ρ)	Spearman correlation coefficient
RP	Recording period
SD	Standard Deviation
SEM	Standard Error of Measurement
SV95C	95th Centile of the Stride Velocity

Primary Endpoint Qualification of SV95C in ambulant patients with DMD

1. Question #1

Please discuss whether the gaps identified and approaches to address these, i.e. "collecting additional data with patient reported outcome through health-related quality of life questionnaires to strengthen the anchoring and refinement of a MCT for the SV95C", and "to use a relevant secondary endpoint assessing muscle or strength function in the design of the future clinical trials using SV95C as a primary endpoint to confirm consistency" do not contradict the qualification of the SV95C as 'essential' primary endpoint in ambulatory DMD.

In the briefing document we presented evidence that ambulation is a key aspect of DMD and that all stakeholders (patients, caregivers, clinicians, patient advocacy groups, industry and regulators) agree that there is a need for a validated clinical outcome assessment (COA) to assess mobility in this population that more accurately reflects the patients daily functioning in real-life, that is not limited to performance on a clinic-based assessment completed at a specific point in time in an artificial setting, and that reduces the burden on sites, staff and patients completing these tests.

SV95C is a measure that addresses these limitations with existing COA. Quantitative evidence established through a panel of variate studies demonstrated that SV95C, when measured with the wearable ActiMyo® device, is accurate, reliable, clinically relevant based on the correlations with existing COA and its ability to distinguish patient from subject without any muscle condition, and sensitive to change even with small group of subjects enrolled in multiple international clinical sites.

Completion of a questionnaire does capture social and contextually activity on top of performance. Patient reported outcome (PRO) are therefore subjective and, when completed by a proxy, answers may diverge from the patient's perspectives. In that context, a PRO is key to the design of a clinical trial in complement of other more objective performance metrics but might not define a meaningful change threshold (MCT) robustly by itself. In the current application dossier, we worked with data obtained from different natural history studies and clinical trials, and therefore using clinical outcome assessments chosen by different sponsors. Only one clinical trial that was prematurely stopped due to lack of efficacy, used patient reported outcome and agreed to share data with us at the time we prepared the briefing document. Unfortunately, in addition to be available on a very few participants, those PRO combine both limitations: they were completed by a proxy (the clinician for CGI-C and the parents for PODCI) and they are directly impacted by the placebo effect. Having the opportunity to get PRO completed by patients themselves would be of great interest but not commonly used in DMD clinical trials. Nevertheless, we are confident that additional data collected from other ongoing studies may reduce the variability around the PRO and will reinforce the estimation of 0.1 m/s for the MCT.

The Guideline on medicinal products for the treatment of Duchenne and Becker muscular dystrophy - EMA/CHMP/236981/2011 – version 2015[1] mentions:

"The primary pathophysiological effect of DBMD is a decline in muscle strength and motor function and these are therefore important parameters to measure. Muscle strength and motor function are closely related but quite distinct motor system parameters. Many additional factors other than muscle strength may influence the ability to function (e.g., the patient`s ability to walk is affected by other factors than muscle strength alone). Although it is well known and recognised that there is no linear correlation between muscle strength and function in boys with DMD, for total evidence of clinical efficacy an effect on motor function should be supported by an effect on muscle strength. In addition, treatment effects on functionality should be backed up by effects in the activities of daily living (ADL). Similarly, a compound aiming at increasing or maintaining muscle mass should show in addition to efficacy on muscle strength also an effect (or at least no detrimental effect) on function to evaluate the clinical relevance. Two endpoints should be selected from the domains muscle strength (depending on the functional status and

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy_en.pdf

the compound tested) and motor function. According to the motor system parameter estimated to be particularly affected, one should be selected as primary endpoint and the other as secondary endpoint. Effects on the single selected primary endpoint should be supported by results from the most relevant secondary endpoints for consistency."

We are sorry that this statement was misunderstood. We simply wanted to mention that as SV95C is a functional measure, it should be also- following the guideline- accompanied by key secondary endpoint measuring strength in clinical trials for total evidence of clinical efficacy. This statement was thus simply to explain how SV95C should be considered in the context of guideline EMA/CHMP/236981/2011 – version 2015.

2. Question #2

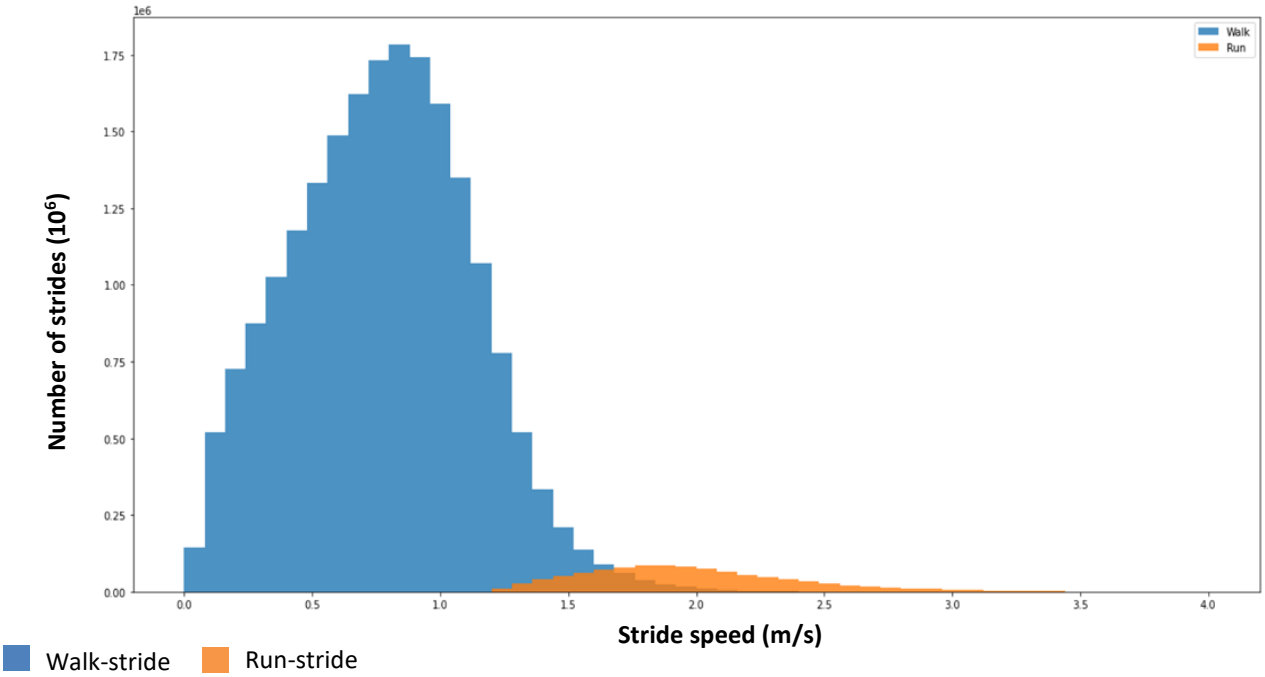
Please discuss the potential of the SV95C to predict important milestones in DMD.

Natural history of DMD goes through the successive loss of very significant milestones, such as the loss of ability to run, the loss of ability to climb stairs, the loss of ability to stand from floor, and the loss of ability to walk. Several natural history studies have demonstrated that these different milestones were related to each other: the earlier an individual loses the ability to stand from the floor or to climb stairs, the earlier this individual will lose ambulation. Age at loss of ambulation predicts also future important milestones such as the need of ventilation.

Age of ambulation happens fortunately several years after clinical trials end up, and the precise information is difficult to obtain. We thus explored the correlation between SV95C and other important milestones that happen earlier, such as the loss of ability to run and the loss of ability to climb stairs. These two important milestones appear earlier than the loss of ambulation in the course of the disease, and do not require thus massive and very long-term data like loss of ambulation.

Based on an algorithm developed to classify strides as run or walk based on the stance/swing ratio, stride speed, and stride frequency, preliminary results on 34[2] patients from the CT-A study demonstrated that walking strides were the main component of walking episodes and that most of walking strides velocity were below 1.3 m/s (Figure 1). In addition, we observed a strong correlation between SV95C and the percentage of running strides (N=34, Spearman's Rho = 0.859, P-value <0.001). Lastly, less than 4% of run-strides were detected for DMD-patients with SV95C below than 1.5 m/s, and no run-strides were detected with a SV95C below than 1.1 m/s (Figure 2). The evolution of SV95C in patients who have still maintained the ability to run may thus predict the loss of this ability.

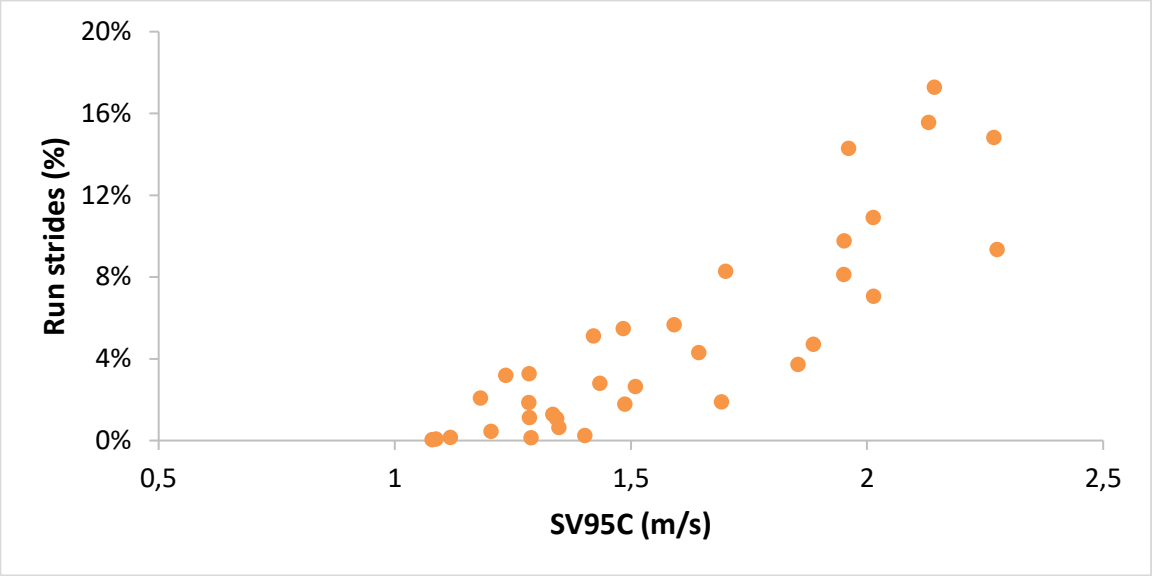
Figure 1: Stride speed of the total number of strides performed by a subset of 34 patients with DMD from CT-A study during their first recording period.



CT = Clinical trial; DMD = Duchenne muscular dystrophy

[2] Result for only 1 patient of CT-A was missing due to a quality check alert that was not investigate at the time of the preliminary analysis.

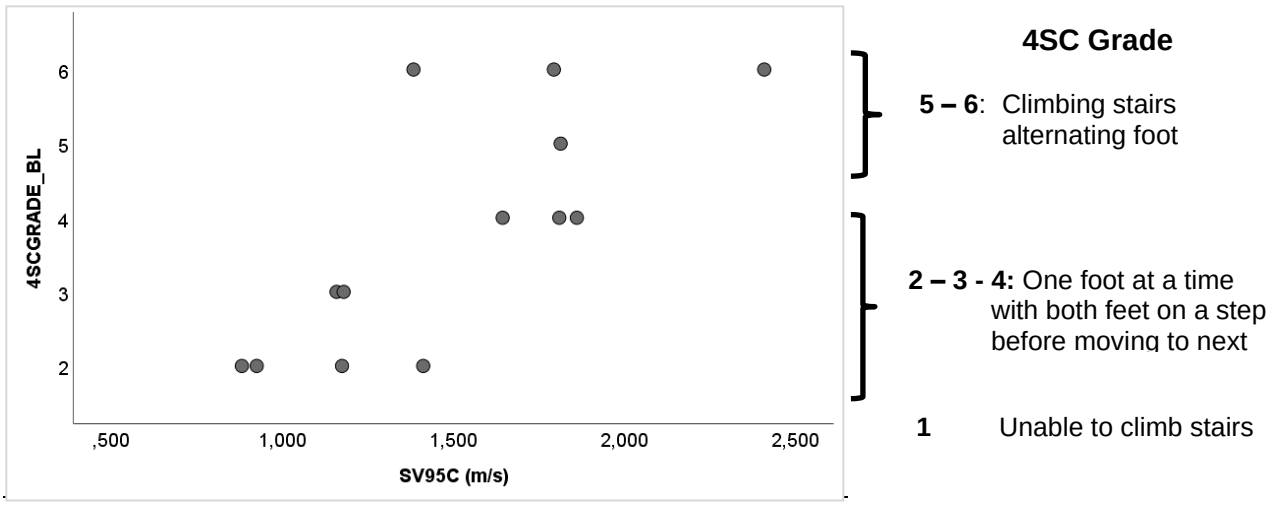
Figure 2: Percentage of run-stride as a function of SV95C of a subset of 34 patients with DMD from CT-A study during their first recording period.



CT = Clinical trial; DMD = Duchenne muscular dystrophy; SV95C = 95th centile of the stride velocity

Similarly, we studied if we may identify a threshold regarding the ability to climb stairs. On a subset of the 13 patients enrolled in NHS-B where the quality of climbing stairs during the four-stair climbing test (4SC) was assessed and available at the time of the analysis, we observed a significant relationship between the SV95C and the ease in which patients are able to climb stairs (N=13, Spearman correlation coefficient ρ=0.722, p-value=0.005) and that all patients able to climb stairs presented with a minimal SV95C around 1 m/s (Figure 3).

Figure 3: Relationship between the SV95C and the ability to climb stairs.

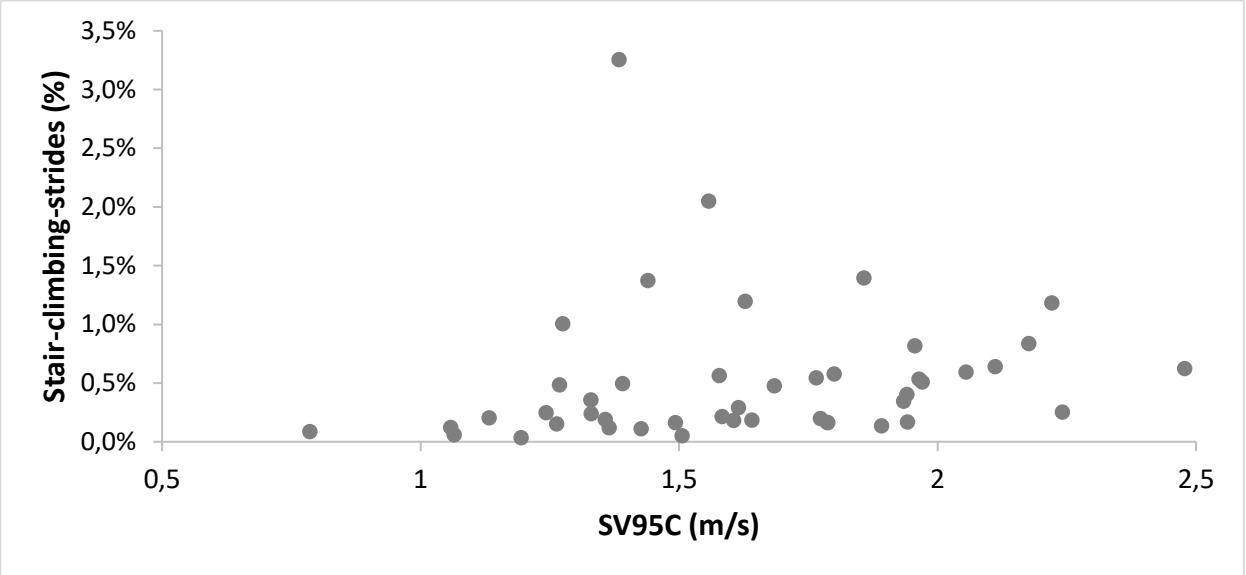


4SC = 4-stair climbing test; CT = Clinical trial; DMD = Duchenne muscular dystrophy; SV95C = 95th centile of the stride velocity

Based on a machine-learning algorithm designed to classify strides as stair-strides or non-stair-strides, 51 patients with DMD enrolled in the CT-B study, we observed that except for one patient, stair-climbing strides represented less than 2% of the total of strides performed in a recording period. Less than 1% of

strides were detected as stair-climbing strides in DMD-patients with SV95C below than 1 m/s. No stair-climbing strides were detected in patients with SV95C below than 0,8 m/s (Figure 4).

Figure 4: Percentage of stair-stride as a function of SV95C of a subset of 51 patients with DMD from CT-B study during their first recording period.

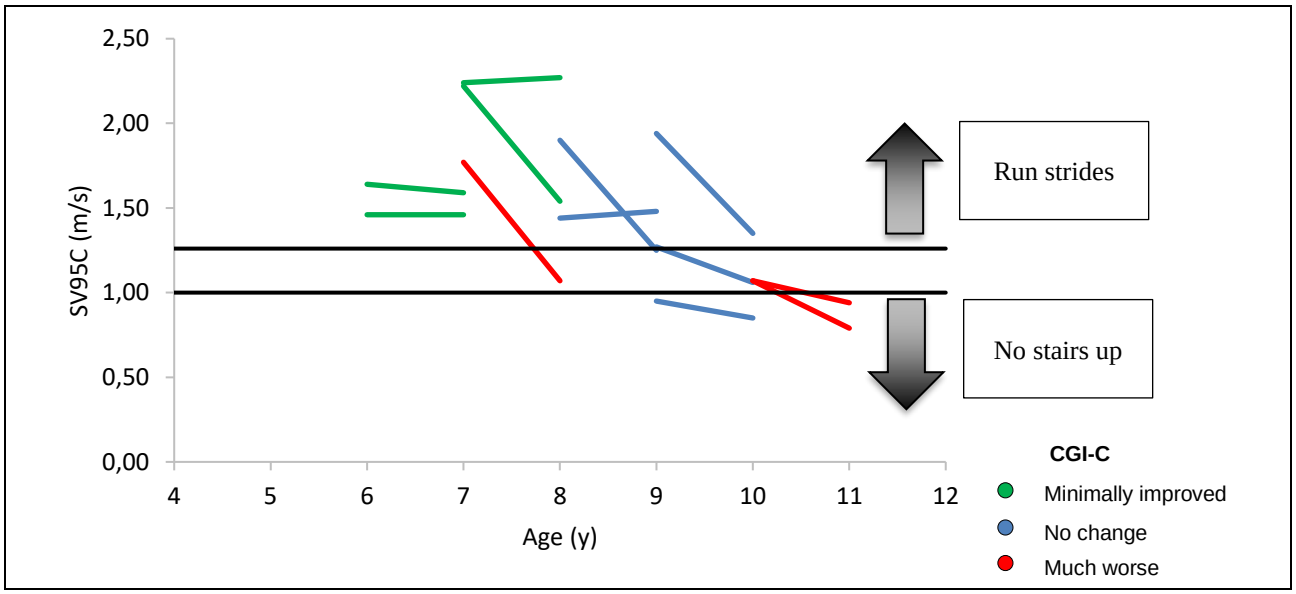


CT = Clinical trial; DMD = Duchenne muscular dystrophy; SV95C = 95th centile of the stride velocity

The existence of potential thresholds around 1 to 1.3 m/s to be able to climb stairs or to run respectively needs to be further confirmed but they may reinforce the clinically meaningfulness of the SV95C which could be a prognostic factor of this major ambulation milestones in DMD.

Drawing those thresholds on Figure 5 (data on the 12 available DMD-patients from CT-B study that completed CGI-C) reinforce our suggestion that completion a questionnaire is an activity directly impacted by the current context. In the present case, a negative change in CGI-C reported by the clinicians seems associated with an important change in the clinical state of their patients corresponding to a noticeable milestone in the course of the disease as the loss of running ability or the inability to climb stairs.

Figure 5: Evolution of SV95C 48 weeks apart



In green: clinicians reporting a minimally improvement, in blue: parents reporting no change, in red: clinicians reporting a worsening

Future research

Finally, we propose updates to the SAWP, post qualification, with additional comprehensive data collected in the coming years. SV95C is currently collected in 5 clinical studies with DMD, the qualification as a primary endpoint could significantly increase the number of studies in which data are collected and help fine tuning of the MCT. As SV95C has been pioneering the outcome measure qualification process in neuromuscular diseases, we commit to continue working closely with EMA to update and refine the metrics properties of the measure.

We have already identified relevant post-qualification milestones:

- Anchoring SV95C threshold with PROs: As suggested, due to their subjective nature, clear anchor will require several studies. The ongoing study is a global pivotal Ph3 study evaluating the therapeutic benefits of micro dystrophin gene therapy in DMD in which SV95C is listed as a secondary endpoint. Several potential anchors are included in the protocol, including the NSAA and various PROs. We are negotiating with the sponsor of the trial authorization to share data with the SAWP and use it to further refine the proposed MCT. We have been authorized following the List of Issue, to share data from the study. We will include the results as soon a PRO data are shared with us.
- Anchoring SV95C to functional milestones: Would EMA agree that losing the ability to run or to climb stairs constitute important milestones in the natural history of the disease, and that a clear correlation between SV95C and these two milestones can constitute a clear clinical anchor for the SV95, we propose:

  a. To substantiate the correlation between SV95C and stair climbing and/or running on the full set of data (this additional analysis could not be conducted in the time available)

  b. To study how patients who cross or do not cross the SV95C threshold associated with these two milestones lose or do not lose these milestones.

  These analyses will require 3 months.

  In addition, long term data on age at loss of ambulation will be collected retrospectively and prospectively, but no timeline can be given to be able to use robustly these data. We thus propose to formally update EMA in 3- and 5-years post qualification.

- Long term evidence: We want to further substantiate data from answer 2, with loss of ambulation which is a long term and key milestone for ambulation. We are co-funding a 3-year natural history study for DMD patients to gather long term SV95C data and expect to have latest patients included Q3 2022, so 3-year results by end of 2025. Furthermore, we are investigating the possibility to have longer term follow up on some of patients of previous clinical trials

3. Question #3

Please comment on results of the qualitative research, indicating that measures of ambulation ability, e.g., distance walked, or stairs climbed as related performance measures, could be rated as more important than SV95C.

We believe respondent (e.g., patient or parents/caregivers) and ability to link concept to one's life reality has an impact on the answer for meaningfulness. This was first noticed during a preparatory phone call with the head of a patient association and her son affected by a progressive neuromuscular disease. Both agreed that their perspectives were different and that having the questionnaire completed by parents and patients independently would be more informative.

We designed 2 surveys with same questions, one link was dedicated to patients and the other to parents or caregivers. By doing this, we wanted to get their own perspectives regarding the mobility, the use of a wearable device, the participation to clinical trial and the outcome measure meaningfulness that we supposed may diverged as carers do not perceive the symptoms of the disease as their loved one.

Considering responses from all ambulant NMDs together, results confirmed that perspectives are different from patients to their families or caregivers. At the question: Among the followings, which best represents improvement in ambulation (max 3 items), patients answered in order of importance: 1. Fatigue during ambulation, 2. Ability to walk fast, 3. Ability to climb stairs, while carers answered 1. Fatigue during ambulation as well, but 2. Distance walked before stop and 3. Number of falls per day. For ambulant patients with an NMD leading to a progressive muscle weakness, ability to walk fast came as the second-best marker of improvement in ambulation after fatigue, which is much more difficult to characterize and quantify. Even if there are many other ambulation factors that we may consider, this answer supported the development of the SV95C that measures the maximal walking speed.

Due to the age range of the population, respondents for DMD categories were mainly parents (46 parents vs 3 patients) preventing us to compare results from patients to carers in this population as stated on page 42 of the briefing package. Parents of ambulant patients with DMD answered that Fatigue during ambulation best represents improvement in ambulation followed by Distance walked before stop and number of falls per day. While inability to keep up with peers is often one major reason to consult a physician, the ability to walk fast was not reported as a potential marker of improvement in ambulation. It is not surprising that harder to define concepts like ability to walk fast does not come to mind first. It requires high level of insights for caregivers and parents to link SV95C to the potential social impact for the patient. For instance, most control subjects without any muscle conditions (CTRL) younger than 10-year-old have SV95C of 2.3 to 3.5 m/s (Figure 44 of the briefing package) while DMD ambulant patients have SV95C of 1 to 2 m/s. So "ability to walk fast" is for the young DMD patients only the "ability to walk half as fast as other kids of their age" and in effect, ability to function, to participate in the playground and keep up with their friends. We also assume that similarly to the mother we initially talked with, the empathy of seeing her child falls and the stress and fatigue in daily living to carry your loved one in stairs or for long walks, does put a very pragmatic focus on those measures. More expert groups like the healthcare professionals probed in the HCPs survey or patients' associations we interacted with are unanimous regarding ability to walk fast as an important aspect of ambulation.

Whilst we acknowledge that other aspects of ambulation, i.e., distance walked and stairs climbed, are also performance measures and may be considered even more meaningful by some patients/parents because much easier to visualize improvement in daily living activities, they are highly related to the patient activity and environment. For instance, as seen on Figure 4 and in question #2 of this document, some patients who can ambulate well (SV95C of 2.0m/s or above) are almost not climbing stairs, which simply results from the fact that their family may have adapted their environment to limit the necessity of stair climbing, while others may not have done so yet. The sensitivity/specificity with which such performance measures can be measured is challenging and SV95C is considered a more reliable measure of the meaningful concept of ambulation during a clinical trial.

4. Question #4

Please discuss results of the HCP survey, considering that only part of participants responded to the question in figure 2 (#15 in the briefing document, #17 in annex 7.1.2) with high rates of agreement in those who responded. Please clarify if participants only answered selected questions and discuss how not answering questions could be counted.

Fifty-two healthcare professionals (HCP) responded to the survey. Only the first question was mandatory meaning that respondents might skipped subsequent questions if they wanted to. The table below shows that some questions were poorly answered and that there was an attrition in rate of completion with the question number. Thirty-eight HCP responded at question 17 (which is higher than the previous question and the second highest rate of the last 10 questions) and all of them agreed that measuring the maximal speed of a patient is important to assess changes (deterioration or improvement) in his ability to walk meaning that at least 73% of HCP contacted agreed with this statement.

Table 1: Rate of completion in the healthcare professionals survey

Question number	Answered	Skipped	Rate of completion
Q1	52	0	100%
Q2	51	1	98%
Q3	51	1	98%
Q4	51	1	98%
Q5	51	1	98%
Q6	48	4	92%
Q7	47	5	90%
Q8	47	5	90%
Q9	15	37	29%
Q10	26	26	50%
Q11	24	28	46%
Q12	25	27	48%
Q13	30	22	58%
Q14	30	22	58%
Q15	29	23	56%
Q16	31	21	60%
Q17	**38**	**14**	**73%**
Q18	40	12	77%
Q19	18	34	53%

5. Question #5

Overall, it is difficult to follow from which study patients were included in the quantitative analyses. The criteria for not including patients and controls are unclear and it can only be assumed that there was no selection of patients. Please clarify that all available patients were included in the analyses and provide a justification that pooling of the data for the analyses (e.g. for the RCTs) is appropriate.

Data used in the present qualification package came from studies for which sponsors authorized Sysnav to use data for regulatory perspectives and from patients with available SV95C at baseline and are summarized in table 1 of briefing document package. SV95C was computed as soon as 50 hours were recorded during a recording period. **All available data were used without any selection for convenience at the patient level, as well as all available clinical outcome measures provided by sponsors.**

In addition to the number of subjects listed in the method section for quantitative evidence (section 3.2.1), for the sake of clarity, we have detailed for each analysis where the patients come from and their characteristics at baseline in terms of Age, SV95C, 6MWD, NSAA, 4SC (Table 2).

Table 2: Characteristics at baseline of population used in all statistical analyses of the briefing document

Analysis	Data selection	Study	Variable	N	Mean	Median	SD	Min	Max
Cross sectional analyses									
Known-group validity – DMD vs CTRL at BL	DMD + $SV95C_{BL}\neq0$	NHS-A (x2) NHS-B (x13) NHS-C (x11) CT-A (x34) CT-B (x 51) CT-C (x 7) In Clinic (x7)	Age (y)	125	8.1	8.0	1.94	5.0	14.0
			SV95C (m/s)	125	1.571	1.563	0.3818	0.723	2.470
			6MWD (m)	109	389.4	389.0	75.63	25.0	512.0
			NSAA (#)	109	22.8	23.0	6.28	2	33
			4SC (s)	109	3.85	3.40	1.631	1.29	8.70
	CTRL + $SV95C_{BL}\neq0$ + age [5 – 14]	NHS-A (x62) NHS-B (x4)	Age (y)	66	9.6	9.3	2.16	6.0	14.2
			SV95C (m/s)	66	2.621	2.713	0.4578	1.474	3.556
			6MWD (m)	63	606.7	605.0	63.46	464.0	761.0
			NSAA (#)	-	-	-	-	-	-
			4SC (s)	3	1.3	1.3	0.17	1	2
Test-Retest reliability	DMD + recording duration >= 50h at M1 and M2	NHS-B (x10) NHS-C (x11) CT-A (x31)	Age (y)	52	8.1	7.8	2.25	5.0	14.0
			SV95C (m/s)	52	1.570	1.551	0.397	0.723	2.426
			6MWD (m)	51	394.6	395.5	72.11	151.0	512.0
			NSAA (#)	52	23.3	23.5	6.1	8	33
			4SC (s)	52	3.77	3.20	1.76	1.29	8.7
Convergent validity	DMD + $SV95C_{BL}\neq0$ + $6MWD_{BL}\neq0$ + $NSAA_{BL}\neq0$ + $4SC_{BL}\neq0$	NHS-B (x12) NHS-C (x11) CT-A (x34) CT-B (x50)	Age (y)	107	8.3	8.0	1.93	5.0	14.0
			SV95C (m/s)	107	1.586	1.576	0.3792	0.723	2.470
			6MWD (m)	107	390.0	389.0	75.73	25.0	512.0
			NSAA (#)	107	22.9	23.0	6.32	2	33
			4SC (s)	107	3.82	3.40	1.578	1.29	8.70
MCT Distribution-based threshold	DMD + recording duration >= 50h during both half of a recording period	NHS-A (x3) NHS-B (x13) NHS-C (x6) CT-A (x29) CT-B (x43) CT-C (x5) In clinic (x4)	Age (y)	103	8.1	8.0	2.0	5.0	14.0
			SV95C (m/s)	102	1.577	1.570	0.386	0.723	2.470
			6MWD (m)	93	388.4	385.0	80.2	0.0	512.0
			NSAA (#)	91	23.4	23.0	6.1	8.0	33.0
			4SC (s)	91	3.88	3.40	1.64	1.29	8.70
Longitudinal analyses									
		CT-B (x43)	Age (y)	43	8.4	8.0	1.58	6.0	11.0

Analysis	Data selection	Study	Variable	N	Mean	Median	SD	Min	Max
Convergent validity – 3M	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M3}\neq0$ + $6MWD_{BL}\neq0$ + $6MWD_{M3}\neq0$ + $NSAA_{BL}\neq0$ + $NSAA_{M3}\neq0$ + $4SC_{BL}\neq0$ + $4SC_{M3}\neq0$		SV95C (m/s)	43	1.576	1.590	0.3427	0.790	2.240
			6MWD (m)	43	387.1	383.0	60.24	173.0	507.0
			NSAA (#)	43	22.1	22.0	6.02	8	33
			4SC (s)	43	3.90	3.50	1.502	1.62	7.75
Convergent validity – 6M	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M6}\neq0$ + $6MWD_{BL}\neq0$ + $6MWD_{M6}\neq0$ + $NSAA_{BL}\neq0$ + $NSAA_{M6}\neq0$ + $4SC_{BL}\neq0$ + $4SC_{M6}\neq0$	CT-B(x20)	Age (y)	20	8.5	8.5	1.79	6.0	11.0
			SV95C (m/s)	20	1.654	1.640	0.2570	1.130	2.240
			6MWD (m)	20	402.8	398.0	47.09	312.0	510.3
			NSAA (#)	20	21.8	22.0	5.53	11	32
			4SC (s)	20	3.75	3.45	1.320	1.62	7.00
Convergent validity – 9M	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M9}\neq0$ + $6MWD_{BL}\neq0$ + $6MWD_{M9}\neq0$ + $NSAA_{BL}\neq0$ + $NSAA_{M9}\neq0$ + $4SC_{BL}\neq0$ + $4SC_{M9}\neq0$	CT-B (x24)	Age (y)	24	8.3	8.0	1.57	6.0	11.0
			SV95C (m/s)	24	1.663	1.705	0.3617	0.950	2.240
			6MWD (m)	24	409.3	407.0	55.40	270.0	510.3
			NSAA (#)	24	23.8	22.5	5.64	16	33
			4SC (s)	24	3.42	3.20	1.197	1.62	7.22
Convergent validity – 12M	DMD + NHS+ $SV95C_{BL}\neq0$ + $SV95C_{M12}\neq0$ + $6MWD_{BL}\neq0$ + $6MWD_{M12}\neq0$ + $NSAA_{BL}\neq0$ + $NSAA_{M12}\neq0$ + $4SC_{BL}\neq0$ + $4SC_{M12}\neq0$	CT-B (x15)	Age (y)	15	8.3	8.0	1.54	6.0	11.0
			SV95C (m/s)	15	1.596	1.640	0.4040	0.950	2.240
			6MWD (m)	15	380.3	383.0	52.04	270.0	462.0
			NSAA (#)	15	21.9	21.0	5.32	15	33
			4SC (s)	15	3.72	3.40	1.376	1.62	7.22
Responsiveness Natural course of the disease – 3M – SV95C	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M3}\neq0$	NHS-B (x5) NHS-C (x5) CT-A (x25) CT-B (x46)	Age (y)	81	8.3	8.0	1.81	5.0	13.7
			SV95C (m/s)	81	1.571	1.580	0.3461	0.723	2.240
			6MWD (m)	80	390.8	388.5	66.39	151.0	512.0
			NSAA (#)	81	22.8	23.0	5.98	8	33
			4SC (s)	81	3.80	3.30	1.542	1.62	8.70
Responsiveness Natural course of the disease – 3M – 6MWD	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M3}\neq0$ + $6MWD_{BL}\neq0$ + $6MWD_{M3}\neq0$	CT-B (x43)	Age (y)	43	8.4	8.0	1.58	6.0	11.0
			SV95C (m/s)	43	1.576	1.590	0.3427	0.790	2.240
			6MWD (m)	43	387.1	383.0	60.24	173.0	507.0
			NSAA (#)	43	22.1	22.0	6.02	8	33
			4SC (s)	43	3.90	3.50	1.502	1.62	7.75
Responsiveness Natural course of the disease – 3M – NSAA	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M3}\neq0$ + $NSAA_{BL}\neq0$ + $NSAA_{M3}\neq$	CT-B (x46)	Age (y)	46	8.4	8.0	1.59	6.0	11.0
			SV95C (m/s)	46	1.592	1.605	0.3396	0.790	2.240
			6MWD (m)	45	391.1	389.0	62.19	173.0	510.3
			NSAA (#)	46	22.5	22.0	6.11	8	33
			4SC (s)	46	3.83	3.40	1.480	1.62	7.75
Responsiveness		CT-B (x46)	Age (y)	46	8.4	8.0	1.59	6.0	11.0

Analysis	Data selection	Study	Variable	N	Mean	Median	SD	Min	Max
Natural course of the disease – 3M – 4SC	DMD + NHS + SV95C$_{BL}$≠0 + SV95C$_{M3}$≠0 + 4SC$_{BL}$≠0 + 4SC$_{M3}$≠0		SV95C (m/s)	46	1.592	1.605	0.3396	0.790	2.240
			6MWD (m)	45	391.1	389.0	62.19	173.0	510.3
			NSAA (#)	46	22.5	22.0	6.11	8	33
			4SC (s)	46	3.83	3.40	1.480	1.62	7.75
Responsiveness Natural course of the disease – 6M – SV95C	DMD + NHS + SV95C$_{BL}$≠0 + SV95C$_{M6}$≠0	NHS-C (x6) CT-A (x26) CT-B (x27)	Age (y)	59	8.3	8.0	1.96	5.2	13.7
			SV95C (m/s)	59	1.583	1.590	0.3464	0.723	2.426
			6MWD (m)	58	391.4	392.3	72.07	151.0	512.0
			NSAA (#)	59	22.5	23.0	5.91	8	33
			4SC (s)	59	3.68	3.24	1.534	1.62	8.70
Responsiveness Natural course of the disease – 6M – 6MWD	DMD + NHS + SV95C$_{BL}$≠0 + SV95C$_{M6}$≠0 + 6MWD$_{BL}$≠0 + 6MWD$_{M6}$≠0	NHS-C (x4) CT-A (x11) CT-B (x20)	Age (y)	35	8.4	8.2	1.97	5.2	13.7
			SV95C (m/s)	35	1.610	1.640	0.2795	0.969	2.240
			6MWD (m)	35	405.7	400.0	59.37	290.0	512.0
			NSAA (#)	35	22.5	23.0	5.97	8	33
			4SC (s)	35	3.68	3.30	1.579	1.62	8.70
Responsiveness Natural course of the disease – 6M – NSAA	DMD + NHS + SV95C$_{BL}$≠0 + SV95C$_{M6}$≠0 + NSAA$_{BL}$≠0 + NSAA$_{M6}$≠0	CT-B (x21)	Age (y)	21	8.4	8.0	1.78	6.0	11.0
			SV95C (m/s)	21	1.666	1.640	0.2567	1.130	2.240
			6MWD (m)	20	402.8	398.0	47.09	312.0	510.3
			NSAA (#)	21	21.8	22.0	5.40	11	32
			4SC (s)	21	3.72	3.40	1.297	1.62	7.00
Responsiveness Natural course of the disease – 6M – 4SC	DMD + NHS + SV95C$_{BL}$≠0 + SV95C$_{M6}$≠0 + 4SC$_{BL}$≠0 + 4SC$_{M6}$≠0	CT-B (x21)	Age (y)	21	8.4	8.0	1.78	6.0	11.0
			SV95C (m/s)	21	1.666	1.640	0.2567	1.130	2.240
			6MWD (m)	20	402.8	398.0	47.09	312.0	510.3
			NSAA (#)	21	21.8	22.0	5.40	11	32
			4SC (s)	21	3.72	3.40	1.297	1.62	7.00
Responsiveness Natural course of the disease – 9M – SV95C	DMD + NHS + SV95C$_{BL}$≠0 + SV95C$_{M9}$≠0	CT-A (X11) CT-B (x28)	Age (y)	39	8.3	8.0	1.75	6.0	13.7
			SV95C (m/s)	39	1.650	1.600	0.3283	0.950	2.240
			6MWD (m)	38	413.6	418.7	51.35	270.0	510.3
			NSAA (#)	39	23.9	23.0	5.34	16	33
			4SC (s)	39	3.47	3.20	1.146	1.62	7.22
Responsiveness Natural course of the disease – 9M – 6MWD	DMD + NHS + SV95C$_{BL}$≠0 + SV95C$_{M9}$≠0 + 6MWD$_{BL}$≠0 + 6MWD$_{M9}$≠0	CT-B (x24)	Age (y)	24	8.3	8.0	1.57	6.0	11.0
			SV95C (m/s)	24	1.663	1.705	0.3617	0.950	2.240
			6MWD (m)	24	409.3	407.0	55.40	270.0	510.3
			NSAA (#)	24	23.8	22.5	5.64	16	33
			4SC (s)	24	3.42	3.20	1.197	1.62	7.22
Responsiveness		CT-B (x26)	Age (y)	26	8.3	8.0	1.62	6.0	11.0

Analysis	Data selection	Study	Variable	N	Mean	Median	SD	Min	Max
Natural course of the disease – 9M – NSAA	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M9}\neq0$ + $NSAA_{BL}\neq0$ + $NSAA_{M9}\neq0$		SV95C (m/s)	26	1.659	1.705	0.3567	0.950	2.240
			6MWD (m)	25	410.1	414.0	54.36	270.0	510.3
			NSAA (#)	26	24.0	23.0	5.55	16	33
			4SC (s)	26	3.49	3.20	1.222	1.62	7.22
Responsiveness Natural course of the disease – 9M – 4SC	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M9}\neq0$ + $4SC_{BL}\neq0$ + $4SC_{M9}\neq0$	CT-B (x26)	Age (y)	26	8.3	8.0	1.62	6.0	11.0
			SV95C (m/s)	26	1.659	1.705	0.3567	0.950	2.240
			6MWD (m)	25	410.1	414.0	54.36	270.0	510.3
			NSAA (#)	26	24.0	23.0	5.55	16	33
			4SC (s)	26	3.49	3.20	1.222	1.62	7.22
Responsiveness Natural course of the disease – 12M – SV95C	DMD + NHS+ $SV95C_{BL}\neq0$ + $SV95C_{M12}\neq0$	CT-A (x12) CT-B (x16)	Age (y)	28	8.5	8.1	1.79	6.0	13.7
			SV95C (m/s)	28	1.571	1.532	0.3551	0.950	2.240
			6MWD (m)	28	395.6	398.0	55.78	270.0	476.0
			NSAA (#)	28	22.7	21.5	5.20	15	33
			4SC (s)	28	3.87	3.40	1.555	1.62	8.70
Responsiveness Natural course of the disease – 12M – 6MWD	DMD + NHS+ $SV95C_{BL}\neq0$ + $SV95C_{M12}\neq0$ + $6MWD_{BL}\neq0$ + $6MWD_{M12}\neq0$	CT-A (x5) CT-B (x15)	Age (y)	20	8.6	8.4	1.82	6.0	13.7
			SV95C (m/s)	20	1.596	1.570	0.4009	0.950	2.240
			6MWD (m)	20	391.7	394.0	61.04	270.0	476.0
			NSAA (#)	20	22.9	22.5	5.62	15	33
			4SC (s)	20	3.95	3.53	1.691	1.62	8.70
Responsiveness Natural course of the disease – 12M - NSAA	DMD + NHS+ $SV95C_{BL}\neq0$ + $SV95C_{M12}\neq0$ + $NSAA_{BL}\neq0$ + $NSAA_{M12}\neq0$	CT-B (x15)	Age (y)	15	8.3	8.0	1.54	6.0	11.0
			SV95C (m/s)	15	1.596	1.640	0.4040	0.950	2.240
			6MWD (m)	15	380.3	383.0	52.04	270.0	462.0
			NSAA (#)	15	21.9	21.0	5.32	15	33
			4SC (s)	15	3.72	3.40	1.376	1.62	7.22
Responsiveness Natural course of the disease – 12M – 4SC	DMD + NHS+ $SV95C_{BL}\neq0$ + $SV95C_{M12}\neq0$ + $4SC_{BL}\neq0$ + $4SC_{M12}\neq0$	CT-B (x15)	Age (y)	15	8.3	8.0	1.54	6.0	11.0
			SV95C (m/s)	15	1.596	1.640	0.4040	0.950	2.240
			6MWD (m)	15	380.3	383.0	52.04	270.0	462.0
			NSAA (#)	15	21.9	21.0	5.32	15	33
			4SC (s)	15	3.72	3.40	1.376	1.62	7.22
Responsiveness Natural course of the disease over 12 months on 17 subjects	DMD + NHS + $SV95C_{BL}\neq0$ + $SV95C_{M3}\neq0$ + $SV95C_{M6}\neq0$ + $SV95C_{M9}\neq0$ + $SV95C_{M12}\neq0$	CT-A (x10) CT-B (x7)	Age (y)	17	8.0	7.9	1.83	6.0	13.7
			SV95C (m/s)	17	1.712	1.640	0.2729	1.339	2.240
			6MWD (m)	17	417.1	420.5	39.84	345.0	476.0
			NSAA (#)	17	23.5	23.0	4.21	18	31
			4SC (s)	17	3.30	3.24	0.959	1.62	5.00
Responsiveness		NHS-A (x2)	Age (y)	11	6.8	6.4	1.50	5.0	9.7

Analysis	Data selection	Study	Variable	N	Mean	Median	SD	Min	Max
Treatment effect – 3M	DMD + TTT+ $SV95C_{BL}\neq0$ + $SV95C_{M3}\neq0$	NHS-B (x1) CT-C (x1) In-clinic (x7)	SV95C (m/s)	11	1.419	1.444	0.3077	1.076	1.920
			6MWD (m)	3	344.7	325.0	62.85	294.0	415.0
			NSAA (#)	1	-	-	-	-	-
			4SC (s)	1	-	-	-	-	-
Responsiveness Treatment effect – 6M	DMD + TTT+ $SV95C_{BL}\neq0$ + $SV95C_{M6}\neq0$	NHS-A (x1) In-clinic (x6)	Age (y)	7	6.9	6.4	1.52	5.1	9.7
			SV95C (m/s)	7	1.534	1.506	0.3223	1.076	1.920
			6MWD (m)	1	-	-	-	-	-
			NSAA (#)	-	-	-	-	-	-
			4SC (s)	-	-	-	-	-	-
Responsiveness Treatment effect – 9M	DMD + TTT+ $SV95C_{BL}\neq0$ + $SV95C_{M9}\neq0$	NHS-A (x1) In-clinic (x6)	Age (y)	7	6.9	6.4	1.52	5.1	9.7
			SV95C (m/s)	7	1.534	1.506	0.3223	1.076	1.920
			6MWD (m)	1	-	-	-	-	-
			NSAA (#)	-	-	-	-	-	-
			4SC (s)	-	-	-	-	-	-
Responsiveness Treatment effect – 12M	DMD + TTT+ $SV95C_{BL}\neq0$ + $SV95C_{M12}\neq0$	NHS-A (x1) In-clinic (x4)	Age (y)	5	6.7	6.5	0.72	6.0	7.6
			SV95C (m/s)	5	1.497	1.480	0.3598	1.115	1.920
			6MWD (m)	1	-	-	-	-	-
			NSAA (#)	-	-	-	-	-	-
			4SC (s)	-	-	-	-	-	-
MCT Anchor -based threshold – CGI-C	DMD + $SV95C_{M12} \neq 0$ + $CGI\text{-}C_{M12} \neq 0$	CT-A (x12)	Age (y)	13	8.2	8.0	1.59	6.0	11.0
			SV95C (m/s)	13	1.562	1.460	0.4303	0.950	2.240
			6MWD (m)	13	380.8	383.0	53.92	270.0	462.0
			NSAA (#)	13	21.8	21.0	5.82	15	33
			4SC (s)	13	3.95	4.00	1.540	1.62	7.22
MCT Anchor -based threshold – PODCI	DMD + $SV95C_{M12} \neq 0$ + $PODCI_{M12} \neq 0$	CT-A (x15)	Age (y)	15	8.3	8.0	1.54	6.0	11.0
			SV95C (m/s)	15	1.596	1.640	0.4040	0.950	2.240
			6MWD (m)	15	380.3	383.0	52.04	270.0	462.0
			NSAA (#)	15	21.9	21.0	5.32	15	33
			4SC (s)	15	3.72	3.40	1.376	1.62	7.22

4SC = 4-stair climb test; 6MWD = 6-minute walking distance; CT = clinical trial; DMD = Duchenne muscular dystrophy; M = month; MCT = Minimal change threshold; NHS = Natural history study; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity

Sources of data used in the qualification opinion package were presented in Table 1 of the briefing package. Description of studies are given in Table 4 and in the confidential Appendix 7.8 of the briefing package.

Using a broader population obtained by pooling data from various clinical studies to demonstrate the metric properties of SV95C would either reinforce the conclusions. Nevertheless, know group validity analyses (section 3.2.2.3.1. of the briefing package) indicated that population characteristics (SV95C, 6MWD, NSAA, 4SC) at baseline were not statistically different between studies (Tables 26-29 of the briefing package). The same analysis for the population "NHS" used to study correlation with existing COA and responsiveness over 1 year verifies that populations were similar overtime and confirms that pooling data was appropriate (Table 3 to Table 7).

Table 3: Comparison of population "NHS" used in the briefing document – At baseline

At Baseline	N	Mean	Median	SD	Min	Max	P-value*
SV95C (m/s)							
CT-A	34	1.620	1.573	0.354	1.066	2.426	0.821
CT-B	51	1.599	1.600	0.378	0.790	2.470	
NHS-B	11	1.503	1.411	0.440	0.925	2.408	
NHS-C	11	1.519	1.539	0.459	0.723	2.031	
6MWD (m)							
CT-A	34	414.5	426.3	56.2	290.0	512.0	0.127
CT-B	50	384.7	386.0	82.3	25.0	510.3	
NHS-B	10	368.3	362.0	56.4	290.0	475.0	
NHS-C	11	367.6	395.5	102.8	151.0	492.5	
NSAA (#)							
CT-A	34	24,1	24,0	5,1	13,0	33,0	0.428
CT-B	51	22,4	22,0	6,8	2,0	33,0	
NHS-B	11	24,3	24,0	5,4	18,0	33,0	
NHS-C	11	19,6	23,0	7,7	8,0	29,0	
4SC (s)							
CT-A	34	3.63	3.40	1.50	1.70	8.70	0.075
CT-B	51	3.90	3.40	1.56	1.62	8.00	
NHS-B	11	4.87	4.93	2.25	1.29	8.57	
NHS-C	11	3.12	2.80	1.33	1.90	6.69	

Selection: DMD + NHS + SV95CBL≠0

List of subjects: 1, 2, 3, 4, 5, 6, 7, 8, 9, 15, 16, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114,

Origin: CT-A (x34), CT-B (x51) , NHS-B (x11), NHS-C (x12)

4SC = 4-stair climb test; 6MWD = 6-minute walking distance; DMD = Duchenne muscular dystrophy; M = month; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity

*Independent-Samples Mann-Whitney U Test (when 2 samples) or Independent-Samples Kruskal-Wallis Test (when more than 2 samples).

Table 4: Comparison of population "NHS" used in the briefing document – At month 3

At M3	N	Mean	Median	SD	Min	Max	P-value*
SV95C (m/s)							
CT-A	25	1.563	1.562	0.317	1.003	2.158	0.627
CT-B	46	1.531	1.520	0.353	0.730	2.310	
NHS-B	5	1.462	1.635	0.337	0.931	1.743	
NHS-C	5	1.260	1.409	0.521	0.660	1.937	
6MWD (m)							
CT-A	-	-	-	-	-	-	-
CT-B	43	386.1	393.0	64.5	155.5	495.0	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
NSAA (#)							
CT-A	-	-	-	-	-	-	-
CT-B	46	22.9	22.0	6.4	8.0	34.0	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
4SC (s)							
CT-A	-	-	-	-	-	-	-
CT-B	46	4.48	3.40	3.03	1.94	21.00	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	

Selection: DMD + NHS + SV95CM3≠0

List of subjects: 1, 2, 4, 5, 15, 19, 20, 23, 28, 29, 31, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 51, 52, 53, 54, 55, 56, 57, 58, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 82, 83, 84, 85, 88, 89, 92, 93, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105, 106, 108, 109, 110, 111, 112, 114,

Origin: CT-A (x25), CT-B (x46) , NHS-B (x5), NHS-C (x5)

4SC = 4-stair climb test; 6MWD = 6-minute walking distance; DMD = Duchenne muscular dystrophy; M = month; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity

*Independent-Samples Mann-Whitney U Test (when 2 samples) or Independent-Samples Kruskal-Wallis Test (when more than 2 samples).

Table 5: Comparison of population "NHS" used in the briefing document – At month 6

At M6	N	Mean	Median	SD	Min	Max	P-value*
SV95C (m/s)							
CT-A	26	1.527	1.467	0.391	0.885	2.559	0.475
CT-B	27	1.530	1.490	0.312	0.870	2.270	
NHS-B	-	-	-	-	-	-	
NHS-C	6	1.271	1.350	0.529	0.599	1.962	
6MWD (m)							
CT-A	11	426.4	456.0	75.1	275.0	511.0	0.465
CT-B	21	408.8	409.0	42.2	344.0	513.7	
NHS-B	-	-	-	-	-	-	
NHS-C	4	358.3	405.5	146.0	146.0	476.0	
NSAA (#)							
CT-A	-	-	-	-	-	-	-
CT-B	21	22.5	21.0	5.5	13.0	32.0	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
4SC (s)							
CT-A	-	-	-	-	-	-	-
CT-B	21	4.32	3.80	2.04	1.83	10.00	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	

Selection: DMD + NHS + SV95CM6≠0

List of subjects: 19, 20, 23, 25, 28, 29, 33, 34, 35, 37, 38, 40, 41, 42, 43, 46, 48, 49, 51, 52, 53, 54, 56, 58, 60, 61, 63, 65, 68, 69, 72, 74, 75, 81, 82, 83, 84, 85, 87, 89, 92, 93, 95, 96, 97, 98, 99, 100, 101, 102, 103, 105, 106, 108, 109, 110, 111, 112, 114,

Origin: CT-A (x26), CT-B (x24) , NHS-C (x6)

4SC = 4-stair climb test; 6MWD = 6-minute walking distance; DMD = Duchenne muscular dystrophy; M = month; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity

*Independent-Samples Mann-Whitney U Test (when 2 samples) or Independent-Samples Kruskal-Wallis Test (when more than 2 samples).

Table 6: Comparison of population "NHS" used in the briefing document – At Month 9

At M9	N	Mean	Median	SD	Min	Max	P-value*
SV95C (m/s)							
CT-A	11	1.489	1.471	0.301	1.007	2.093	0.755
CT-B	28	1.548	1.520	0.384	0.890	2.520	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
6MWD (m)							
CT-A	-	-	-	-	-	-	-
CT-B	25	370.0	377.0	62.3	250.0	485.0	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
NSAA (#)							
CT-A	-	-	-	-	-	-	-
CT-B	26	22.0	21.5	6.1	10.0	33.0	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
4SC (s)							
CT-A	-	-	-	-	-	-	-
CT-B	26	4.44	3.97	2.68	1.43	14.81	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	

Selection: DMD + NHS + SV95CM9≠0

List of subjects: 31, 33, 34, 36, 37, 40, 44, 45, 46, 47, 49, 51, 52, 53, 54, 55, 57, 60, 64, 67, 68, 69, 71, 74, 75, 76, 79, 80, 81, 82, 83, 96, 97, 98, 99, 100, 109, 110, 111,
Origin: CT-A (x11), CT-B (x28)
4SC = 4-stair climb test; 6MWD = 6-minute walking distance; DMD = Duchenne muscular dystrophy; M = month; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity
*Independent-Samples Mann-Whitney U Test (when 2 samples) or Independent-Samples Kruskal-Wallis Test (when more than 2 samples).

Table 7: Comparison of population "NHS" used in the briefing document – At Month 12

At M12	N	Mean	Median	SD	Min	Max	P-value*
SV95C (m/s)							
CT-A	12	1.324	1.416	0.325	0.777	2.005	0.963
CT-B	16	1.334	1.315	0.385	0.790	2.270	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
6MWD (m)							
CT-A	5	406.1	405.0	110.3	236.5	541.0	0.089
CT-B	15	336.8	349.0	56.8	234.0	428.5	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
NSAA (#)							
CT-A	-	-	-	-	-	-	-
CT-B	15	19.7	19.0	7.0	10.0	32.0	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	
4SC (s)							
CT-A	-	-	-	-	-	-	-
CT-B	15	5.84	4.50	4.57	1.48	20.28	
NHS-B	-	-	-	-	-	-	
NHS-C	-	-	-	-	-	-	

Selection: DMD + NHS + SV95CM12≠0
List of subjects: 31, 33, 34, 36, 38, 44, 45, 46, 47, 51, 55, 68, 69, 72, 75, 80, 81, 82, 83, 95, 96, 97, 98, 99, 100, 109, 110, 111,
Origin: CT-A (x12), CT-B (x16)
4SC = 4-stair climb test; 6MWD = 6-minute walking distance; DMD = Duchenne muscular dystrophy; M = month; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity
*Independent-Samples Mann-Whitney U Test (when 2 samples) or Independent-Samples Kruskal-Wallis Test (when more than 2 samples).

6. Question #6

Please discuss how the convergent validity of the change in SV95C will be further substantiated, considering that the correlation between change in SV95C and change in 6MWD, NSAA and 4SC is poor.

SV95C, 6MWD, NSAA, and 4SC are clinical outcome measures assessing the motor function and more precisely the ambulation or ability to walk. But they are all measuring different aspects of ambulation. For instance, the 6MWT measures a combination of maximal ability to ambulate and of fatigability, NSAA does include aspects of balance, 4SC can include an aspect of upper limb ability when pulling on handrail. Our results demonstrated moderate correlations between SV95C and other functioning outcome measures with correlation coefficients comparable to those of correlations between usual functioning outcome measures (Table 33 of the briefing package). Correlations between functioning clinical outcome measures, including SV95C, were maintained over time but magnitude of changes were globally not correlated even after 12 months of follow up and despite decline characterized with all functioning outcome measures.

Figure 2 above, suggests a threshold around 1.3 m/s below which no run-stride are detected. Due to the very limited number of subjects with SV95C<1.3m/s at baseline, we considered all 33 available patients with SV95C<1.5m/s (6 from NHS-B, 5 from CT-A, and 22 from CT-B). Only 9 had SV95C and 6MWD available at month 12 (2 from CT-A and 7 from CT-B). (Table 8, Table 9).

Table 8: List of DMD Subjects With SV95C<1.5 m/s at baseline

Timepoint	Patient ID
Baseline	33, 38, 44, 45, 55, 72, 80, 95, 99

DMD = Duchenne muscular dystrophy

Table 9: Characteristics of DMD subjects with SV95C<1.5 m/s at baseline

	N	Mean	Median	SD	Min	Max
At Baseline						
Age (y)	9	9.6	9.6	2.10	6.0	13.0
SV95C (m/s)	9	1.236	1.270	0.198	0.950	1.460
6MWD (m)	9	350.1	345.0	61.03	270.0	473.5
NSAA (#)	9	19.9	19;0	5.06	15	29
4SC (s)	9	5.04	4.80	1;84	3.20	8.70

4SC = 4-stair climb test; 6MWD = 6-minute walking distance; DMD = Duchenne muscular dystrophy; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity

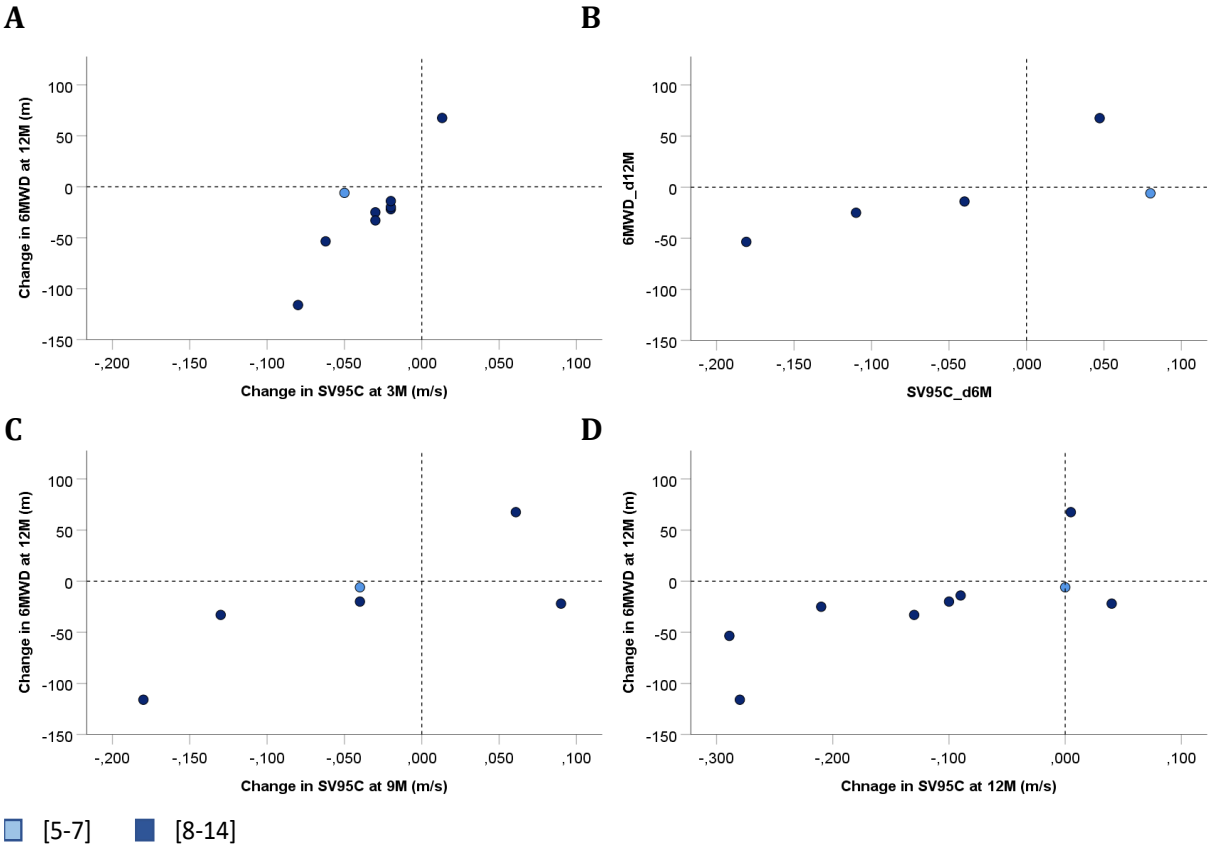
We observed a strong correlation between change in SV95C and change in 6MWD at month 12 (Spearman's Rho = 0.8). Interestingly, our results also indicate correlations between change in 6MWD at month 12 and changes in SV95C since month 3, suggesting that change in SV95C as early as month 3 may predict the change in 6MWD at 12 months in subjects who lost ability to run (Table 10, Figure 6). Nevertheless, the magnitude of change in this very limited sample of subjects prevent us to draw any other conclusion than decline in SV95C characterize a decline in the walking ability of a subject as measured by 6MWD or time to climb 4 stairs (4SC).

Table 10: Correlation Matrix Between changes in SV95C at 3, 6, 9, and 12 months and Other Functioning Outcome Measures at month 12

	Non-parametric correlation	SV95C_3M	SV95C_6M	SV95C_9M	SV95C_12M
6MWD_12M	Spearman's Rho	.745*	.900*	.600	.800**
	Sig. (bilat)	.021	.037	.208	.010
	N	9	5	6	9
NSAA_12M	Spearman's Rho	.300	1.000	.205	.450
	Sig. (bilat)	.513	.	.741	.310
	N	7	3	5	7
4SC_12M	Spearman's Rho	-.847*	-.500	-.900*	-.679
	Sig. (bilat)	.016	.667	.037	.094
	N	7	3	5	7

4SC = 4-stair climb test; 6MWD = 6-minute walking distance; DMD = Duchenne muscular dystrophy; M = month; NSAA = North Star Ambulatory Assessment; SD = standard deviation; SV95C = 95th centile of the stride velocity

Figure 6: Relationship Between changes in SV95C and Other Functioning Outcome Measures at Baseline (by Age Group)



Change in 6MWD at 12 months and: **A.** change in SV95C at 3 months**, B.** change in SV95C at 6 months, **C.** change in SV95C at 9 months, **D.** change in SV95C at 12 months

It must be noted that same results have been observed in non-ambulant patients, several outcome measures such as the Motor Function Measure (MFM32), the Fat infiltration as measured by MRI, the

grip strength, and the pinch strength are correlated with each other, are inversely correlated with age, detect individually a change over a 1 year or 3 years period, but there is no correlation between the change of one of them and the change of another of them [1,2]. This is related to the fact that these measures are only partially correlated, and that noise may impact the change over 1 year much more than the absolute value.

7. Question #7

Please further discuss / justify / reconsider the 0.10 - 0.20 m/s as a meaningful change threshold considering the scientific discussion above.

The results of the distribution-based analysis of meaningful change suggested that a change score of ≈-0.10 to ≈-0.20 would be required for the change in DMD patients to be beyond measurement error (the largest estimate of change beyond measurement error is the minimum detectable change MDC 95% at -0.197m/s).

- The 0.5*SD approach recommended for the distribution-based estimate approach[3] doesn't consider measurement error as it doesn't incorporate a factor of reliability, MCT is estimated at 0.191 m/s above the standard error of measurement (SEM) estimated at 0.07m/s.
- A MCT at 0.1 to 0.2 m/s is consistent with the change score measured in patients who worsened based on traditional functional tests (NSAA and 6MWD). To answer the concern about a potential selection of population for convenient values, as the variability in the results attested, we did not select any participant. For consistency with the anchor based on PRO analysis, we studied patients from CT-B study.

The anchor-based analysis based on CGI- and PODCI (transfer and basic mobility module) suggested that a change score of between -0.20 and -0.30 would be meaningful.

- To explain the comment about CGI-C categories, only 3 of the 7 change categories of the CGI-C are shown in the briefing document because no patients experienced change at the extreme ends of the scale (as indicated by the counts presented in Table 68 of the briefing package) so we thought it made sense to collapse the change categories into the three overarching categories presented.
- As explain above, in answering question 1, PROs are highly subjective and, when completed by a proxy, answers may diverge from the patient's perspectives. In the current application dossier, we worked with data obtained from a clinical trial that was prematurely stopped due to lack of efficacy, and therefore directly subject to the placebo effect. In that context, a PRO may hardly define a meaningful change threshold (MCT) robustly and a change score of between -0.20 and -0.30 m/s for meaningfulness may be overestimated.

Our qualitative study through survey also supports that a change of SV95C of 0.1 to 0.2 m/s would be clinically meaningful for DMD-patients and their family.

- Even if a change in top speed while walking was recognized by most of respondents as an improvement in ambulation, they have probably no idea of their maximal stride velocity. For this reason, we thought it was not relevant to ask them the magnitude of change they would consider as an improvement in ambulation. Nevertheless, we asked question for the distance walked in 6 minutes. In the population of ambulant patients with DMD answers were as follow:
    - Change of 5 to 10 m, i.e., 0,01 to 0,03 m/s, at 6MWD was considered as acceptable improvement for 11 respondents and unacceptable improvement for 11 as well (4 who answered NA)
    - Change of 20 to 40 m, i.e., 0,06 to 0,11 m/s, at 6MWD was considered as an acceptable improvement for 22 respondents and unacceptable improvement only for 1 respondent (2 answered NA)
    - Change of 50 to 100 m, i.e., 0,14 to 0,28 m/s, at 6MWD was considered as an acceptable improvement for 22 respondents and unacceptable improvement for none of respondent (1 answered NA)

Data presented in the briefing package on MCT estimated based on the distribution of 103 DMD-patients demonstrated that a change in SV95C between 0.10 and 0.20 m/s is a meaningful detectable change (MDC80% = 0.129 m/s, MDC90% = 0.165 m/s, MDC95% = 0.197 m/s. meaningful threshold. This value of MDC coincides with the answer given by participant to the survey who considered a change about 0.1 to 0.2 m/s during the 6MWT as an acceptable improvement in ambulation. A change in SV95C between 0.1 and 0.2 m/s may then constitute an acceptable meaningful change threshold.

8. Question #8

The approach to derive an anchor based MCT clearly suffers from the fact that the clinical trial data come from a prematurely stopped study due to absence of efficacy. It remains unclear how the absence of a treatment effect can introduce bias towards a higher MCT. Please discuss this aspect further.

We probably should not use the word “bias”. We have data from a non-efficacious study that gave an MCT estimate which was higher than the distribution-based estimate. It’s not unusual for the anchor-based MCT to be higher than the distribution-based MCT.

In our case, our assumption is that PRO completed during a clinical trial are most subject to the placebo effect. Results of patients and carers survey demonstrated that patients and caregivers most reported that they expect a treatment to at least slow down or prevent the progression of the disease (Table 17 of the briefing document). Walking is an important aspect of ambulation for DMD patients, and it is the function that they would most like to see restored in a clinical trial. Therefore, the hope in the treatment efficacy of patients enrolled in a clinical trial aiming to demonstrate the efficacy of a new drug and their family may affect their objectivity in the progression of the disease until the patient reaches a major milestone in ambulation (inability to run or climb stairs).

9. Question #9

Please provide further information on the patient cohort that was followed over time (section 3.2.2.4.3, table 56 and figure 23 of the briefing document).

The population characteristics at BL and over time: Age, 6MWD, NSAA, 4SC, SV95C (N, Mean, Median, SD, Min, Max) are provided in Table 11 below.

Table 11: Population Characteristics Including Age, SV95C and Existing COA Scores at Baseline, 3, 6, 9, and 12 months

	N	Mean	Median	SD	Min	Max
At Baseline						
Age	17	8.0	7.9	1.83	6.0	13.7
SV95C (m/s)	17	1.712	1.640	0.2729	1.339	2.240
6MWD (m)	17	417.1	420.5	39.84	345.0	476.0
NSAA (#)	17	23.5	23.0	4.21	18	31
4SC (s)	17	3.30	3.24	0.959	1.62	5.00
At 3 months						
SV95C (m/s)	17	1.663	1.620	0.2441	1.297	2.158
6MWD (m)	7	419.1	422.0	30.10	375.0	475.0
NSAA (#)	7	24.1	24.0	3.53	20	30
4SC (s)	7	3.50	3.20	1.335	2.40	6.30
At 6 months						
SV95C (m/s)	17	1.634	1.540	0.2749	1.285	2.270
6MWD (m)	11	421.5	409.0	47.17	355.0	505.0
NSAA (#)	7	23.4	23.0	3.69	20	31
4SC (s)	7	3.57	3.30	1.503	1.83	6.40
At 9 months						
SV95C (m/s)	17	1.533	1.471	0.2485	1.158	2.093
6MWD (m)	7	362.3	337.0	50.82	318.0	459.0
NSAA (#)	7	22.9	22.0	4.30	17	31
4SC (s)	7	3.96	3.93	1.768	1.43	7.00
At 12months						
SV95C (m/s)	17	1.487	1.426	0.3208	0.904	2.270
6MWD (m)	11	394.7	377.0	61.79	298.0	541.0
NSAA (#)	7	22.0	22.0	5.51	13	31
4SC (s)	7	4.43	4.21	1.784	1.48	6.30

10. Question #10

Please elaborate on the analysis presented during the pre-submission meeting on age groups. It is not fully clear why the data for comparison to NSAA were not presented in the briefing package and include a different number of patients for SV95C (total number 40 for SV95C assessments).

Due to ceiling effect, NSAA was not performed by the control population who will score the maximum (i.e., 34). In addition, at the time of the analyses for the briefing document package, a very few control subjects performed the 4SC test. Therefore, only the 6MWD was used for the known-group validity (section 3.2.2.3.1. of briefing package). NSAA and 4SC was used as existing COA in analyses of convergent validity (at baseline and overtime) (section 3.2.2.3.2. of briefing package). responsiveness (section 3.2.2.4. of briefing package), and in the estimation of MCT anchor-based on traditional endpoints (section 3.2.2.5.2. of briefing package).

We detected a mistake in the legend of Table 30 of the briefing document: it mentions NSAA and 4SC but it is an error while copy/past. We cannot compare the NSAA and 4SC of DMD vs CTRL at different age group because NSAA and 4SC were not available for CTRL.

11. Question #11

Please provide an update on studies that could add data for qualification and if these could allow an assessment in the population below 5 years of age and a more robust derivation of an anchor based MCT.

We have been authorized very recently to share data from the study. We did not yet receive clinical data, but we shared, on the 20th of June, results we obtained with SV95C. The PRO PODCI was used in this study. One participant aged 4 years was enrolled.

We are collecting additional data in 4 ongoing clinical studies:

- The ongoing study is a global pivotal phase 3 study evaluating the therapeutic benefits of micro dystrophin gene therapy in DMD in which the new Syde® device is a mandatory assessment and has SV95C listed as a secondary endpoint. Several potential anchors are included in the protocol including the NSAA and various PROs. which will be used to further refine the proposed MCT. Among 82 subjects screened and equipped at the time of these responses. 19 were aged 4 and 18 aged 5.
- The ongoing natural history study NHS-B has been extended to follow 50 DMD patients from 5-year-old over 3 years. Several potential anchors are included in the protocol, including 6MWD, 4SC, NSAA and the personal global impression of change (PGI-C) which will be used to further refine the proposed MCT and the prognostic value of SV95C. The 3-year follow up data should be available by End 2025.
- The ongoing study is a natural history dedicated to get long term baseline data to support a gene therapy trial. 48 participants from 4 years old have been enrolled in NHS. 3 patients have enrolled in the associated gene therapy.

Three additional clinical trials in DMD in which the new Syde® device is a mandatory assessment should start by the End of 2022. They aim to enroll a total of about 167 patients with DMD

Having SV95C qualified as a primary endpoint would help gathering more data to update EMA in 3 and 5 years post qualification.

Secondary endpoint in progressive neuromuscular diseases with proximal muscle weakness.

12. Question #12

Please discuss how validity of change in SC95C as secondary endpoint will be further substantiated per NMD condition, considering their heterogeneity in signs and symptoms and difference in rate progression.

These diseases have indeed a very different heterogenous rate of progression but in nearly all cases slower than DMD. Indeed, in DMD, patients may evolute from the ability to run to the loss of ambulation in 6-8 years. which will not happen in FSHD or in most of LGMD. In this context, classical outcomes have failed to point out a clinically significant change over a 1-year period. The objective of a clinical trial conducted over the period of time is therefore likely to demonstrate a benefit rather than a stabilization. Power calculation based on natural history decline therefore does not apply. The estimation of the meaningful change threshold and the long-term change of the SV95C will be substantiated by further data collection. It is very likely that the primary qualification in DMD, which would demonstrate the possibility for a digital outcome to be fully qualified, and the qualification as secondary endpoint for other NMD condition will be instrumental for data acquisition.

Clinical trials on SMA and FSHD including the new wearable device Syde® are currently nearly to start. The protocols of ongoing studies sponsored by in SMA and FSHD have prespecified SV95C as an endpoint.

All subjects with SMA are nowadays proposed a treatment. Therefore, no additional data on untreated SMA patients are expected. Patients treated with nusinersen may not respond to the treatment. The mean improvement of 6MWT in treated patients was measured of 8.25 m[4] far below the minimal clinical important difference established on DMD (28,5 m)[5]. Consequently, the sensitivity to change in SMA may be challenging to estimate. Additional data on different therapeutical strategies are collecting.

If SV95C is qualified as secondary endpoint, sponsors will be more inclined to add SV95C as clinical outcome assessment in their clinical trials. This will help to collect additional data to support complementary analyses to confirm interest of SV95C and to define meaningful change thresholds adapted by NMDs

13. Question #13

Please discuss the observed discrepancy in morning and afternoon recordings of SV95C in patients with FSHD (figure 42 C).

Figure 42 of the briefing package displays data from all participants at all recording periods. Discrepancy observed between morning and afternoon may represent somehow fatigue or fatigability. A French consortium has been awarded funding to study fatigue in SMA (Hospital-University research 5: SMART see here for more details). Sysnav is a partner of this initiative and conclusion of this 5-year project will very likely shed light on this aspect of daily variability, fatigability, and its specificities in NMDs.

Nevertheless. discrepancy observed for SV95C higher than 1.5m/s that can count running strides. may also correspond to higher intensity activities in the morning as compared to the afternoon.

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