Overview of comments on draft Qualification Opinion for Stride velocity 95th centile as a primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy

Comments from:

Name of organisation or individual
1. **Duchenne Community Advisory Board**
2. **Duchenne Parent Project Belgium**
3. **Duchenne Parent Project Spain**
4. **Duchenne UK**
5. **EAN Scientific Panel of Muscle and NMJ Disorders**
6. **EFPIA**
7. **EPNS**
8. **EuropaBio**
9. **Little Steps**
10. **Pfizer**
11. **Roche**
12. **Solid Biosciences**
13. **WDO**

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1. General comments

Stakeholder	General comment (if any)	EMA response
Duchenne Community Advisory Board	The Duchenne Community Advisory Board (CAB) regards the EMA qualification of SV95C as a primary endpoint in studies in ambulatory DMD patients as crucial to enabling real-world ambulation data to be used for drug approval in DMD. SV95C can objectively and continuously measure functional disease progression in DMD, thus providing a more accurate assessment of disease progression than is currently obtainable through traditional in-clinic assessments. Moreover, since SV95C is collected during the normal daily activities of the patient, it will help reduce the burden of participating in clinical trials. This will potentially both improve the clinical trial experience and increase the likelihood of detecting treatment benefits. Digital outcome measures can avoid both the bias as well as the burden and anxiety caused by outcome measures such as the NSAA, 6MWT, TTS etc. currently utilized as primary endpoints in clinical trials. Furthermore, the real-	The comment is acknowledged with the notion that the potential interchangeability between the SV95C and 6MWT as the main argument in favour of the SV95C as an alternative primary endpoint in DMD studies i.e. what would be a clinical meaningful change in the SV95C has still to be established. See CHMP discussion line 2640-2685 page 164-165. We agree that the continuously measured SV95C has the potential to provide an accurate assessment of disease progression with less burden for subjects associated with participating in clinical trials. Further work on comparison of SV95C with in-clinic assessments and specifically functional endpoints that would allow defining milestones in disease progression, and to evaluate potential bias would be welcomed. Feedback from the patients' community on these aspects is appreciated.

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	world data captured by SV95C is more meaningful to patients and their families.	
Duchenne Parent Project Belgium asbl/vzw	Duchenne Parent Project Belgium regards the EMA qualification of SV95C as a primary endpoint in studies in ambulatory DMD patients as crucial to enabling real-world ambulation data to be used for drug approval in DMD. SV95C can objectively and continuously measure functional disease progression in DMD, thus providing a more accurate assessment of disease progression than is currently obtainable through traditional in-clinic assessments. Moreover, since SV95C is collected during the normal daily activities of the patient, it will help reduce the burden of participating in clinical trials. This will potentially both improve the clinical trial experience and increase the likelihood of detecting treatment benefits.	The comments are acknowledged with the notion that the potential interchangeability between the SV95C and 6MWT as the main argument in favour of the SV95C as an alternative primary endpoint in DMD studies i.e. what would be a clinical meaningful change in the SV95c has still to be established. See CHMP discussion line 2640-2685 page 164-165. We agree that the continuously measured SV95C has the potential to provide an accurate assessment of disease progression with less burden for subjects associated with participating in clinical trials. Further work on comparison of SV95C with in-clinic assessments and specifically functional endpoints that would allow defining milestones in disease progression, and to evaluate potential bias would be welcomed. Feedback from the patients' community on these aspects is appreciated.

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	Digital outcome measures can avoid both the bias as well as the burden and anxiety caused by outcome measures such as the NSAA, 6MWT, TTS etc. currently utilised as primary endpoints in clinical trials. Furthermore, the real-world data captured by SV95C is more meaningful to patients and their families.	
Duchenne Parent Project Spain	Duchenne Parent Project Spain (DPP Spain) regards the EMA qualification of SV95C as a primary endpoint in studies in ambulatory DMD patients as crucial to enabling real-world ambulation data to be used for drug approval in DMD. SV95C can objectively and continuously measure functional disease progression in DMD, thus providing a more accurate assessment of disease progression than is currently obtainable through traditional in-clinic assessments. Moreover, since SV95C is collected during the normal daily activities of the patient, it will help reduce the burden of participating in clinical trials. This will potentially both improve the clinical trial experience and increase the likelihood of detecting treatment benefits. Digital outcome measures can avoid both the bias as well as the burden and anxiety caused by outcome measures	The comment is acknowledged with the notion that the potential interchangeability between the SV95C and 6MWT as the main argument in favour of the SV95C as an alternative primary endpoint in DMD studies i.e. what would be a clinical meaningful change in the SV95C has still to be established. See CHMP discussion line 2640-2685 page 164-165.. We agree that the continuously measured SV95C has the potential to provide an accurate assessment of disease progression with less burden for subjects associated with participating in clinical trials. Further work on comparison of SV95C with in-clinic assessments and specifically functional endpoints that would allow defining milestones in disease progression, and to evaluate potential bias would be welcomed. Feedback from the patients' community on these aspects is appreciated.

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	such as the NSAA, 6MWT, TTS etc. currently utilized as primary endpoints in clinical trials. Furthermore, the real-world data captured by SV95C is more meaningful to patients and their families.	
Duchenne UK	Duchenne UK has produced this submission in collaboration with the World Duchenne Organisation (WDO). Duchenne UK believes that more nuanced patient-led, outcome measures that can more accurately capture disease progression, and hence, the impact of new treatments, are needed in Duchenne muscular dystrophy (DMD). Therefore, we consider the EMA qualification of SV95C as a primary endpoint as a critical step towards its adoption and regular use to enable real-world, ambulation data to be collected in DMD clinical trials and used for drug approval. SV95C can objectively and continuously measure functional disease progression in DMD, thus providing a more accurate	The comments are acknowledged with the notion that the potential interchangeability between the SV95C and 6MWT as the main argument in favour of the SV95C as an alternative primary endpoint in DMD studies i.e. what would be a clinical meaningful change in the SV95C has still to be established. See CHMP discussion line 2640-2685 page 164-165. We agree that the continuously measured SV95C has the potential to provide an accurate assessment of disease progression with less burden for subjects associated with participating in clinical trials. Further work on comparison of SV95C with in-clinic assessments and specifically functional endpoints that would allow defining milestones in disease progression, and to evaluate potential bias would be welcomed. Feedback from the patients' community on these aspects is appreciated.

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	assessment of disease progression than is currently achievable through traditional in-clinic assessments, and potentially increasing the likelihood of detecting treatment benefits. Moreover, since SV95C is collected during the performance of daily activities of the patient, it can help reduce the burden of participating in clinical trials, improving the clinical trial experience. Digital outcome measures can avoid both the bias as well as the burden on patients caused by outcome measures such as the NSAA, 6MWT, TTS etc. currently utilized as primary endpoints in clinical trials. Furthermore, the real-world data captured by SV95C is more meaningful to patients and their families.	
Prof. Gabriele Siciliano, MD, PhD, on behalf of EAN Scientific Panel of Muscle and NMJ Disorders	SV95C is a clinical outcome assessment derived from a digital and passive data collection device based on magneto-inertial technology that aims to measure the maximal stride velocity of patients living with DMD.	The comment is acknowledged and agreed. We agree that SV95C can be considered an accurate outcome measure derived in a real-life setting. Use as a primary endpoint should be supported by established efficacy measures as secondary endpoints.

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	There are sufficient evidences that the SV95C can be considered an accurate digital and clinically meaningful outcome in a real-life setting thus supporting its use as a primary efficacy endpoint in clinical trials targeting ambulant patients with DMD.	
EFPIA	EFPIA strongly supports the qualification of this new primary endpoint, expected to provide a more objective and sensitive, and less burdensome tool that will benefit the entire DMD community. In order to encourage a learning ecosystem, the EMA could update the Q&A on digital technology based methodologies to reflect the learnings from this procedure. (https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf EFPIA would also like to suggest to take up the results of this qualification	The comments are acknowledged. When the documents referred are revised and updated the learnings from this qualification procedure will be taken into account, where applicable.

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	opinion into the DMD guidance (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-duchenne-becker-muscular-dystrophy_en.pdf). As suggested in the EMA guidance on the amendment of relevant guidances as appropriate (page 8 of https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-novel-methodologies-drug-development-guidance-applicants_en.pdf)	
EFPIA	Based on the current understanding of disease, the **context of use** should be extrapolated to patients as early as 4 years old: - Natural history studies in Duchenne Muscular Dystrophy (DMD) have identified comparable disease progression, as well as a significant functional and biological overlap in patients	The arguments for expanding the **Context of Use** to DMD patients as early as 4 years of age are: 1) Younger DMD subjects lag behind their peers in walking abilities despite achieving walking developmental milestones and the SV95C is expected to be detect this. 2) The vast majority of recent trials in ambulatory DMD now include patients from 4 years of age and use the same outcome measures in 4 to 7 year old participants, which include the 6MWT. 3) A major advantage of SV95C is its increased objectivity and sensitivity.

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	between age 4 to 7 [1; 2](*). Although the life threatening morbidities (i.e. cardio-respiratory failure) of DMD tend to present at a later age, DMD does cause symptoms and difficulties in 4 year old patients and younger [3, 4] (*)). The effects of muscle breakdown is serologically evident from birth as shown by high levels of creatinine kinase , and although patients do achieve walking developmental milestones eventually, they crucially lag behind their peers in all aspects of movement from this early point onward [3, 5, 6] (*). - In addition, due to the progressive and irreversible nature of the disease, earlier treatment is expected to have the largest disease-modifying effect. In fact, in DMD, earlier treatment with steroids has been suggested to demonstrate more beneficial effects compared to later treatment [9] (*), and other neuromuscular diseases	4) It would also reduce the burden to study participants. The arguments are well-taken. The main reason for the restriction of the context of use to the 5 years of age was the lack of data beyond 5 years of age. It was not expected that for children between 4-5 years of age, who are able to wear the device appropriately, that the performance of the SV95C would be different. The Applicant (Sysnav) argues that with the small size and weight of the latest version of the device (Syde®), it is now acceptable to use it in young patients and that a few ongoing studies (ActiLiège-Next, SRP-9001-301) enrolled patients from 4 years old and have shown that compliance is as good in these young patients as in older subjects. Reference is made to the general comment of stakeholder 11 i.e. to F. Hoffmann-La Roche Ltd page 18. Considering all this, there appears to be no objection to expand the lower age limit to 4 years of age. The Qualification Opinion is adapted accordingly.

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	have similarly found that earlier treatment is more effective in ameliorating the disease [10] (*). As a result, the vast majority of recent trials in ambulatory DMD now include patients from 4 years of age and use the same outcome measures in 4 to 7 year old participants [11, 12, 13, 14, 15, 16] (*) - North Star Ambulatory Assessment (NSAA) is the most used clinical efficacy endpoint in recent pivotal DMD trials involving ambulatory boys and is considered a suitable efficacy outcome in children as early as 4 years old [13, 14,17] (*). As Sponsors want to include 4 year olds patients in clinical trials, restricting the context of use of SV95C to patients aged 5 and above would prevent the use of the SV95C in favour of NSAA. - Timed function tests and physiotherapy assessments require compliance with	

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	instructions which may lead to younger children struggling to perform the test, therefore there is a pressing need to develop outcome measures that can be used in younger populations in clinical trials. A major advantage of SV95C when compared to other efficacy outcomes is the increased objectivity and sensitivity which may allow for a reduction in sample size, and by extension, of the time to marketing authorisation. It would also reduce the burden to study participants. Therefore, broadening the context of use of SV95C to patients from 4 years of age would reflect the current understanding of disease, significantly increase the uptake of the endpoint, and result in benefits to the DMD community.	
European Paediatric Neurology Society (EPNS)	We agree with general conclusion by CHMP that SV95C could qualify as primary endpoint in superiority studies in ambulatory individuals with Duchenne	The comment is acknowledged and only partly agreed. We agree that SV95C can be used as primary endpoint supported by established efficacy measures as secondary endpoints.

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	muscular dystrophy as an alternative to 6MWD, or the NSAA, provided the outcome measure is supported by consistent findings in established secondary endpoints. We wish nevertheless to highlight some issues that should be taken into consideration when reaching a final decision. These are: Natural history data in DMD studied with the SV95C. The data provided are coherent in pinpointing the correlation between the SV95C and other outcome measures, and also indicate a range of MCID between 0.09-0.3 ms (in some section it is suggested the MCID of 0.1m/s could be considered a reasonable measure). The coherence of the data presented is encouraging. It would have nevertheless been helpful to have more information re: how much the study population is representative of the broader DMD population; have additional information on the standards of care followed in the studied population for example. Reassuringly, a proportion of	We acknowledge the comment that the population included in the longitudinal studies to evaluate the correlation with established endpoints measured were in an in-clinic setting. The population included is considered representative of an ambulatory population that would be recruited in clinical trials in which ab ambulatory population over a reasonable trial duration would be targeted. The same considerations as for use of 6MWT as a primary endpoint in this target population apply. It is noted that data for analysis comparing to established endpoints come from a natural history setting and clinical trials. We do not concur with the statement on "much larger variability" in younger patients. Data presented by the Applicant show comparable variability in subjects with DMD and controls when comparing between age ranges below 8 years and 8 years and above (table 31). However, we acknowledge that growth and disease progression can be considered factors potentially influencing variability. Variability in the low age range could be expected to be higher than in the higher age range due to well-known effects of development. Additionally, (variable) disease progression could impact observed variability over time. However, the same considerations apply to 6MWT as endpoint in clinical trials. Reference values published for 6MWT in the lower age range down to 4 years do not suggest a large increase in variability with low age. More granular data from the Applicant analysing within- and between subject variability by age could be helpful. The comment on only 2 patients initiating steroid treatment is not understood, as more data from patients initiating steroid treatment are available in the submission and these were followed over time up to 12 months (table 64). Overall we agree that careful considerations on the inclusion criteria are required in clinical trials targeting an ambulatory population and assuming a slightly lager variability in the lower age range for planning purposes may apply to all potential primary endpoints (including 6MWT).

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	the participants were in clinical trials, but the majority were in natural history studies. Also: the population studied is predominantly a stable, slowly declining ambulant population. Very few young children were studied, and indeed the variability of the SV95C in these children was much larger than in the older children. What is the lower age limit at which SV95C is deemed to be robust? Conversely how does the precarious late walking ability of DMD who are taking more than 10 seconds to walk 10 metes or who have lost ability to rise from the floor translate into SV95C It is unfortunate that only 2 patients were studied while steroids were initiated. While in several parts the author refers to "DMD who have initiated steroids", in reality these are only 2 children. It would have been ideal to follow a larger cohort for a period up to 3 or 6 months. As lack of progression could be determined in 59 DMD boys after 6 months, it would have been	Other neuromuscular conditions than DMD are not in scope of this qualification opinion.

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	helpful to see the effect of improvement in a cohort of children started on steroids as presumably the N required would have been much reduced (similarly to what other outcome measures have shown). Regarding DMD therefore, careful considerations should be used if SV95C is considered a primary outcome measure as different scenarios in the younger improving population (not a central consideration in the current application), and in the older population might apply (for example the range of SV95C measured appears different in the younger age group compared to the older, stable or declining patients population, which is where most of the data have been derived from in DMD it will therefore be important to define the age/ functional range should SV95C be considered a primary outcome measure, and optimal inclusion/exclusion criteria and definitions of ITT populations need to be carefully describe.	

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	As the potential of SV95C for other neuromuscular conditions, while the authors make a logical argument, more data regarding the range of SV95C changes; the impact of fatigability and other variables which are likely to be relevant for this novel outcome measure in conditions with different trajectories and clinical characteristics , before the SV95C could be considered for other conditions	
EuropaBio	The draft qualification opinion (lines 21-22) indicates that "*Acceptance of the SV95C variable is device agnostic provided accuracy and reliability of measurement are established (using a digital and passive wearable device and system[1]).*" "*[1] All data included in the present qualification package have been recorded with the ActiMyo® device(...)*" To date, the SV95C algorithm and parameters have been proprietary to the ActiMyo® and Syde® devices. Will this opinion now require licensing to other	The qualification of the SV95C is device agnostic. Whether Sysnav would be open to make their software applicable for other wearables can only be answered by Sysnav. From a regulatory perspective, it is foreseen that some validation may be needed comparing the accuracy and reliability of the new device to the performance of ActiMyo®.

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	vendors? Will Sysnav be open to migrating this to other wearables?	
EuropaBio	The qualification (e.g. lines 4-6) concerns use of the SV95C as primary endpoint in **superiority studies** in ambulatory DMD as alternative to the 6MWT, **provided** that the usual connotation that if the primary endpoint is met the study is a success, is not made. Could the Agency elaborate more on **why only superiority studies**, and why meeting the primary endpoint would not qualify the study as a success? **Which additional success criteria** would have to be met?	<u>Superiority studies</u> Non-inferiority studies should fulfil two related requirements i.e. there should be assay sensitivity and a non-inferiority margin can be defined. Assay sensitivity can only be concluded if a treatment shows separation from placebo in a randomised placebo-controlled trial with that treatment. Moreover, this separation should be consistent and constant over the placebo-controlled studies. The reason is that only then, if a non-inferiority study is preformed, we would be confident that the response observed would have separated from placebo if the non-inferiority study had included a placebo study arm. Only then a non-inferiority margin can be defined. The non-inferiority margin should reflect the minimal importance difference. To our knowledge both requirements have not been fulfilled for the SV95C. Hence non-inferiority trials cannot be justified. <u>Primary endpoints are not all equal.</u> From a methodological perspective, the primary endpoint is the variable for which the study is powered and if statistical significance is met, the study would be considered a success. From a clinical perspective, the primary endpoint is the endpoint that reflects /represents the underlying condition best, and if an effect on the primary endpoint is observed, then it would be concluded that an effect on the underlying condition is clear. In the orphan diseases, including DMD, the methodological perspective and clinical perspective do not fully coincide. Often a sensitive measure is chosen to establish a treatment effect that does not fully reflect the underlying condition. That has to be complemented by secondary endpoints.

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		Further, for accepting a single pivotal study, such a study should be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. In the context of an orphan condition, the consistency of the totality of the evidence collected may be more important than statistical significance. Hence, efficacy will be concluded based on the totality of the evidence collected and presented.
Little Steps Association for children with Duchenne & Becker Muscular Dystrophy	SV95C can objectively and continuously measure functional disease progression in DMD, thus providing a more accurate assessment of disease progression than is currently obtainable through traditional in-clinic assessments. Moreover, since SV95C is collected during the normal daily activities of the patient, it will help reduce the burden of participating in clinical trials. This will potentially both improve the clinical trial experience and increase the likelihood of detecting treatment benefits. Digital outcome measures can avoid both the bias as well as the burden and anxiety caused by outcome measures such as the NSAA, 6MWT, TTS etc. currently utilized as primary endpoints in	The comment is acknowledged and agreed. We agree that the continuously measured SV95C has the potential to provide an accurate assessment of disease progression with less burden for subjects associated with participating in clinical trials. Further work on comparison of SV95C with in-clinic assessments and specifically functional endpoints that would allow defining milestones in disease progression, and to evaluate potential bias would be welcomed. Feedback from the patients' community on these aspects is appreciated.

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	clinical trials. Furthermore, the real-world data captured by SV95C is more meaningful to patients and their families.	
F. Hoffmann-La Roche Ltd.	**Context of use** The lower age limit of 5 years in the proposed context of use could result in the impracticability of the qualified endpoint in clinical trials in ambulant patients, as opposed to NSAA which is accepted for patients from 4 years of age. It is understood that the data submitted by the Applicant did not initially include patients below 5 years of age, however, based on the well-known natural history of the disease, the context of use could be extrapolated to patients aged 4 and above. In addition, the original ActiMyo® device and the new Syde® wearable devices are suitable for and used by patients as young as 3 years in various indications. The wearing compliance data from the interventional Study SRP-9001-301 (EMBARK) and the non-interventional study Actiliege-Next in Duchenne Muscular Dystrophy (DMD) patients of different ages are now available. As can be seen in Tables 1 and 2, and Figure 1 below, DMD patients aged 4 show the	The comment is acknowledged and the additional data on patients of 4 years of age are welcomed. Data show that wearing compliance of suitable devices (ActiMyo and Syde) is similar for patients with age of 4 years compared to older age groups. Importantly, compliance data on wearing for this age group satisfy criteria (>50 h or >180 h of wearable data) set up in the previous qualification procedure for SV95C to ensure data quality. Considering all the arguments put forward and the concern with respect to the decreasing compliance seems unjustified there appears to be no objection to expand the context of use to the lower age limit of 4 years of age Adapted accordingly.

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same level of wearing compliance as that of older subjects aged 5 and above.

This confirms that the wearable devices can be used successfully in clinical studies involving patients as young as 4 years old, and that these patients can successfully be included in pivotal studies in DMD where the wearable technology is deployed and SV95C is captured as a primary endpoint.

Table 1: Compliance data from the natural history study ActiLiege Next[1]

ActiMyo wearing compliance during a 4 week recording period*	Age at baseline					
	4 year old		5 to 7 year old		Total	
	n	%	n	%	n	%
> 180	4	100 %	46	82 %	50	83 %
>50	0	0 %	5	9 %	5	9 %
<50	0	0 %	5	9 %	5	9 %
Total	4		56		60	

[1] ActiLiege Next Study is a Multicenter clinical study organized by the Centre de Référence Liégeois des Maladies Neuromusculaires

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	(CRMN). The goal of the Actiliège-next study is to gather more natural history data in Duchenne muscular Dystrophy (ambulant and non-ambulant patients), and in patients with Facio-Scapulo-Humeral Dystrophy. It consists of obtaining longitudinal data for the patients, as well as normative data for the control subjects, with particular emphasis on paediatric subjects using new medical devices. ** The thresholds selected are discussed as part of the previous qualification procedure (EMA/CHMP/SAWP/178058/2019): "If the cumulative recorded period exceeds 180 hours in the period, the compliance is considered very good. Between 50 and 180 hours, the compliance is acceptable. Below 50 hours, the compliance is considered as not acceptable, and no variable should be calculated for that period."* **Figure 1: Compliance data from the natural history study ActiLiege Next** **Table 2: Compliance data of Study SRP-9001-301 (EMBARK; EudraCT 2019-003374-91)** Syde Wearing Compliance during a 3-week recording period prior to randomisation (h)* / Age at baseline (years): 4 years old (n, %); 5 to 7 years old (n, %); Total (n, %)	

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	<table><tr><td>> 180</td><td>20</td><td>69</td><td>66</td><td>68</td><td>86</td><td>68</td></tr><tr><td>> 50</td><td>9</td><td>31</td><td>29</td><td>30</td><td>38</td><td>30</td></tr><tr><td><50</td><td>0</td><td>0</td><td>2</td><td>2</td><td>2</td><td>2</td></tr><tr><td>Total</td><td>29</td><td>100</td><td>97</td><td>100</td><td>126</td><td>100</td></tr></table>	
Solid Biosciences, Inc.	Solid Biosciences appreciates the opportunity to comment on the EMA qualification opinion as agreed by the Committee for Medicinal Products for Human Use. Solid Biosciences, Inc. is a life sciences company developing genetic medicines for neuromuscular and cardiac diseases, including Duchenne muscular dystrophy (DMD). Solid Biosciences concurs that better endpoints are needed than existing clinical outcome assessments (e.g., the 6 Minute Walking Test, 6MWT) that are often used as primary endpoints to demonstrate a treatment effect in clinical trials targeting ambulant patients with DMD. The advantages of stride velocity 95th centile (SV95C) using a valid and	The comments are acknowledged with the notion that the potential interchangeability between the SV95C and 6MWT as the main argument in favour of the SV95C as an alternative primary endpoint in DMD studies i.e. what would be a clinical meaningful change in the SV95C has still to be established. See CHMP discussion line 2640-2685 page 164-165.

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	suitable wearable device include that it captures maximal functional ability; is more objective; less sensitive to factors such as time of day and day-to-day fluctuations in patient functioning; less burdensome for patients, caregivers, and healthcare providers; and less likely to induce unnecessary fatigue in the children participating than the 6MWT. The ability to use this endpoint as a primary endpoint is a step toward overcoming the challenges of participant recruitment and endpoint selection when developing much-needed new treatments for DMD. We support the qualification of SV95C as a primary endpoint to assess new drug efficacy in modifying the progression of DMD in clinical trials for patients older than 5 years of age. We base our support on the further quantitative data that EMA requested upon its qualification of SV95C as a secondary endpoint (EMA/CHMP/SAWP/178058/2019), through studies of greater numbers of	

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	patients with DMD and lengthier follow up to support accuracy and test-retest reliability. The additional data demonstrates SV95C has high correlation with the 6MWT, is more sensitive than the 6MWT, and is able to detect change during the natural course of disease and after a treatment. We also believe it is reasonable at this time to expect support from consistent findings in established efficacy endpoints included as secondary endpoints. We agree that SV95C measures the same aspect of walking as the 6MWT (speed/velocity), so the 6MWT would not need to be a secondary endpoint in clinical studies that use SV95C to measure this aspect. Functional aspects that are most important to patients and caregivers are important considerations for secondary endpoint selection. Thank you again for this opportunity to provide support for this EMA qualification opinion.	

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World Duchenne Organization	The World Duchenne Organization regards the EMA qualification of SV95C as a primary endpoint as crucial to enabling real-world ambulation data to be used for drug approval in DMD- SV95C can objectively and continuously measure functional disease progression in DMD, thus providing a more accurate assessment of disease progression than is currently obtainable through traditional in-clinic assessments. Moreover, since SV95C is collected during the normal daily activities of the patient, it will help reduce the burden of participating in clinical trials. This will potentially both improve the clinical trial experience and increase the likelihood of detecting treatment benefits. Digital outcome measures can avoid both the bias as well as the burden and anxiety caused by outcome measures such as the NSAA, 6MWT, TTS etc. currently utilized as primary endpoints in clinical trials. Furthermore, the real-world data captured by SV95C is more meaningful to patients and their families.	The comment is acknowledged with the notion that the potential interchangeability between the SV95C and 6MWT as the main argument in favour of the SV95C as an alternative primary endpoint in DMD studies i.e. what would be a clinical meaningful change in the SV95C has still to be established. See CHMP discussion line 2640-2685 page 164-165. We agree that the continuously measured SV95C has the potential to provide an accurate assessment of disease progression with less burden for subjects associated with participating in clinical trials. Further work on comparison of SV95C with in-clinic assessments and specifically functional endpoints that would allow defining milestones in disease progression, and to evaluate potential bias would be welcomed. Feedback from the patients' community on these aspects is appreciated.

2. Specific comments on text

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
9-12	Prof. Gabriele Siciliano, MD, PhD, on behalf of EAN Scientific Panel of Muscle and NMJ Disorders	It is accepted that the SV95C can be applied at home setting, therefore it can be less sensitive to timing of assessment and patient motivation. However, some other issues could be occurred, about potential risks of errors in recording or positioning. Proposed change (if any): add a note about that	The comment is acknowledged and partly agreed. The data provided by the Applicant allow assessing variability of the SV95C measurements over time. For trial-related procedures at home, appropriate training should be provided to ensure accurate measurements; monitoring of compliance data should be considered (see e.g. the EMA/HMA Recommendation Paper on Decentralised Elements in Clinical Trials). No change is envisaged.
102-104	Prof. Gabriele Siciliano, MD, PhD, on behalf of EAN Scientific Panel of Muscle and NMJ Disorders	Comment: The applicant suggests the use of SV95C as secondary outcome measures in other muscular dystrophies and SMA3. Considering the high variability of these conditions, further natural history data on larger cohorts need to be collected. Moreover, the use of a wearable device to assess walking related abilities should be integrated with other ambulation parameters, that could be useful especially in adult patients. Proposed change (if any): add a note about that, lines 1879-1880	The comment is acknowledged. Other neuromuscular diseases are not in the scope of this qualification opinion. No change is envisaged.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
Lines 2555-2556	EFPIA	Comment: It was concerning that the applicant made the absolute statement on line 30 that SV95C "does not rely on patient motivation or subjective assessment". It was encouraging that CHMP's discussion made the more reasonable and limited statement that it "relies LESS on patient motivation or subjective assessment" [emphasis added]. It is important that we continue to allow for the possibility that monitored behaviors like ambulation may still be influenced by such factors. Proposed change: No change. This is only a statement of agreement.	Acknowledged and appreciated.
Lines 2576-2577 With respect to the content validity of the SV95C it is noted that face validity of the SV95C is not straightforward: ambulation has many features, and it is difficult to	EFPIA	Comment: The sentence "With respect to the content validity of the SV95C it is noted that face validity of the SV95C is not straightforward:…" is confusing as content validity and face validity are different concepts. It is unclear whether content validity, or face validity, or both of them are considered questionable. Proposed change (if any): With respect to SV95C as a measure of ambulation, content validity and face validity are not straightforward:	Face validity and content validity are closely related concepts and refer to subjective judgement that a scale look reasonable. Face validity indicates whether an instrument assess the qualities desired on the face of it whereas content validity refers to the judgment whether an instrument samples all the relevant content or domains. The comment is accepted as being clearer and adapted accordingly.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
imagine to which extent a change		ambulation has many features, and it is difficult to imagine to which extent a change (this change should also be made in line 2587: "content and face validity".)	
Lines 2591-2593 Thus, overall results are supportive for use of a wearable device to assess walking related abilities. This would also include other ambulation related endpoints, e.g. total walking distance, distance covered with walking bouts, stair climbing	EFPIA	Comment: It is unclear how much endorsement is intended for 'other ambulation-related endpoints'. Is the intent to suggest that the data currently presented would support qualification of other outcomes, or just an openness to consider these types endpoints?	The message is general i.e. that wearable device also may be used to evaluate features of walking other than stride velocity; thus openness to other ambulation based endpoints. No adaptation is envisaged.
Lines 2691-2693 However, the face validity the SV95C is less clear. In fact, change in stair-climbing, ability to	EFPIA	Proposed change (if any): However, the **content validity and** face validity of SV95C as a measure of ambulation is less clear. In fact, change in stair-climbing, ability to self transfer and walking ability and fatigue appear more important to the	The comment is accepted as being clearer and adapted accordingly.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
self transfer and walking ability and fatigue appear more important to the patients/caregivers than stride velocity.		patients/caregivers than **maximal** stride velocity"	
Lines 2713-2716 Of note, this might have been different if the anchor-based methods had allowed for a conclusion on the meaningful change threshold (MCT) of SV95C. The Applicant indicated during the discussion meeting that further research is intended to further substantiate the MCT and to evaluate the predictive value of the SV95C for	EFPIA	Comment: We disagree with the notation that this might have been different if the anchor-based methods had allowed for a conclusion on the meaningful change threshold (MCT) of SV95C. The qualification opinion argued both SV95C and 6MWT require consistent findings to support them as outcome measure that reflects / represents the underlying condition. Proposed change (if any): ~~Of note, this might have been different if the anchor-based methods had allowed for a conclusion on the meaningful change threshold (MCT) of SV95C~~ The Applicant indicated during the discussion meeting that further research is intended to further substantiate the MCT and to evaluate the predictive value of the SV95C for functional milestone	The argument made is accepted. Indeed consistent findings to support them as outcome measures that reflect / represents the underlying condition even if the MCT would have been established. The statement can be perceived as is contradictory which was not intended. Adapted accordingly

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
functional milestones			
Lines 2717-2721	EFPIA	Comment: Separate these two sentences into two paragraphs to make the device agnostic statement and final conclusion clearer. Proposed change (if any):	No objection against this and adapted accordingly.
Lines 2718-2721 In conclusion, considering all the above, a qualification of the SV95C as primary endpoint in superiority studies in ambulatory DMD as alternative to the 6MWT is considered acceptable provided that the usual connotation that if the primary endpoint is met the study is a success, is not made.	EFPIA	Comment: The conclusion statement needs to be written more clearly. Proposed change (if any): In conclusion, considering all the above, a qualification of the SV95C as primary endpoint in superiority studies in ambulatory DMD as alternative to the 6MWT is considered acceptable. As indicated in EMA Guideline EMA/CHMP/236981/2011, Corr. 11, "effects on the single selected primary endpoint should be supported by results from the most relevant secondary endpoints for consistency."	Not fully agreed. The last sentence is a high level message applicable in general to studies in orphan diseases. We can add the sentence as proposed to concretise this for this specific case. Adapted.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
72 and beyond	EuropaBio	Comment: While the SV95C measurement is considered a Clinical Outcome Assessment (COA), the opinion may want to specifically note that this is a Performance Outcome (PerFO) measure. This change should be applied throughout the opinion document.	Page 3 through 162 is the EXECUTIVE SUMMARY and background as provided and submitted by the Applicant. The Applicant is the content owner and as such amendments are not appropriate as it would no longer reflect the background of the Applicant submitted. Further, if this text would be changed the basis for the CHMP discussion and position statement would change and would formally need re-assessment.
209	EuropaBio	Comment: Table 3 indicates meaningful change values that have been derived to interpret SV95C changes over time. Given the small sample size, it should be explicitly stated that individual sponsors should confirm these values within the trial context using multiple anchors.	Idem. See comment above.
228-235	EuropaBio	Comment: The opinion states that "*In addition, while overall data are in favor of a MCT of about 0.1 m/s, the clinical relevance of the change from patients perspectives was determined only on results from questionnaires completed by parents and clinicians during a*	Idem. See comment above.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
		clinical trial prematurely stopped due to lack of the investigational medicinal product efficacy leading to a high MCT of about 0.2 to 0.3 m/s, as compared with the MDC calculated based on the distribution of 0.127 to 0.194 m/s regarding the level of confidence interval from 80% to 95%. Collecting additional data with patient reported outcome through health-related quality of life questionnaires will help to strengthen the anchoring and refinement of a MCT for the SV95C." Proposed change (if any): The last statement should be revised to read: "*In addition to confirming within other clinical trials, with larger sample sizes, additional COAs (e.g., PROs) should be used to generate the totality of evidence to aid in interpretation of SV95C results.*"	
Section 1.4.2 Quantitative Evidence	Pfizer Inc.	We suggest further specifying or defining the "50 hours of recordings" for participants to be included in the analyses. For example, we suggest clarifying whether the 50 hours of recordings mean 50 hours of continuous data (i.e., 2 days +2 hours) or something different. Additionally, we suggest specifying any criteria for daily compliance, and how the SV95C would be computed explicitly from the 50+	The comment is acknowledged and partly agreed. The period of data recording was addressed in the previous qualification opinion for SV95C as secondary endpoint. Continuous wearing is not expected, as e.g. during sleep time the device is not expected to be worn.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
		hours recordings. If there are missing data or gaps in between recordings, it would be helpful to include how this should be handled. Finally, we suggest clarifying how to handle drop-outs between recording periods.	Handling of truly missing data should generally be done considering the estimand framework described in the ICH E9 (R1) addendum. No general recommendation can be given, but intermediate missing data in the context of usually defined study visit windows may be handled differently than study drop-outs. No change is envisaged.
Section 3.1.1 Qualitative Evidence (Content Validity)	Pfizer Inc.	The document presents thorough results for content validity. We suggest the agency include whether it is seeking any evidence on comfort and wearability.	The comment is acknowledged. It is not clear how the comment relates to the content validity of the endpoint, but it is acknowledged that wearing compliance has an impact on the properties of the measure. Feedback on discomfort and tolerability of the device was described for the ActiMyo device (table 23). No change is envisaged.
Section 3.2.2.1 Population Table 24	Pfizer Inc.	The age distribution is presented per study; however, multiple analyses include age groups [5-7] and [8-14]. We suggest presenting these age distributions within the age groups as well. Additionally, we suggest inclusion / exclusion of ambulatory participants within the age groups.	The comment is acknowledged. Information on age groups of (ambulatory) patients is part of the briefing document (e.g. in table 30). No change is envisaged.
Section 3.2.2.3.1. Known-groups Validity	Pfizer Inc.	The normative values for SV95C for controls were reported in range of 2.6- 2.7 m/s (max 3.6 m/s). For DMD patients this range was	The comment is acknowledged and partly agreed.

Line number(s) of the relevant text *(e.g., Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	General comment (if any)	EMA response
Tables 26, 30, 31		around 1.57 m/s on average (max 2.5 m/s). Does the SV95C include running, as these high values suggest, or only walking? We suggest stating this in the document. We also suggest clarifying whether the height of the participants was accounted for in the analysis as covariate across age groups.	As the SV95C captures motion during real life activities, running may be part of the recorded data if patients are capable of running. This would need no explicit statement. Additional exploratory analysis for covariates in available and future data on impact of SV95C and other data derived from actigraphy could be valuable. No change is envisaged.
Section 3.2.2.5.3 Overall estimate of MCT for SV95C	Pfizer Inc.	MCT is derived from natural history studies and proposed as -0.1 m/s for natural disease deterioration. Would this threshold be accepted by the agency for proof of prevention of deterioration in interventional studies?	The comment is acknowledged. Concerns on the limitations of the data supporting of the derived MCT are clearly expressed in the qualification opinion. Additional research is necessary to further substantiate the MCT using anchor-based methods before a threshold in interventional studies can be accepted (see discussion on quantitative evidence and overall discussion section in the qualification opinion). No change is envisaged.

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