7 April 2023

Submission of comments on *'Draft Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies*' (EMA/SA/0000083386)

Comments from:

Name of organisation or individual
EFPIA

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 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)	
	As established in the qualitative evidence, change in stair-climb, limiting falls, ability to self-transfer, and walking (i.e., ability to perform activities of daily living), were considered by patients and caregivers to be more important than	

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	stride velocity. These outcomes could be developed as complementary, patient-relevant secondary endpoints.	
	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 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]. This becomes more evident over time as children with DMD begin to become weaker and have their quality of life impacted by their impaired physical ability [7, 8]. - 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 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]	

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	- 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 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.**	

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)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 2555-2556		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.	
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 imagine to which extent a change		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: ambulation has many features, and it is difficult to imagine to which extent a change	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		(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		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?	
Lines 2691-2693 However, the face validity the SV95C is less clear. In fact, change in stair-climbing, ability to self transfer and walking ability and fatigue appear more important to the patients/caregivers than stride velocity.		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 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 functional milestones		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~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		~~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	
Lines 2717-2721		Comment: Separate these two sentences into two paragraphs to make the device agnostic statement and final conclusion clearer. Proposed change (if any):	
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.		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."	

Please add more rows if needed.

List of References

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