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Short communication

European regulators' views on a wearable-derived performance measurement of ambulation for Duchenne muscular dystrophy regulatory trials ☆

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Abstract

Development of novel therapies for Duchenne muscular dystrophy (DMD) are driving the need for more efficient ways of detecting changes in disease- progression in DMD [1]. However, medicines' approval must be based on outcome measures that are acceptable from a regulatory perspective. In this article, European regulators provide an update on the recent regulatory consideration of a new endpoint (Stride Velocity 95th Centile (SV95C)) that could be used in therapeutic DMD trials. This new endpoint aims to quantify a patient's ambulation directly, reliably and continuously in a home environment with a wearable device.

Keywords: Duchenne muscular dystrophy; Gait Variables; European regulators; Clinical trial endpoints.

1. Introduction

Before new medicines can be placed on the market, medicines' developers have to generate and submit evidence to regulators that the benefits outweigh the risks of the new medicine in the targeted indication. A critical part of such evidence is the design of the pivotal clinical trial and the choice of endpoints. For regulators, a primary endpoint in a pivotal trial needs to be accurate, reliable, sensitive to change, reflect the objectives of the trial, and be relevant to patients and clinicians. In general, secondary endpoints should also support the efficacy of the selected primary endpoint. In judging whether a new medicine is approvable or not, regulators weigh the overall data on benefits, against any safety issues and remaining uncertainties on the new medicine. The current DMD EU regulatory guidance [2] recommends that in pivotal trials, two endpoints be selected from the domains muscle strength and motor function, one as primary and the other as secondary endpoint with the choice depending on the treatment goals.

Amongst functional measures, regulators recognize that loss of ambulation is an important milestone in DMD; the 6-minute walk test (6 MWT) [3,4] has been used in a modified version as an endpoint in this setting. Known limitations with the 6 MWT include: a learning effect, high inter- and intra-person variability, the impact

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of age and motivation, and the applicability to ambulant patients only. Regulators currently recommend that if the 6 MWT is selected as the primary endpoint, results on efficacy should be supported by secondary clinical outcomes such as timed-function tests, pure motor function tests, muscle strength, disability, activities of daily living or cardio-pulmonary function testing.

One way of seeking regulatory endorsement of a potential new endpoint is the European Medicines Agency's qualification procedure for novel methods. Teams of regulators assess whether a novel method could be used in trials for regulatory decision making and what weight could be given to it, as in the case for Stride Velocity 95th Centile (SV95C) [5].

2. Gait Variables measured by a wearable device as an endpoint to demonstrate efficacy in drug development clinical trials of ambulant DMD patients

The proposed Gait Variables measured by a suitable and valid wearable device were intended to be used in a home-based environment (the system uses battery operation lasting 16 h and is composed of two watch-like sensors – each containing a tri-axial accelerometer, gyrometer, magnetometer and barometer that record the linear acceleration, the angular velocity, the magnetic field of the movement in all directions and the elevation meters – as well as one docking station).

Five Gait Variables measured were assessed for their validity in measuring a patient's ambulation ability in a continuous manner: the 95th centile of the stride velocity (SV95C), the median stride velocity, the 95th centile of the stride length the median stride length and the distance walked/recorded hour. The gait parameters are detected directly by the wearable device every time the wearer walks.

To validate relevant measures for ambulant DMD subjects, the following studies were performed by the Applicant based on ambulant DMD patients ranging from 5 to 14 years with a mean age of 8.3±2.1 years:

1. A study of the validity of gait measures by demonstrating that the distance measured from reconstruction of foot trajectory of ambulant patients as assessed by the magneto-inertial sensor corresponds to the real distance as measured manually.
2. Measurement of the variability of Gait Variables and studying the influence of poor compliance to generate recommended minimal use.
3. Cross validating these measures with 6 MWT and North Star Ambulation Assessment (NSAA).
4. Studying the sensitivity to change over a 6 month and a 1 year period in patients older than 6 years old and walking less than 450 m in 6 MWT. The Applicant also collected normative data in age-matched controls, and evaluated the accuracy of measurements using the device compared to an optical motion capture system in healthy subjects.

3. Discussion

When reviewing the regulatory utility of SV95C, regulators considered data on accuracy, reliability, sensitivity to change and clinical relevance. The data revealed a high rate of accuracy for measurements of stride length and velocity compared to an optical motion capture system, and that the stride parameters measured with the system are consistent with the 6 MWT distance taking into account the "turn" distance, which is not counted by the physiotherapist.

In terms of reliability, the SV95C was calculated from a period of 180 h of summed recorded data per individual. This period seemed to ensure low variability while keeping good compliance. Daily recording including weekends is needed for representative data. Therefore, in ambulant DMD patients, 30 day wearing periods are proposed to ensure that sufficient data are generated during a set period for almost all patients. In clinical trials, one month measurement periods will be proposed at various study time points (e.g. baseline, months 3, 6, 12). Whilst compliance rates presented were quite high, the handling of missing data would need to be addressed in any study protocol, together with other measures such as training, and instructions.

For clinical relevance and sensitivity to change, regulators first examined the correlations of SV95C with other validated DMD endpoints such as 6 MWT, NSAA or 4 stairs climbing (4SC) test. These assessments (6 MWT, NSAA or 4SC) provide a snapshot of the patient's supposed maximal functional ability in a test environment, but also have limitations as mentioned above. In contrast, direct and continuous maximal stride speed (SV95C) is reflective of actual maximal performance. Therefore the expectations for correlation of SV96C with 6 MWT are in terms of relationship rather than replacement or reproduction of a less than perfect gold standard. However, this also means that uncertainties such as a full understanding of clinically relevant changes remain to be resolved as discussed below.

A correlation analysis was presented based on cross-sectional SV95C data from 45 DMD patients vs 6 MWT, NSAA and 4SC. The number of patients included in the tests is low, but the data were consistent and SV95C was significantly correlated with the validated 6 MWT and NSAA.

Regarding sensitivity to change, longitudinal (31 patients at 6 months and 11 patients at 12 months for SV95C vs 6 MWT) changes observed for the SV95C are in line with those observed in DMD studies for 6 MWT. Baseline normative data indicate that stride speed and stride length clearly discriminate between controls and DMD, especially when expressed as the 95th centile. Further research to expand normative data in comparison to the 6 MWT in healthy age-matched controls is encouraged.

For the minimally clinically important difference (MCID), the Applicant used distribution methods as applied [3,6] for the 6 MWT (MCID of 30 m) proposing an MCID of 0.1 m/s for SV95C. To assess whether this MCID for SV95C is in the same order of magnitude as that for the 6 MWT, two

calculations were presented: The first was to convert the speed at this MCID directly in the distance achieved over 6 min. Thus, a patient walking at this MCID (0·1 m/s) for 6 min achieves a distance walked of 36 m. Secondly, using the slope (0·42 m/s per 100 m of 6 MWT) of the linear correlation between SV95C and 6 MWT data, an MCID of 0·1 m/s was equivalent to 23·8 m. Whilst these comparisons are limited given the impact of motivation on the 6 MWT, they indicate that the distribution-based MCID for SV95C and 6 MWT are in the same order of magnitude.

Based on the correlation slope between SV95C and non-linearized NSAA, 0·1 m/s for SV95C corresponds to 2·32 points on the non linearized North Star, (approximately to 7 points in the linearized North Star). This is considered as the MCID for NSAA [7].

Ideally, anchor-based approaches to estimate MCID for SV95C would relate a drop in the SV95C to loss of ambulation, quality of life measures, or other scales such as patients' or clinical global assessments. Such approaches would provide greater understanding of clinical and patient relevance of changes in SV95C. For SV95C as a primary endpoint in DMD trials, such anchor-based approaches together with more robust data on the long term correlation of SV95C with currently used tests (increased sample and longer follow-up, and expanded normative data) could be supportive.

Data on quality of walking, fall, sway, real world stairs, time to stand, and correlation with patient well-being are not currently available with the system. Such measures are of interest together with further assessment in younger children and in non-ambulant patients (e.g. based on upper limbs).

In summary, European regulators consider that for ambulant DMD patients 5 years of age and above SV95C [5] is an acceptable secondary endpoint in pivotal or exploratory drug therapeutic studies for regulatory purposes, when measured by a valid and suitable wearable device to quantify a patient's ambulation directly in a continuous manner, in a home-based environment and as an indicator of maximal performance, or to gather information on a patient's baseline performance in such studies. In order to support use as a primary endpoint in pivotal trials, additional data collection are needed. Education and training for carers, subjects and staff is important to support the implementation of this tool in clinical trials. The final regulatory opinion published following public consultation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.06.003.

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