EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2018
EMA/CHMP/SAWP/527447/2018
Product Development Scientific Support Department

Draft qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

Draft agreed by Scientific Advice Working Party	12 April 2018
Adopted by CHMP for release for consultation	26 April 2018
Start of public consultation	21 September 2018
End of consultation (deadline for comments)	30 November 2018

Comments should be provided using this template. The completed comments form should be sent to Qualification@ema.europa.eu

Keywords	Activity monitor, Duchenne Muscular Dystrophy (DMD), Real World Data, Stride Velocity, Ambulation

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Reader's guidance

This report provides a final agreed draft Context of Use for public consultation describing where Stride Velocity measured at the ankle 95th Centile is deemed by CHMP as an appropriate endpoint in studies to support regulatory decision making on medicines for the treatment of Duchenne Muscular Dystrophy (DMD), together with CHMP's scientific consideration of the submission leading to the draft opinion. The document also includes the questions posed by the applicant and also raised by CHMP to the Applicant, and all the data provided by the applicant in support of the Application.

Draft Context of Use adopted by CHMP

Based on data provided by the Applicant and State of the art science in the field,

CHMP considers that for ambulant Duchenne Muscular Dystrophy (DMD) patients 5 years of age and above:

- Stride velocity 95th centile measured at the ankle (SV95C) 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 ability directly and reliably in a continuous manner in a home environment and as an indicator of maximal performance.
- Stride velocity 95th centile measured at the ankle may also be used to quantify a patient's baseline performance in such studies.
- Regarding use as primary endpoint for pivotal trials in this setting, although promising, more robust data gained with additional patients and longer follow-up could be beneficial: thus strengthening the long term correlation of SV95C with functional tests, expanding normative data and further supporting the justification of the clinical relevance of the proposed MCID in the PEP setting is recommended.

Introduction

The applicant requested qualification of novel Gait Measurements via a valid and suitable wearable device in a specific regulatory context of use, submitting supportive questions and data to CHMP. Specific issues were raised by SAWP for clarification and discussion within the qualification procedure and discussed with the Applicant on 6 Nov 2017, and 7 March 2018.

This document summarizes the, the Committee's scientific considerations and resulting opinion on the fitness for regulatory use of the novel method. The data provided by the Applicant are also included.

This opinion refers to the nature and use of the clinical measure as fit for purpose in trials for regulatory decision making. The technical validity of the wearable device per se used to make these clinical measures is not in scope of the EMA and not considered henceforth. This distinction means that the clinical measure is the focus of the opinion and the measuring device/system used is assumed to be valid and referred to as a 'suitable and valid wearable device'.

The Proposed Gait Variables measured with a valid and suitable wearable device and system [1]* quantifies a patient's ambulation ability in a continuous manner across five different variables:

* 1 The recording device and accompanying system* used two watch-like sensors - each containing tri-axial accelerometer, gyrometer, magnetometer(s) and barometer that record the linear acceleration, the angular velocity, the magnetic field of the movement in all directions and the barometric altitude – as well as one docking station. For ambulant patients one device is placed near the ankle and the other is placed on the second ankle or worn as wristwatch.
The device should be able to detect all strides at all paces (slow to fast and turning strides). The segmentation of the start and end of a stride is based on a model linking the ankle acceleration and angular velocity on the principle that the lower limb is in rotation around the heel. The length and velocity of the strides should be accurately measured with an error at 1 sigma (68% confidence interval) under 2.5 %.
Tests for security (EN 60601-1:2007 professional healthcare and EN 60601-1-11:2015 at home), electromagnetic compatibility (IEC 60601-1-2:2014 professional healthcare and IEC 60601-1-2:2014 at home), biocompatibility (ISO 10993-1:2009) and usability (IEC 60601-1-6:2010 and IEC 62366-1:2015) for CE marking are associated. Software development follows EC 62304. Communication channels are encrypted (SSH, HTTPS) - Only the researcher has access to a patient identifier code that indicates that a device has

- the 95th percentile of the stride velocity measured at the ankle,
- the median stride velocity measured at the ankle,
- the 95th percentile of the stride length measured at the ankle,
- the median stride length measured at the ankle,
- and the distance walked/recorded hour.

The gait parameters are detected directly every time the wearer walks.

To validate relevant measures for ambulant DMD subjects, the following work has been done to date by the Applicant:

1. A study of the validity of gait measures by demonstrating that the distance measured from reconstruction of ankle trajectory of ambulant patients as assessed by the magneto-inertial sensor corresponds to the real distance as measured manually (validity study).
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 6MWT and 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 6MWT.

In the sections below, CHMP's scientific considerations are presented, as well as the Applicant's initial questions, issues raised by the Agency for clarification and discussion during the procedure, and finally the Applicant submissions, and responses to questions.

CHMP Scientific discussion

The Applicant posed a series of 4 questions to the CHMP culminating in the overarching question that in consideration of the low variability, the clinical relevance, and the sensibility of the methods, whether the EMA would agree to qualify the Proposed Gait Variables (as recorded by the device) as an endpoint to demonstrate efficacy in drug development clinical trials of ambulant DMD patients. It was further clarified in a discussion meeting that the Applicant wishes to in particular qualify stride velocity 95th centile of the ankle (SV95C) when measured by a suitable and valid wearable device as either a primary or secondary endpoint in pivotal clinical trials testing the efficacy of therapies to modify the progression rate of Duchenne muscular dystrophy (DMD) in patients 5 years of age and above.

The Proposed Gait Variables measured by a suitable and valid wearable device are intended to be used in a home-based environment (the system uses battery operation lasting 16 hours and is composed of two watch-like sensors - each containing a tri-axial accelerometer, gyrometer, magnetometer(s) and barometer that record the linear acceleration, the angular velocity, the magnetic field of the movement in all directions and the altitude – as well as one docking station). For ambulant patients one sensor is worn as wristwatch and the other placed near the ankle. For non-ambulant patients, the second sensor is placed on the armrest. During the discussion meeting with the Applicant, it was clarified that in patients who could transition to non-ambulant as it is the case in the population of interest, ankle/wrist recording is better than ankle/ankle recording as it offers the opportunity of a continuous measure across loss of ambulation. In younger patients, where top performance as climbing stairs or running could be considered, ankle/ankle recording is likely preferable.

Data are stored in an internal memory inside each watch-like device and transferred to the docking station, every night, when they are put to charge. Data collected in the docking station can be sent anonymously directly via internet on a dedicated and secure web-cloud or can be stored on an internal

been used by the same patient in a certain recording period. But the link between a patient identifier code and the personal details is only stored by the clinical centre together with the clinical and medical information. Data are stored in an internal memory inside each watch-like device and transferred to the docking station, every night, when they are put to charge. Data collected in the docking station can be sent anonymously directly via Internet on a dedicated and secure web-cloud or can be stored on an internal USB drive for up to three months. Computation of variables is performed afterwards for each patient using the recorded magneto-inertial data. Recording does not rely on individual patient calibration and contrary to optical motion capture systems it can be used continuously, including in the home environment.

USB drive for up to three months. Computation of variables is performed afterwards for each patient using the recorded magneto-inertial data.

Data protection and privacy issues were discussed during the discussion meeting. A risk analysis has been conducted by the Applicant to identify, address and mitigate the potential risks. Minimization measures were considered acceptable.

The EMA guideline on Duchenne and Becker Muscular Dystrophy (EMA/CHMP/236981/2011, Corr. 1) recommends that two endpoints should be selected from the domains muscle strength (depending on the functional status and the compound tested) and motor function. The Proposed Gait Variables are aiming at the motor function domain. The variables that are measured include:

- Stride length (in quantiles of all strides in a defined period)
- Stride velocity at the ankle (in quantiles of all strides in a defined period)
- Distance walked

The Applicant requests whether the Proposed Gait Variables measured by a suitable and valid wearable device can be considered clinically relevant and well correlated to other validated outcomes such as six-minute walking test (6MWT), North Star Ambulation Assessment (NSAA) or 4 stairs climbing (4SC) test currently used as endpoints in interventional trials in the ambulant Duchenne muscular dystrophy (DMD) population. All these assessments (6MWT, NSAA or 4SC) are episodic, and provide a snapshot overview of the supposed maximal patient's functional ability. They have specific limitations related to patient motivation at the time of assessment which the proposed system intends to overcome. All existing measures require patients to travel to specialist neuromuscular centers, often some considerable distance away. This, alone, causes major stress and disruption to patients and family. In addition, motivation is known to play an important factor in the 6MWT; experiences have shown that a child can increase significantly the distance walked if offered an incentive to perform better.

In addition, parameters such as *steps taken / meters walked* can be influenced by seasonal variation, family lifestyle, motivation and height. Contrastingly, ankle stride speed and stride length are largely independent of such factors. During the Discussion meeting, it was clarified that the method was considered as a digital biomarker / biometric data and not as a "patient reported outcome", since no active participation from the patient is requested. The system captures data passively when worn. This is agreed.

Biological plausibility and clinical logic, face validity

The Applicant wishes to concentrate on the 95th percentile stride velocity measured at the ankle, which is another way of measuring top velocity, but is not dependent upon motivation as the 6MWT.

Content validity, accuracy

During the Discussion meeting, the Applicant presented the work undertaken so far. Validation tests in 8 healthy controls were undertaken in an optical motion capture room and revealed a high rate of accuracy for measurements of length and velocity of the ankle when compared to the reference optical motion capture with an error rate of under 2.5 %.

Data from 23 DMD patients on 31 6MWTs showed that the stride parameters measured with the system are consistent with the 6MWT distance taking into account the "turn" distance, which is not counted by the physiotherapist.

Reliability

The duration of 180 hours of recorded data at baseline was used to correlate between Proposed Gait Variables measured by a suitable and valid wearable device and 6MWT, NSAA, 4 SC test for four main

reasons: 1) the drop in variability with recording duration appeared to decrease in all patients at this period of time; 2) it is short enough to be considered during a screening or a baseline periods, and it covers weekly patterns for example, including in families with separated parents where the activity of the child may considerably vary from one week to another; 3) disease progression is not expected over a period of 180 hours; 4) patient burden it not considered to be too strenuous to achieve 180 hours. These 180 hours of recording for each patient corresponds approximately to 2-3 weeks of recording and has been achieved during the first month by 90% of the ambulant patients who have used the suitable and valid wearable device for at least one month. Using 180 hours seems to ensure low variability while keeping good compliance. However, meaningful variables can still be calculated with shorter duration of recordings.

Table 1 Variability of Proposed Gait variables measured at the ankle when averaged on 50h and 180h of recording. [Source Table 4 of briefing document 20180108]

Proposed Gait Variables	N	Mean (SD) variability at 50h of recordings	Mean (SD) variability at 180h of recordings
50th Percentile (median) stride length (m)	28	3.55% (1.05%)	2.24% (0.73%)
95th Percentile stride length (m)	28	3.40% (1.74%)	2.22% (1.34%)
50th Percentile (median) stride velocity (m/s)	28	5.31% (1.47%)	3.35% (1.24%)
95th Percentile stride velocity (m/s)	28	6.38% (2.60%)	4.41% (2.33%)
Distance walked/hour	28	26.27% (6.66%)	15.83% (5.77%)

At 50 hours recording, the variability found for the 95th percentile of stride velocity measured at the ankle is 6.38% which is still acceptable if the majority of patients have more than 180 hours of recordings per period.

It is recommended that patients use the device every day including weekends to capture a representative picture and smooth the day to day variability. Data presented seem to indicate no difference between morning and afternoon recordings.

Compliance rates of 90% were observed amongst patients who agreed to use the system. This compliance rate is quite high considering that continuous total monitoring for the entire study period was requested rather than 1 month blocks at set periods. However, this is considered as the optimal situation with a limited number of volunteers. The compliance rate after 6 months was lower (79%; i.e. 31 of 39 patients had more than 50 hours of recording) It is not clarified how missing data are being treated (~10%, 5 out of 48 patients). During the discussion meeting it was clarified that all recordings periods are analysed individually for each patient. If no steps are detected on the ankle sensors, and if no movement is recorded, the individual recording file will be discarded for that recording period. See (Figure 22 below in Applicant´s response document to CHMP List of Questions). Then, the sum of the durations of all files recorded is computed to evaluate the compliance.

During the discussion meeting, inversion of sensors was discussed as a possible confounding factor. In that rare case, inversion is detected because strides will no longer be detected on the supposed ankle sensor but on the wrist sensor. In that case the correction is done during data analysis. With respect to the possibility of the device being worn by somebody else and not the child suffering from DMD, the Applicant responded that it is somewhat harder to monitor, and cannot really be verified but is mitigated trough good training, and clear instructions in the informed consent of the importance of good compliance to the end result of the trial.

Concurrent validity

There are cross-sectional data from 45 DMD patients obtained on 180 hours of recording at baseline for correlation with 6MWT, NSAA and 4SC, and longitudinal data from 31 patients at 6 months and

from 11 patients at 12 months in comparison to the 6MWT. The number of patients included in the tests is low, however data are very consistent.

Apart from these studies, work to generate normative data in comparison to the 6MWT in 130 healthy age-matched controls (100 children and 30 adults) is ongoing and preliminary baseline data were presented ("ActiLiège" protocol).

Stride length and velocity describing spontaneous walking during 180h of recording at baseline are significantly correlated with the validated 6MWT and NSAA.

Table 2 *Correlation coefficients between the Proposed Gait Variables recorded over 180h at baseline and 6MWT, NSAA and 4SC at baseline. r: Pearson coefficient, ρ: Spearman coefficient; *: statistically significant at 0.05, **: statistically significant at 0.01. Source Table 2* of briefing document 20180108

		6MWT		NSAA		4SC		Age		Height	
Proposed gait Variables	N	P	R	ρ	R	ρ	r	ρ	r	ρ	r
50th Percentile stride length (m)	45	0,552 **	0,649 **	0,554 **	0,607 **	0,126	0,066	0.263	0.312 *	0.353 *	0.394 **
95th Percentile stride length (m)	45	0,679 **	0,772 **	0,779 **	0,816 **	-0,301 *	-0,251	-0.073	-0.004	0.067	0.125
50th Percentile stride velocity (m/s)	45	0,652 **	0,758 **	0,712 **	0,724 **	-0,161	-0,195	-0.161	-0.114	-0.077	-0.108
95th Percentile stride velocity (m/s)	45	0,542 **	0,616 **	0,645 **	0,689 **	-0,547 **	-0,484 **	-0.505 **	-0.488 **	-0.425 **	-0.396 **
Distance walked/hour	45	0,371 *	0,436 **	0,424 **	0,435 **	-0,304 *	-0,313 *	-0.449 **	-0.431 **	-0.447 **	-0.409 **

Sensitivity to change, variability, known groups discrimination

Variability for stride length and stride velocity decreased for long recording durations up to a plateau at 180 hours where the variability was less than 5% (see above). Therefore, in ambulant DMD patients, 30 day wearing periods are proposed in order to ensure that enough data (sufficient compliance) are generated during a set period for almost all patients. The duration of 30 days ensures at least 180 hours of recording in patients wearing the device at least once every two days (12 hours/day). In clinical trials one month measurement periods will be proposed at various study time points (e.g. baseline, months 3, 6, 12).

The Applicant presented data in support of the sensitivity of the proposed 5 gait variables at 6 and 12 months compared to the 6MWT. Applicant's data from subjects older than 6 years and with a 6MWT baseline distance lower than 450 meters show a significant decrease of -2.4% for the 95th percentile of stride length, -4.7% for median stride velocity and -8.5% for the 95th percentile of stride velocity. In studies in DMD, the mean change from baseline in the 6MWT at 24 weeks ranged from 0.9% to 4% and at 48 weeks from 6% to 8%. The changes observed for Applicant's variables are thus in line with those observed in DMD studies for 6MWT.

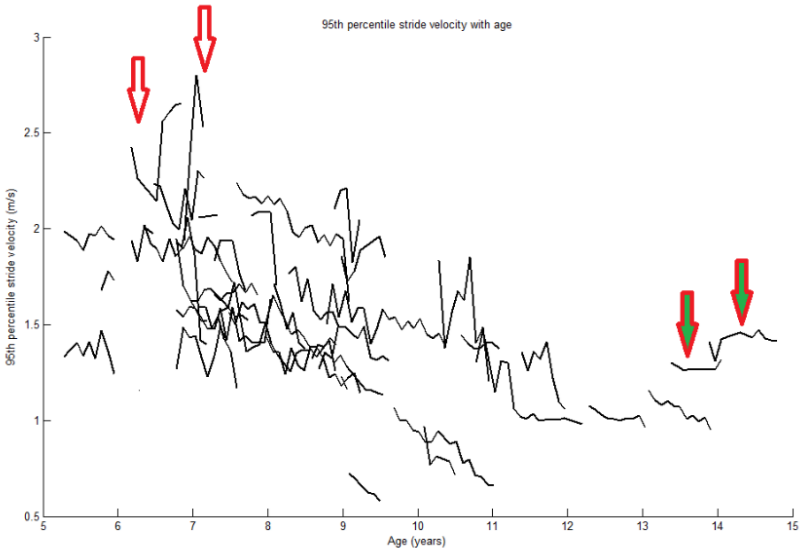
Apart from that, preliminary results based on baseline data from the "ActiLiège" study indicate that descriptive variables, such as stride speed and stride length discriminate between controls and DMD accurately, especially when expressed as 95th percentile.

It appears comprehensible that the individual 95% percentiles are more sensitive to change than the medians suggesting that the maximum ability to walk of a given patient appears to be a more sensitive

endpoint than the average or median stride length or velocity. On the other hand, larger percentiles might be more prone to outliers generated by artificial effects.

Though it is assumed that the 95% percentile could still be robust enough considering the amount of data taken from a given patient within a period of 180 h, a more comprehensive evaluation of the effects of individual outliers would be helpful to appreciate the robustness of the considered parameters. During the discussion meeting two kinds of outliers were discussed, see Figure 1 below.

Figure 1 Evolution of proposed 95th percentile of stride velocity as a function of age. [Source Figure 25 of Applicant's Responses to CHMP's issues for Discussion]



1. Two patients with well-preserved ambulation at the age of 14 (Red/Green arrow) have 6MWT of 455 m and 473.5 m at baseline, which strongly demonstrates a well-preserved ambulation. These two patients present a rather stable evolution at a 1-year period
2. Two patients with a large variability (RED/WHITE arrow) at 1-year period. In these patients, the variability occurs much more clearly in the top performance (95th percentile) and is not present in the 50th percentile evolution (Median).

When considering the whole group of patients, the variability related to the use of the 95th percentile value of stride speed and stride length reach 4.5% rather than 3.2% when using the median for the same variables. However, the sensitivity to change of the 95th percentile still appears much greater (see figure 26 below of Applicant's Responses to CHMP's issues for Discussion).

Clinical relevance and MCID

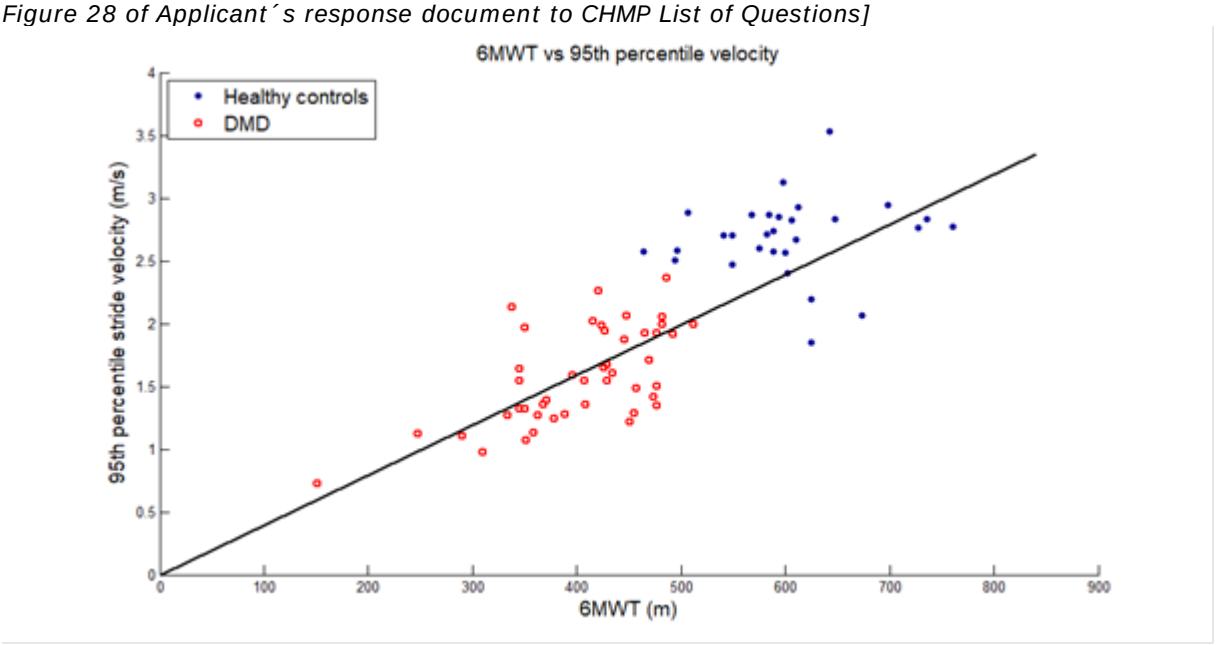
Patients with at least 50 hours of recording for both of the two first periods of 15 days were selected for the analysis. 40 patients were included; the variables were calculated on the recordings of the first 15 days and on the recordings of the following 15 days. The intra-correlation has been calculated taking the correlation between these two series and given in Table 3. The mean and the standard deviation of the variables have also been calculated.

Table 3 MCID estimated for the Proposed Gait variables using the standard deviation of the baseline population and the intra-correlation. [Source Table 3 of briefing document 20180108]

	Mean	SD	Intra-correlation	MCID	Relative MCID
50th Percentile (median) stride length	0.825 m	0.087 m	0.957	0.0179 m	2.17%
95th Percentile stride length	1.101 m	0.129 m	0.951	0.0284 m	2.58%
50th Percentile (median) stride velocity	0.836 m/s	0.116 m/s	0.942	0.0278 m/s	3.33%
95th Percentile stride velocity	1.578 m/s	0.391 m/s	0.937	0.0985 m/s	6.24%
Distance walked/hour recorded	162.6 m/h	87.9 m/h	0.839	35.3 m/h	21.7%

There are several ways of estimating MCID. The Applicant used the methods applied by Craig Mc Donald et al. (2010) when they estimated an MCID of 30 meters for the 6MWT. Using the same methods, a MCID of 0.1 m/s for the 95th percentile stride speed, (which corresponds to 36 m in 6 min at top speed), was found. The number of meters in the 6MWT that corresponds to this MCID was estimated based on a linear correlation between the 95th percentile stride speed and the 6MWT. The slope of the linear correlation between the 95th percentile of stride velocity and the 6MWT is 0.42 m/s per 100 m of 6MWT (see Figure 28 in Applicant´s response document to CHMP List of Questions).

Figure 2: Correlation between 95th percentile stride velocity and 6MWT for DMD patients. [Source Figure 28 of Applicant´s response document to CHMP List of Questions]



It means that a delta of 0,1m/s in the 95th percentile stride speed is correlated to a delta of 23,8 m in the 6MWT (100/4.2). Thus, 0.1m/s for the 95th percentile stride speed correspond to 24 meters during 6 minutes at maximum speed.

Upon further request the Applicant also presented data on the MCID comparison for the NSAA.

The correlation slope between 95th percentile stride speed and non-linearized NSAA (scored on 34) is 0.04295 m/s per 1-point NSAA. It means that 0,1m/s on the 95th percentile stride speed is correlated with 2,32 points on the non linearized North Star, which corresponds approximatively to 7 point in the linearized North Star. This is considered as the MCID for NSAA (Mayhew et al. 2013)

Predictive validity

Other anchor based approaches to estimate MCID would be to relate a drop in the 95th percentile stride speed with a probability to lose ambulation, and / or with HrQoL measures, and other scales such as global assessments. Such approaches are encouraged.

However, for this a significant higher number of patients and longer follow-up would be required. A more robust correlation and clearer relationship with measures shown to be predictive of loss of ambulation could be supportive, notwithstanding that multiple intercurrent issues may impact on loss of ambulation.

Other gait variables

It is agreed that currently used endpoints in DMD trials such as the 6MWT, NSAA and 4SC have deficiencies as described above and that the proposed variables measured by a suitable and valid wearable device are promising. The system could potentially provide improved measurements of the 6 MW Distance. However, data on quality of walking, fall, sway, real world stairs, time to stand, and correlation with patient well-being are not available. It appears that the sensors of the system can record additional data apart from stride length and stride velocity and potentially related to gait pattern. The Applicant is strongly encouraged to conduct further work on this. The Applicant is also encouraged to conduct further work in younger and in non-ambulant patients. The use of upper limb measures is also considered of clinical interest; validation against current assessment tools is encouraged.

CHMP Conclusion

Based on data provided by the Applicant and State of the art science in the field,

CHMP considers that for ambulant Duchenne Muscular Dystrophy (DMD) patients 5 years of age and above:

- Stride velocity 95th centile (SV95C) 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 ability directly and reliably in a continuous manner in a home environment and as an indicator of maximal performance.
- Stride velocity 95th centile may also be used to quantify a patient's baseline performance in such studies.
- Regarding use as primary endpoint for pivotal trials in this setting, although promising, more robust data gained with additional patients and longer follow-up could be beneficial: thus strengthening the long term correlation of SV95C with functional tests, expanding normative data and further supporting the justification of the clinical relevance of the proposed MCID in the PEP setting is recommended.

Questions

List of Applicant's Questions posed to the CHMP

The applicant posed 4 questions to the CHMP

1. Does the EMA agree that the gait variables proposed are clinically relevant and well correlated to other validated outcomes such as 6MWT or NSAA?
2. Does the EMA agree that the variability, and the influence of compliance on variability, on stride length and stride speed as recorded by the device/system is acceptable?
3. Does the EMA agree that the variation on a 6 months and a one year period, and the standard deviation of this variation is compatible with clinical trials lasting six months or one year in the studied population?
4. Considering the low variability, the clinical relevance, and the sensibility of the methods, does the EMA agree to qualify the Proposed Gait Variables as measured by a valid and suitable wearable

device as an endpoint to demonstrate efficacy in drug development clinical trials of ambulant DMD patients?

List of clarifications requested by SAWP/CHMP from the Applicant

During the procedure, SAWP initially requested clarification on the following issues:

- A detailed proposal for context of use
- A discussion of SV95C Vs current Primary endpoints in this indication.
- Information on variables measuring quality of walking, fall, sway, real world (non-controlled) stairs, time to stand, and correlation with patient well-being.
- How potential confounding covariates have been adjusted for, and the impact of extending duration of recording on 6MWT vs 180hrs SV95C
- For the 180 hours data, the distribution of data recording, possible patterns (AM/PM/every day,
- Test /retest data for gait variables.
- Evolution of the device throughout the validation studies.
- Validation in healthy controls.
- Study designs in relation to the validation objective
- Patient characteristics at baseline
- Compliance and patient burden, missing data in the validation studies and any factors that contributed to these.
- Regarding evolution at 6 and 12 months; the impact of small numbers and bias, confounding by age, height and steroid regime.
- Analysis of patient slope data and corresponding figures.
- Analysis of discrimination between more or less severe baseline groups, and those with or without steroids, at baseline, and, longitudinal changes in these groups
- A justification of the clinical relevance of the proposed MCID in more or less severe groups.
- The longitudinal correlation between 6MWT and SV95C
- Measures to ensure data quality specific to continuous monitoring
- General comments regarding data privacy and protection and how this will be handled.

During the procedure SAWP requested clarification on the following issues at the Discussion meetings

- Plans to generate normative data in healthy age-matched controls.
- The influence of compliance on variability, on stride length and stride speed
- The potential influence of outliers on the 95th percentiles of stride length and velocity.
- How changes in stride velocity are linked to a clinically relevant effect.
- Plans to generate more comparative data to conventional ambulation endpoints.
- Plans in interventional clinical trials with respect to the
    - adequate measurement period in randomized controlled trials;
    - sensitivity to change
- Plans of validation in non-ambulatory or younger DMD patients and other indications
- Usability of additional data apart from stride length and stride velocity which could potentially provide information on gait pattern, the quality of walking, falls, sway, climbing stairs and time to stand.

Further to the discussion meeting, SAWP requested further clarification on the following issues

- An explanation of the 24 m statistic in the context of the MCID discussion, and relationship between the 36m, (distance at MCID 95CSV), 23M (distance in 6MWT from correlation) and 30m (distance at MCID 6MWT) –
- Further background and derivation on the 30m MCID for the 6MWT and association with loss of ambulation.
- Any further data / plans for longitudinal correlation with NSAA, 4SC/ the MCIDs of these
- relevant details from ongoing protocols

Data submitted by Applicant

Applicant's Briefing document 20180108.

Summary

Over the last 10 years, most of phase 3 protocols in DMD have used the 6MWT as the primary outcome. This test was initially developed for cardiorespiratory diseases. Clinical experience in the

Duchenne Muscular Dystrophy (DMD) field made it clear that personal motivation (17) is a major factor involved in assessments result, and there is a non-linear variation through the disease course.

Over the last two years, other outcomes such as the 4 stairs climbing test or more recently the North Star Ambulation Assessment scale (NSAA) have also been utilised.

In contrast with the episodic measurement of a patient's peak performance during hospital visits (but which depends on the patients' motivation and clinical condition at the precise time of assessment), monitoring the patients' real life would allow a continuous and completely objective assessment of daily motor activity, and a much more clinically relevant and powerful outcome measure to demonstrate efficacy predictions in DMD clinical trials. Indeed, such measures would not only represent real patient performance during daily life, but also the possibility of averaging the data over a period of time (e.g.1 month) which would make the measure much less dependent of short term clinically meaningless variations that may strongly affect a time-specific assessment.

There is currently no method for continuous home monitoring of these patients, which is a major limitation in efficacy predictions of emerging drugs.

In order to tackle this issue, a device based on magneto-inertial technology was developed; the wearable device and system proposed to measure the gait variables in this qualification which is able to precisely capture all movements through the sensor measurements and dedicated algorithms allowing precise qualification and quantification of patient activity, in non-controlled environment.

Several variables that are robustly measurable in ambulant patients and clinically relevant in the context of DMD have been identified. These are the 95th Percentile of the stride velocity (primary), the median stride velocity, the 95th percentile and the median stride length (secondary), and the distance walked/recorded hour (tertiary). These can constitute important outcome measures as a primary clinical endpoint in all pivotal studies for ambulant DMD patients older than 5 years, with a 6MWD of above 300 meters.

This wearable device and system solution presents a significant advantage over the classic six-minute walking test (6MWT) or clinical scales. It does not rely on patient motivation or subjective assessment and provides continuous monitoring. Thus, it considerably decreases the variability of assessment, which would allow for a smaller number of patients to be included in a study. Using the wearable device and system is likely to also overcome variations in practice encountered across different centres / countries, which also has a significant impact on global studies.

Our proposal creates added value in the scope of rare diseases, by accelerating clinical development and creating new economic activity.

Table 1. Brief summary of individual study analyses and results

Objective	Method	Results
Demonstrate that foot trajectory of ambulant patients as assessed by the magneto-inertial sensor correspond to the real distance as manually measured	We have measured simultaneously the distance performed during 6MWT using the wearable device and system and using the classical method in 31 tests performed by 23 different patients within a large range of clinical conditions.	The 6MWT distance difference between wearable device and system and the corrected reference was within 5%.

Objective	Method	Results
Measure the reliability of Proposed Gait Variables measured by the wearable device and system	Using 28 patients assessed in non-controlled setting, we have studied the relation between the recording period averaging and the variability of the measure, by tracing the Sysnav Variance.	Good stability with low variability from 2.22 and up to 4.41 % for the 95th percentile of stride length and 95th percentile of stride velocity respectively for 180h of wearable device and system use.
Cross validate these measures with reference to clinical outcomes	We have studied the relation in 45 DMD patients between stride velocity, stride length, distance performed per hour and 6MWT, North star ambulatory assessment score and 4 stairs climbing test score for DMD.	Good correlation of 95th percentile of stride length and velocity with 6MWT at baseline (0.68 and 0.54 respectively) and of NSAA (0.78 and 0.64 respectively).
Study the sensitivity to change at 6 months of variables measured by the wearable device and system	We have studied 31 patients for a full 6 months period. , For a subset of 20 patients who were older than 6 years and walking less than 450m in the 6MWT, for over 6 months and among them, 7 over 1 year.	Significant decline of 95th percentile of stride length (2.4%), median stride velocity (4.7%) and 95th percentile of velocity (8.5%) over 6 months for subjects older than 6 and having a 6MWD at baseline lower than 450m
Sample size calculation	We have estimated the number of subjects to include per group in a randomized clinical trial to show a stabilization of the most sensitive outcome using the wearable device and system	Gait variables measured by wearable device and system could reduce the number of subjects to include in a clinical to 20-60 subjects per arm.

Background information on the disease and the intended context of use

Duchenne muscular dystrophy (DMD) is devastating childhood pathology, affecting 1 in 5000 boys (5). DMD is an X-linked disorder caused by mutations in the dystrophin gene and it is the most frequent muscular dystrophy in boys. Diagnosis is confirmed by the demonstration of an out of frame mutation in the dystrophin gene, sometimes requiring muscle biopsy for confirmation. The disease causes progressive and unyielding muscle weakness frequently identified in the early toddler years when the child begins to miss development motor milestones (6). Loss of ambulation occurs generally around the age of 12. Survival is up to the 3rd and 4th decade. Glucocorticoid treatment is the main method to maintain muscle strength and pulmonary function for as long as possible (7). Recently, TranslarnaTM (Ataluren) has been granted conditional marketing approval by the EMA (for nonsense mutations that represent about 10% of the mutations) and Exondys 51TM (Eteplirsen) (for deletions theoretically treatable by exon skipping 51, that represent about 13% of mutations) by FDA.

The number of potentially effective therapeutic approaches in DMD are increasing (8) and thus the demand for validated outcome measures to demonstrate clinically meaningful therapeutic response over time in clinical trials (e.g. one year) is higher than ever.

The 6MWT (the maximum distance covered in meters by the patient during six minutes) is considered the current gold standard evaluation in Duchenne muscular dystrophy (DMD) trials (9) that are focused therapeutically on preservation of ambulation.

However, this measurement reflects patients' peak performance in a clinical setting and addresses only ambulant patients. Most of current trials assess patients over 6 or 7 years of age with performance between 300 and 450 m, because patients of this group seem to have a linear decline over 1-2 years. Patients under 7 years of age are more difficult to assess, notably because most of time they progress on an annual basis (10). Patients scoring below 325 m are at high risk of losing ambulation in a two-year period, and as a result are excluded from being considered in many drug trials.

So far, emerging data from clinical trials fall short of delaying disease progression; one impediment was the failure to demonstrate a significant improvement in the primary outcome measure, determined by the 6-minute walking test in some studies (11, 12). It seems that earlier treatments are more efficient (13), which is understandable given the disease pathophysiology, but since patients tend to increase their motor performance until about the age of 7, most trials focus on patients who seem to be in a linear decline phase.

Furthermore, there is no validated biomarker to demonstrate an early benefit of treatment in patients for which disease progression has not yet begun.

Context of Use

The device and system to record the Proposed Gait Variables for qualification today, is a validated device for monitoring ambulation in patients with DMD over 5 years of age. It is a wearable device, worn continuously during day time hours with one device as a wristwatch and another near the ankle, and docked to transfer data and recharge overnight.

The wearable device and system has been designed for use in pivotal clinical trials testing the efficacy of therapies to modify the progression rate of DMD (measured as loss of ambulation). These trials currently enrol ambulant patients that are able to complete a minimum of 300m walking during a six-minute walk. The six-minute walk test however is considered to have many limitations for use in this targeted population which significantly impacts on its suitability.

The wearable device and system quantifies patient's ambulation ability in a continuous manner across five different variables. It detects the gait parameters directly and reliably every time the wearer walks. The device does not rely on individual patient calibration and contrary to optical motion capture system it can be used continuously, including in the home environment.

Five variables are robustly measurable in ambulant DMD patients while wearing the wearable device and considered clinically relevant. These are the 95th percentile of the stride velocity, the median stride velocity, the 95th percentile and the median stride length, and the distance walked/recorded hour. These are important variables to be considered as important outcome measures that can be used as clinical endpoints in pivotal studies for ambulant DMD patients older than 5 years. The additional threshold of above 300 meters can also be applied if considered necessary to correlate to current practice.

The variable of most significance (clinically and statistically) is defined as the 95th percentile stride velocity, and proposed as a primary or secondary endpoint as appropriate to the study design. This is considered to be a superior means to measuring ambulation over time compared to the currently used six-minute walking test. Because the 95th percentile of the stride velocity reflects the fastest strides taken by a patient it is a good indicator of the peak performance that the patient is able to do. The result presented here also indicates that amongst the variables considered, the 95th percentile of the stride velocity shows the largest decline in a 6-month period. For these reasons, it is expected to be the most sensitive variable to detect a clinical change. The other variables proposed as exploratory

endpoints are the 95th percentile of the stride length, the median stride length, the median stride velocity, and the distance walked/recorded hour.

Background information on the product

Outcome measures currently used in therapeutic trials in the DMD ambulant population are the 6 minutes walking test (14), the North Star Ambulation Assessment (NSAA) (15) and the timed 4-stair climb (16). All these assessments are episodic, and provide a snapshot overview of the supposed maximal patients' functional ability. They also suffer from specific limitations:

- The 6 minutes walking test is the distance walked by a patient asked to walk at the pace of maximal effort (running is not allowed) turning between two 25m-distanced cones. It is an exhausting measure for neuromuscular patients, and it is highly dependent on patient motivation on the day (financial incentive for instance has been demonstrated to boost patients' performance (17)) and ability to concentrate (most of Duchenne patients are not only young but also have attention deficit). The accepted variability for a given patients is about 15%, and the clinically meaningful change is defined to be about 30m (16). Adequate training of evaluators is mandatory and a standardized script is used by all evaluators. There remains however a part of subjectivity, for instance in the way the evaluators encourage the patients through the test.

- NSAA includes 17 different functional activities, including a 10-m walk/run, rising from a sit to standing, standing on 1 leg, climbing a box step, descending a box step, rising from lying to sitting, rising from the floor and jumping. Patients are graded on a 3-point scale (18). It is a subjective measurement, and the clinically meaningful change is very high (8-9 points on the linear scale) (19).

- Four stair climbing test is the minimal time required by the patient to climb four stairs. It not only implies power, but also motor praxis. This timed test may be very rapid, in the order of 2 seconds, which overpowers the reflex time of the patients and the physiotherapist. This leads to either an increase of the number of patients per trial, or to an increase of trial duration.

Considering the declining ambulation trend in DMD patients, gait analysis provides relevant information with regards to the progression of the disease and the benefits of a therapy. Gait analysis of DMD has focused primarily on short-distance assessment using standard laboratory motion capture systems (20, 21). Spatial and temporal gait measurements like walking speed (cm/s), stride length (cm), stride time (s) were assessed in typically developing children (age range 1.3 to 10.9 years) using GAITRite® with a repeatability which ranged from poor to excellent (22). Such measurements are limited by the difficulty of the closed environment of a lab, which cannot convey the actual daily life condition.

Inertial sensors based on accelerometers and gyroscopes have also been used in motor activity and other health status monitoring systems (stroke, Parkinson disease, cerebral palsy) (27). Motion analysis measured with magneto-inertial sensors represents an objective evaluation of the movement in laboratory environment and in everyday life conditions (2). Gait and posture evaluations have determined few variables useful in the evaluation of the DMD patient (21, 26, 28). Gait during the 6MWT was previously assessed by McDonald et al. (14) using an activity monitor based on accelerometry. The number of steps was counted by the device while velocity and step length were derived indirectly from the distance walked. This contrasts with the wearable device and system which allows direct and continuous measurements of stride length and velocity including in home based environment.

Power calculation for pivotal studies depends on the beta and alpha error, and on the mean change and the standard deviation of change. In DMD, taking into account a mean change of 30 meters in the 6 MWT and a standard deviation of 80 meters, it currently leads to groups over 100 patients, and duration of 1 year minimum. These are extremely challenging targets for a rare disease, especially

when several drugs are competitively studied at the same time. Currently there are 10 known companies developing drugs in this indication.

For DMD patients, changes in walking parameters can guide clinical management and be primary endpoints in interventional studies. Thus, it is important to determine whether a change in function is clinically relevant. However, all the above measures are poorly applicable to ambulant patients below a threshold of performance, and even less to non-ambulant patients. This creates a gap of

around 4 years between the two “classical” groups of patients for clinical trials: the ambulant ones walking between 300-450m in the 6MWT, and the non-ambulant patient with a vital capacity of below 80%. Indeed, below 300m, the risk of losing ambulation (and thus to lose all of a sudden 300m or all NSAA points) is high, and this population is unable to climb 4 stairs most of the time.

In addition, all existing measures require patients to travel to specialist neuromuscular centers, often some considerable distance away. This alone causes major stress and disruption to patient and family.

These limitations demand an innovative approach that can monitor patient function continuously, passively, that can be applied also to patients losing ambulation and that can be done away from the hospital environment.

The wearable device and system allows a continuous measure from 5 years of age to advanced non-ambulant stages, providing a consistent real-life monitoring approach across the full disease spectrum, and as a result also fills the gap between different groups of patients targeted for clinical trials.

The wearable device and system is the combination of two identical portable battery-operated sensing devices (25g; 43/36/16mm) and a docking station (Figure 1). Based on magneto-inertial technology, it provides continuous recording and analysis of movements and trajectory. The system aims to measure the physical activity of a patient as measured by the sensors in the three-dimensional space.

The wearable device and system is designed to be used in a home-based environment with battery operation lasting 16 hours, and suitable for use in ambulant and non-ambulant subjects. It can be used from 5 years of age until very advanced stage of the disease, when the Brooke score is 5 (i.e. when the patient is able to hold a pencil).

For ambulant patients one device is worn as wristwatch and the other placed near the ankle, for non-ambulant patients, the second device is placed on the armchair.

Data are stored in an internal memory inside each watch-like device and transferred to the docking station, every night, when they are put to charge. Data collected in the docking station can be sent anonymously directly via Internet on a dedicated and secure web-cloud or can be stored on an internal USB drive for up to three months. Computation of variables is performed afterwards for each patient using the recorded magneto-inertial data.

The strides trajectories are reconstructed from the data provided by the wearable device attached to the ankle. From this trajectory, gait parameters are extracted and in particular the stride length. Figure 3 illustrates the ankle trajectory and orientation reconstructed from wearable device and system measurements during one lap of a 6MWT. Further work is also planned to generate data from patients wearing the device on both ankles, in order to increase the precision in other clinically meaningful outcome, such as stairs climbing.

Figure 1. Main components (A), the wearable device and system *attached to ankle (B) and to the wrist (C)*

Quality development

N/A

Non-clinical development

N/A

Clinical development

To validate relevant measures for ambulant subjects, the following work has been done to date:

1. Study the validity of gait variables measured by the wearable device and system 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. Measure the variability of gait variables measured by the wearable device and system and study the influence of poor compliance to generate recommended minimal use.

3. Cross validate these measures with 6MWT and NSAA.

4. Study 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 6MWT.

5. Evaluate the number of subjects that would be needed to include in a clinical trial to show a significant stabilization of disease evolution.

No previous scientific advice has been requested from the CHMP, national or non-EU (e.g. FDA)

This is a Paediatric only application.

Regulatory status

The latest device which was redesigned for cosmetic purpose is CE marked. This new device has passed independent tests for security (EN 60601-1:2007 professional healthcare and EN 60601-1-11:2015 at home), electromagnetic compatibility (IEC 60601-1-2:2014 professional healthcare and IEC 60601-1-2:2014 at home), biocompatibility (ISO 10993-1:2009) and usability (IEC 60601-1-6:2010 and IEC 62366-1:2015) for CE marking.

No safety issues have been noted with the device to date.

No bridging data is considered necessary as the only changes in the device has been cosmetic and not linked to the sensors and analytic software.

Software development follows EC 62304.

Data protection and privacy issues are not an issue of concern because:

- The data recorded and analysed are only motion sensors of wrist and ankles which do not reveal any private information. For example, contrary to devices based on GPS, there is no absolute positioning possible and no private identification such as name, address or location from the wearable device and system measures.
- Data is stored in a proprietary binary format so even if a third party had access to some recordings, it could get any readable data without the extracting software.
- Communication channels are encrypted (SSH, HTTPS)
- Only the researcher has access to a patient identifier code that indicates that a device has been used by the same patient in a certain recording period. But the link between a patient identifier code and the personal details is only stored by the clinical centre together with the clinical and medical information.

Rationale for seeking advice (Qualification)

The objective of our request is to propose a new marker for continuous monitoring of patient movement in neuromuscular disorders using wearable technology as performance outcome (PerfO) measure.

Measuring disease progression and response to treatment in Duchenne muscular dystrophy (DMD) and other neuromuscular disorders is a challenge for all clinical development plans. Recent difficulties in formally demonstrating the efficacy of new medications (1), underline the challenge and the urgency to develop new and reliable outcomes for this population.

Current methods, such as the 6 minutes walking test (6MWT), the North Star Ambulation Assessment (NSAA) or the 4-stair climbing test require a high number of patients to reach statistical power (NCT00592553 : 174 patients, NCT01826487 : 230 patients; NCT01865084 : 331 patients; NCT03039686 : 159 patients; NCT02851797 : 213 patients). Placebo data from a recent large placebo controlled study (NCT01865084) conducted in declining patients aged more than 7 years and walking less than 400m in the 6MWT demonstrated ratios between annual change and standard deviation of change (6MWT : 1,94; NSAA : 1,35; FSC : 2,83, data available on clinicaltrial.gov) that confirm the need for such large population in phase 3 trial, even in this well-defined subgroup of declining patients (10).

This has recently led to a trend is pivotal trials study design is DMD, to increase study duration to 18 (NCT02851797) or 24 months (NCT02500381)

One of the reasons that probably explains the variability of the decline on a year period is related to patient motivation at the time of assessment (Alfano et al. 2015). All these assessments are episodic, and only provide a snapshot overview of patients' functional ability. These limitations demand an innovative approach that can monitor patient function continuously, passively and away from hospital clinics.

Motion analysis measured with magneto-inertial sensors represents an objective evaluation of the movement in laboratory environment and in everyday life conditions (2).

We have designed a device using magneto-inertial sensors and new algorithms to evaluate selected variables in the home environment. The wearable device and system is an innovative system that enables new and objective variables related to a patient's limb motion to be measured (3). Device

manual and manufacturing details about the device can be found in appendix 1. Compared to conventional actimetry devices, one novel feature of the wearable device and system is the capability to reconstruct trajectories and orientations. The wearable device and system is designed to be used in ambulant and non-ambulant subjects.

The wearable device and system was first used in a clinical study setting in 2012 for home based monitoring of upper-limb movements in non-ambulant Duchenne patients (NCT01611597) demonstrating the autonomy and feasibility of the device use (3). Variables were determined to clinically characterize the upper limb activity of patients. In a second step, they were correlated with the efficacy of patients during a standardized and validated task, which also allowed testing the reliability.

Work done to date using the wearable device and system in ambulant patients have identified several variables like median stride velocity, median stride length, and the distance walked per hour. They are robustly measureable in ambulant patients and most importantly are also clinically relevant in the context of neuromuscular diseases.

Applicant's questions

Question 1

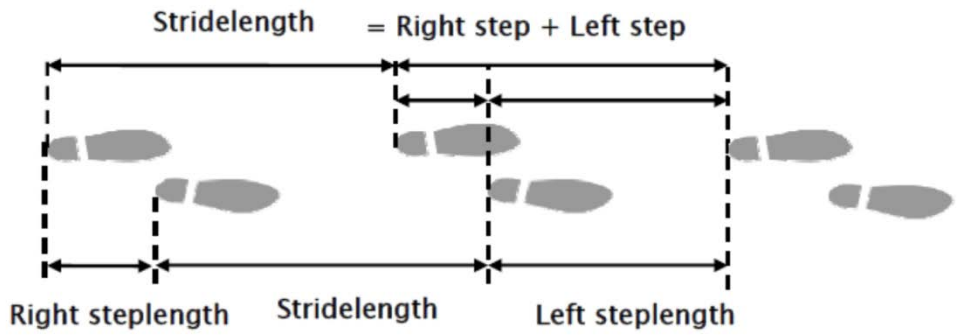
Does the EMA agree that the gait variables proposed are clinically relevant and well correlated to other validated outcomes such as 6MWT or NSAA?

Applicant's position

Walking is an activity requiring the use and coordination of multiple muscles and is therefore directly affected by neuromuscular diseases. When walking becomes constrained by muscle weakness, gait parameters change in response. So, by measuring gait parameters that are correlated to the disease progression, it becomes possible to study the patient response to treatments, stabilisation or assess the disease progression.

A gait cycle is made of two alternating phases, in the first phase the foot is in contact with the floor, in the second swing phase the foot is in the air and moves forward. Based on this cycle, we can define the step and the stride as presented Figure 2. A step starts when one foot touches the floor and ends when the other foot touches the floor. A stride also starts when one foot touches the floor but ends when the same foot touches the floor again at the end of the swing phase. This definition implies that there are two steps during one stride.

Figure 2. Illustration of step and stride definitions



External factors linked to the normal development of gait need to be taken into account e.g. age and patient growth. Other studies exploring the normal gait cycle have defined that step length increases

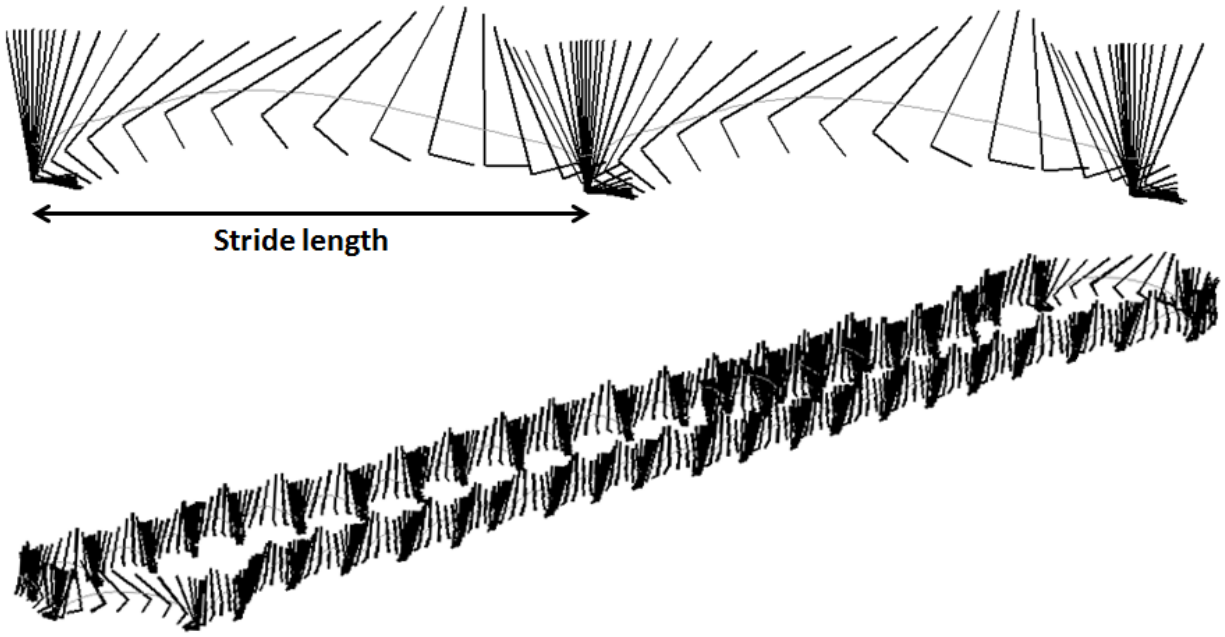
with age/ height/ leg length throughout childhood and up to around 14 years of age, and then generally stays constant.

Gait in children with DMD is affected by progressive muscle weakness, muscle fatigue and joint contractures (hip, knee and ankle). Natural gait velocity is most of the time reduced in DMD children in comparison with that of controls subjects (23). This change is due to decreased step length. When the walking velocities are similar between the two populations, the patient increases the cadence with shorter and faster steps, as a compensation for the reduced step length (24). Typically, when the muscles become weaker, a patient tends to walk at a slower pace and make shorter steps on average. This way, the center of mass is less displaced and gait is less tiresome and less risky (25). Previous gait pattern analysis in DMD patients showed an increase of anterior pelvic tilt and rotation, a decrease hip extension and decrease or absent ankle dorsiflexion (23-26). Stride length, step width and velocity were normalized with respect to the subjects' height by D'Angelo et al. (26). However, height is a complex confounding factor in DMD, since it is related with age, and so with the stage of the disease, but also with steroids intake, which slow down the disease but also the growth. In addition, the error on height measure (especially in children with achylean contracture) may also induce additional noise on the final outcome.

Gait presentation in young patients with DMD is particular, sometimes tiptoed and most of the time waddling. Regardless of the gait pattern of patients, the wearable device and system was able to identify the strides and trajectory. The measurement of foot trajectory is necessary to gait assessment during daily activities in order to describe the gait's characteristics (29).

The distance walked per hour (or other cumulative variables such as the number of steps during a typical day) can vary a lot in regard to the socio-environmental and meteorological factors. Qualitative assessment of stride parameters (23-26) (kinematics and kinetics parameters like angles, forces, moments and powers) require a laboratory setting and thus remains dependent upon hospital environment.

Figure 3. Wearable Device and System reconstructed trajectory during two strides (top) and one lap of a 6MWT (bottom)



The wearable device and system detects the gait parameters directly and reliably every time the wearer walks. The strides are automatically detected using the ankle acceleration and angular velocity measurements recorded. The motion seen by an ankle during a stride may vary from strides to strides, from person to person and for various types of walks but the general gait cycle is common to all strides. During a stride the foot moves forward with a phase where the leg swings around the hip. This makes a general pattern that is detectable with the acceleration and angular velocity measured on the ankle. This explains why step counters worn on the ankle are more reliable than devices placed on other locations.

But where the wearable device and system used distinguishes itself from other ankle worn step counters is its ability to measure the 3D trajectory followed by the ankle during every stride. Other devices worn on the ankle at best estimate the stride parameters based on recognizing patterns or motion intensity to deduce the length. But this does not enable a precise estimation of stride length. Individual calibration may be used to reduce inter-user variability but even an individual user does not always walk in the same manner making it difficult to predict the length. The wearable device and system used approach is fundamentally different as it computes the 3D trajectory of the ankle to deduce the length.

To compute the trajectory, a double integration of the gravity free acceleration is performed. This is reliably for a few seconds integration but grows quadratically for longer duration. To overcome this issue the integration is performed only while the foot is lifted in the air which is a sufficiently short duration for a good trajectory computation. When the foot touches the floor, the ankle speed is corrected using a model patented by Sysnav (WO2017060660). Low error sensors are also needed to compute a reliable trajectory. The wearable device sensors are therefore calibrated using a rate table and temperature compensated, this is not done for most activity trackers.

So this technique does not rely on individual patient calibration and contrary to optical motion capture system, it can be used continuously including in the home environment. Also, because magnetic

measurements are not explicitly used in this technique, the trajectory and the gait parameters deduced are not impacted by magnetic disturbances in the vicinity of the device.

All leg movements taking place during one gait cycle define one stride and the transition between strides occurs when the foot is on the floor.

The stride length is defined in this context as the distance between the start and the end of the stride and derived from the ankle trajectory as shown in Figure 2. The start of a stride is defined when there is a good match with a model that assumes that the lower limb is a solid rotating around the heel. This condition is detected by comparing the angular velocity and the acceleration with the model to ensure a consistent definition of stride segmentation. To utilise all data of strides taken over several days it is proposed that the best data outcome summary are the 50th (or median) and 95th percentile of the stride length of all strides detected in the considered period, for example one month of recordings. The median stride length represents the stride length that is taken by the patient half of the time. The 95th percentile of the stride length represents the highest stride length the patient is able to take 5% of the time and is therefore representative of the maximal effort that can be performed by the patient. These variables are given in meter.

The stride velocity is defined as the stride length divided by its duration, the duration being the time elapsed between the start and the end of the stride as defined by the segmentation criteria on angular velocity and acceleration described for the stride length. The proposed outcomes are the 50th (or median) and 95th percentile of the stride velocity of all strides detected in the considered period, for example one month of recordings. The median stride velocity represents the stride velocity reached by the patient half of the time. The 95th percentile of the stride velocity represents the highest stride velocity the patient reaches 5% of the time and is therefore representative of the maximal effort that can be performed by the patient. These variables are given in meter per second.

The distance walked is calculated by summing all strides taken in the period of time considered. For normalization, this distance is divided by the duration of the wearable device and system use in the period. This variable is given in meter per hour.

The wearable device and system was first used in a clinical study setting in 2012 for home based monitoring evaluation of upper-limb movements in non-ambulant Duchenne patients (NCT01611597) demonstrating the feasibility of the device use (3). Variables were determined to clinically characterize the upper limb activity of patients. In a second phase, data was correlated with the efficacy of patients during a standardized and validated task, which also allowed testing the reliability. We identified variables of interest, such as the norm of angular velocity, the elevation rate and an estimate of the power developed to move the forearm.

Work done to date using the wearable device and system have identified several measures that are robustly measurable in ambulant patients and that are clinically relevant in the context of neuromuscular diseases. These include the 95th centile of the ankle stride velocity (primary), the median ankle stride velocity, the 95th percentile and the median ankle stride length (secondary), and the distance walked/recorded hour (tertiary). Validation of variables relevant to non-ambulatory subjects is still ongoing.

Altogether, this demonstrates that the Proposed Gait Variables measured by the wearable device and system directly measure functions affected by proximal muscle weakness and achylean contracture that are key early symptoms of Duchenne muscular dystrophy.

Selected Gait variables

To evaluate ambulant DMD patients, five variables have been considered for each individual patient: the distance walked per hour, the 50th (or median) and 95th percentile stride length and the 50th (or median) and 95th percentile stride velocity.

Analyses

The validity of the Proposed Gait Variables measured by the wearable device and system was tested by assessing the agreement between the results of the 6MWD measured by the system to the actual gold standard test which is the 6MWD measured by physiotherapists. Indeed, the possibility to precisely measure the stride length and the stride velocity (and from there the distance) using a magneto inertial device located on the ankle has already been demonstrated in controls. Given the specific walking pattern in DMD and the toe walking, we specifically verified that the validated method used in control subjects could also be used in DMD. The validity of the wearable device and system approach was thus tested by correlating the results of the 6MWD measured by the wearable device and system to a fixed distance measured rigorously by physiotherapists. We chose to validate it on a distance long enough to highlight potential biases related to trajectory computation. The 6MWT, which currently constitutes one of the gold standards in DMD was thus selected for this purpose: it provides a very precise measurement of ambulation during a given time, which represents the longest time test proposed to DMD patients. The agreement was tested graphically (Bland and Altman plots) and using Pearson correlation coefficient “r” but also using Spearman’s rank correlation coefficient "ρ", as variables are not all linear.

To capture the sensitivity to change, the significance of the difference between baseline values and months 6 and 12 was tested with a Wilcoxon test.

Data

Data presented here are from ambulant DMD patients. All patients were genetically confirmed and treated with steroids. All patients were recruited from three different ERB approved studies: two natural history studies and one interventional trial. All patients’ legal representatives gave an informed consent. Given the fact that none of these three studies are published yet, we propose to share individual patient data without indicating which study they come from. The sponsor of these three studies gave their agreement for the presentation of the data.

For the validity study, data have been obtained from 23 ambulant DMD patients for 31 six-minute walking tests (some patients performed a second test 6 months later).

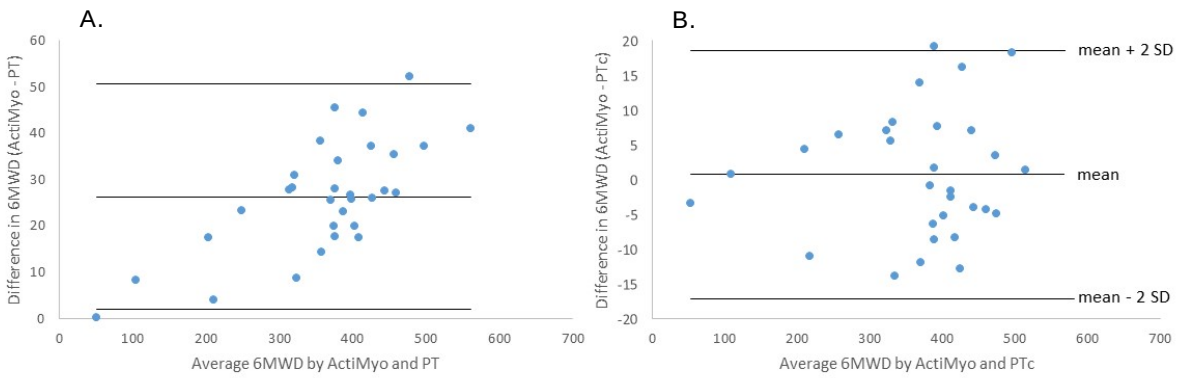
For the other analysis, data have been obtained from 48 ambulant DMD patients ranging from 5 to 14 years with a mean age of 8.3±2.1.

RESULTS

Validity study

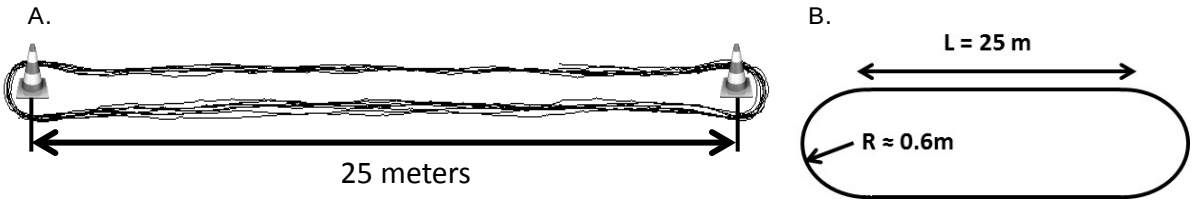
Distances measured by the wearable device and system during the 6MWT were compared to the distances reported by the physiotherapists (reference value). The system distances (mean 331.2 ± 112m) were slightly but systematically higher than the reference values (mean 307.6 ± 103.5m) and the differences were systematically highest for higher distances (Figure 4A). Nevertheless, distances measured by the wearable device and system or physiotherapists were highly correlated (r= 0.997).

Figure 4. Bland and Altman plots for maximal distance walked in 6 minutes as measured by the wearable device and system vs by physiotherapists without correction (A) and with the correction of the PT time (B)



The mean value of the difference differs significantly from 0 (26.29m ± 12.15, T-Test p-value: 0.000), this indicates the presence of fixed bias. This consistent bias is due to the "turn distance" not calculated during the physiotherapists' assessments. After adjusting the physiotherapists distance with the turn correction, the mean value of the difference is near 0 (0.75m ± 8.93, T-Test p-value: 0.643).

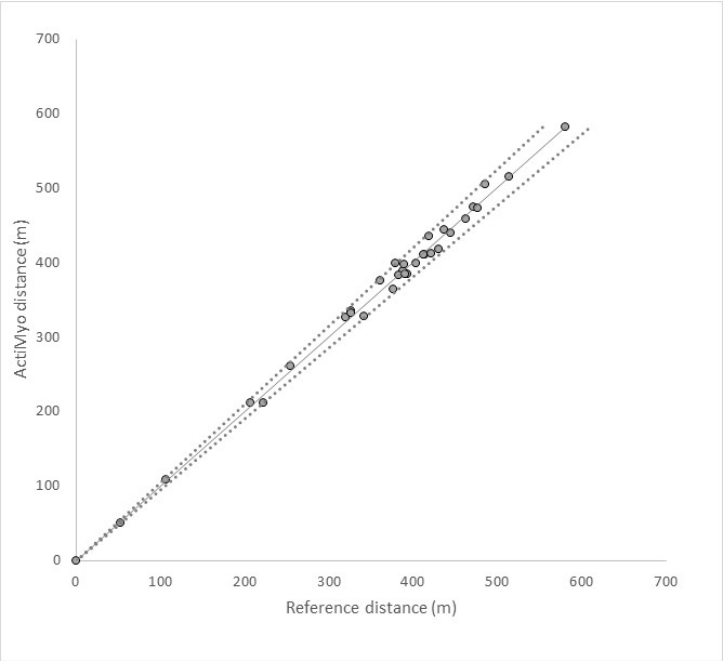
Figure 5. Trajectory of a DMD patient during a 6MWT



The extra distance needed to turn at each end of the 25-meters corridor is illustrated on Figure 5A. These turns are measured by the wearable device and system distance but not by the physiotherapist who only counts 25m for each line. The path followed to turn can vary but on average it can be modeled as a half circle with a radius of about 0.6 meter (Figure 5B).

Assuming that this model is representative, for every 25 meters walked, 1.9 meters were added to the physiotherapists' assessment to account for the turns. The corrected distance allowed then a nearly perfect correlation between the two measures (Figure 6).

Figure 6. Correlation of 6MWT distance as measured by the wearable device and system Vs by the physiotherapist



Correlation between the Proposed Gait Variables measured by the wearable device and system and usual outcome measures in ambulant DMD patients

Correlations between the proposed gait variables obtained on 180 hours of recording and usual outcome measures in ambulant DMD patients have been studied on 45 patients who wore the wearable device for over 180 hours in the first 2 months. Table 2 presents the correlation between 50th (or median) and 95th percentile of stride length and velocity, the distance walked/hour and the maximal values at baseline of the 6MWT distance, the NSAA score and the 4 stairs climbing test (4SC) score at baseline. All the proposed gait variables on stride length and stride velocity considered are significantly correlated with the 6MWT and the NSAA.

*Table 2. Correlation coefficients between the proposed gait variables recorded by the wearable device and system over 180h at baseline Vs 6MWT, NSAA and 4SC at baseline. r: Pearson coefficient, ρ: Spearman coefficient; *: statistically significant at 0.05, **: statistically significant at 0.01*

		6MWT		NSAA		4SC		Age		Height	
Proposed Gait Variables	N	P	r	ρ	R	ρ	r	ρ	r	ρ	r
50th Percentile stride length (m)	45	0,552**	0,649**	0,554**	0,607**	0,126	0,066	0.263	0.312*	0.353*	0.394**
95th Percentile stride length (m)	45	0,679**	0,772**	0,779**	0,816**	-0,301*	-0,251	-0.073	-0.004	0.067	0.125
50th Percentile stride velocity (m/s)	45	0,652**	0,758**	0,712**	0,724**	-0,161	-0,195	-0.161	-0.114	-0.077	-0.108
95th Percentile stride velocity (m/s)	45	0,542**	0,616**	0,645**	0,689**	-0,547**	-0,484**	-0.505**	-0.488**	-0.425**	-0.396**
Distance walked/hour	45	0,371*	0,436**	0,424**	0,435**	-0,304*	-0,313*	-0.449**	-0.431**	-0.447**	-0.409**

Stride length and velocity describing spontaneous walk during 180h of recording are significantly correlated with the validated 6MWT and NSAA.

We also calculated the minimally clinically important difference, using the formula:

$MCID = SD * \sqrt{(1-R)}$

Patients with at least 50 hours of recording for both of the two first periods of 15 days were selected for the analysis. There were 40 patients who satisfied this criterion.

For this group of 40 patients, the variables were calculated on the recordings of the first 15 days and on the recordings of the following 15 days. The intra-correlation has been calculated taking the correlation between these two series and given in Table 3.

The mean and the standard deviation of the variables have also been calculated on the 40 patients population for baseline on the first 15 days. The results are presented in Table 3.

Finally the MCID has been calculated using the baseline standard deviation and the intra-correlation calculated on the first 2 periods of 15 days. And a relative MCID is given by dividing the MCID by the mean of the variables at baseline.

Table 3 MCID estimated for the proposed gait variables using the standard deviation of the baseline population and the intra-correlation

	Mean	SD	Intra-correlation	MCID	Relative MCID
50th Percentile (median) stride length	0.825 m	0.087 m	0.957	0.0179 m	2.17%
95th Percentile stride length	1.101 m	0.129 m	0.951	0.0284 m	2.58%
50th Percentile (median) stride velocity	0.836 m/s	0.116 m/s	0.942	0.0278 m/s	3.33%
95th Percentile stride velocity	1.578 m/s	0.391 m/s	0.937	0.0985 m/s	6.24%
Distance walked/hour recorded	162.6 m/h	87.9 m/h	0.839	35.3 m/h	21.7%

Question 2

Does the EMA agree that the variability, and the influence of compliance on variability, on stride length and stride speed as recorded by the wearable device and system is acceptable?

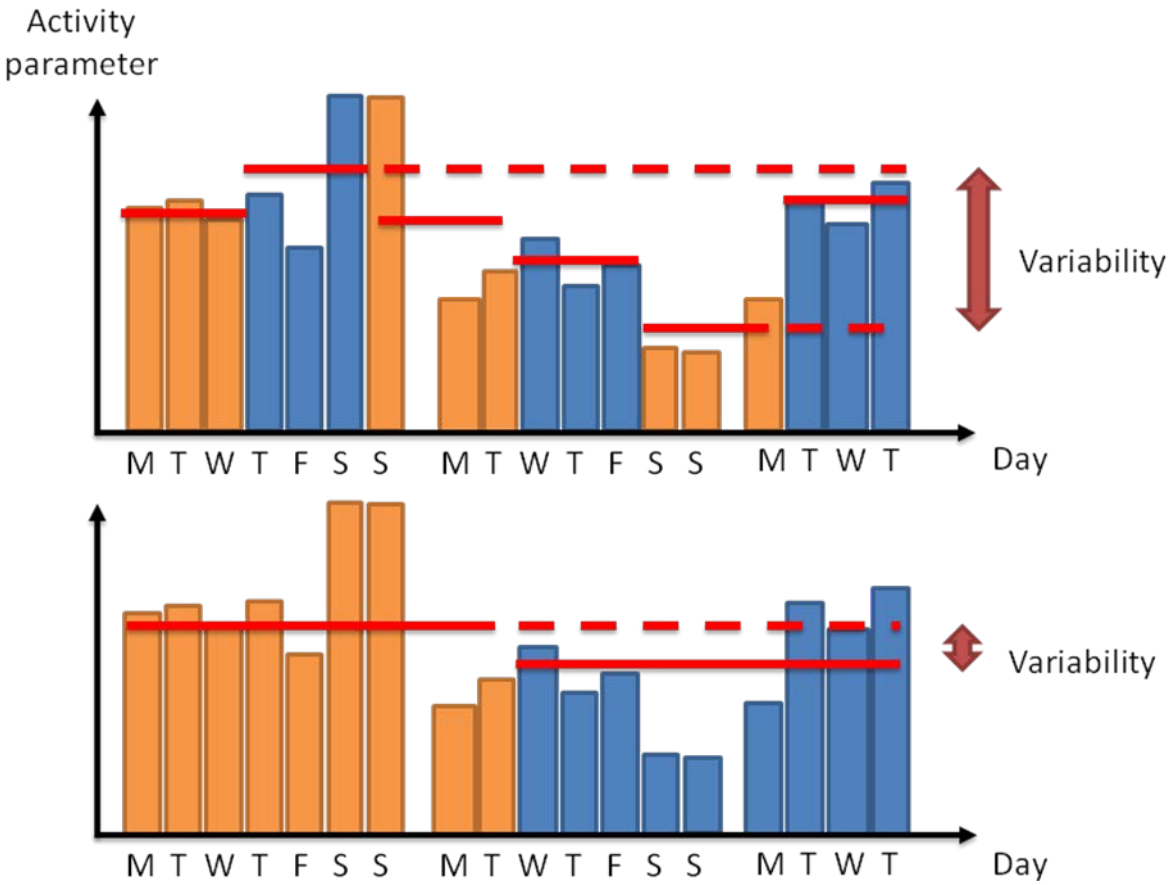
Applicant's position

A systematic way to assess the variability of a variable as a function of the recording duration in a single patient was specifically developed. The objective of this analysis was to determine the optimal number of days over which averaging the Proposed Gait Variables measured by the wearable device and system in order to obtain an estimate with low variability. To do this, all recordings are concatenate together in chronological order and then divided in periods of equal durations. The Proposed Gait Variables are calculated on each successive period. The differences between consecutive periods is used to calculate a standard deviation that represents the variability of the proposed gait variable. This is repeated for various durations for example 10 hours, 50 hours, 100 hours, 180 hours.

This variability is expressed in percentage by dividing the standard deviation by the mean value. To obtain a meaningful variability, the total duration of data used should be an order of magnitude longer for example 10 times longer than the period considered. This means that 1800 hours of data are needed to calculate the 180 hours variability.

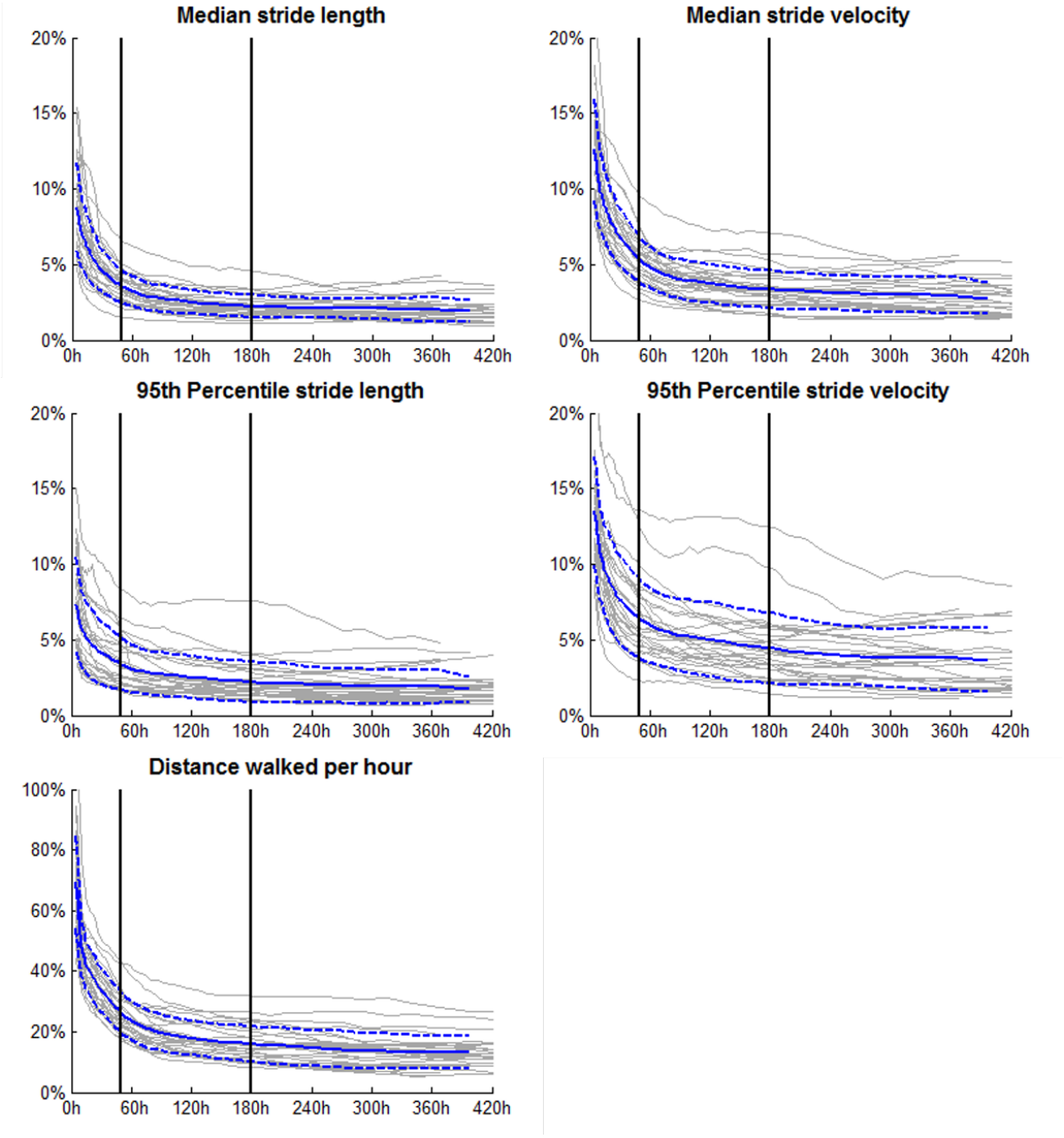
It is expected that the variability will be lower when averaging over a longer period of time. In the example below Figure 7, an activity variable is represented day by day on a 3-day period and on a 9-day period, as the duration used becomes longer, the variable converges towards the long term average with day by day variations being averaged out.

Figure 7. Illustration of 3-day and 9-day variability for an example of daily activity



The Figure 8 shows the graphic results of this method, quantifying the variability as a function of the duration used to calculate the variable. The median and the 95th percentile of the stride length and the median and the 95th percentile of the stride velocity and the distance walked per hour are shown as a function of the duration of recording used to calculate the variable. Variability of the proposed gait variables were calculated for 28 patients having at least 1800 hours of cumulated system recording.

Figure 8. Variability plot for the Proposed Gait Variables as related to the number of hours of data. Blue line indicates mean curve and dashed line mean+/- SD.



For example, the point of a curve at 180 hours indicate the relative variability of the variable when using 180 hours of recording to calculate the data. As can be expected the variability decreases for longer durations of recording. A cumulative duration of 180 hours is achieved in 15 days with a typical 12 hours a day of recording.

The duration of 180 hours of recorded data was used to correlate between the Proposed Gait Variables and 6MWT, NSAA, 4 SC test for four main reasons: 1) the drop in variability with recording duration appeared to decrease in all patients at this period of time; 2) it is short enough to be considered during a screening or a baseline periods, and it covers cycle of life, including in family with divorced parents where the activity of the child may considerably vary from one week to another; 3) disease progression is not expected over a period of 180 hours; 4) patient burden it not considered to be too strenuous to achieve 180 hours. These 180 hours of recording for each patient corresponds

approximately to 2-3 weeks of recording and has been achieved during the first month by 90% of the ambulant patients who have used the wearable device and system for at least one month.

Reported patient burden was considered to be acceptable by patients and family who have used the device to date. Compliance rates of 90% was observed amongst patients who agreed to use the the wearable device and system see Figure 9.This indicates that good adherence of 180 hours data per month can be achieved for the specific purpose of monitoring drug efficacy during a clinical trial. Patients and carers were also compliant with charging and docking the device for data transfer. It's suitability for long term routine care might not achieve such good compliance.

Using 180 hours is an optimal compromise to ensure low variability while keeping good compliance. However meaningful variables can still be calculated with shorter duration of recordings.

Based on the experimental variability found in the patients studied as shown in Figure 8 and summarized in Table 4, we advise using a cutoff at 50 hours of recorded data for longitudinal analyses in order to accommodate for missing data from poorly compliant patients during a clinical trial while still ensuring a reliable estimate of the Proposed Gait Variables measured using the wearable device and system. At 50 hours the variability found for the 95th percentile of stride velocity is 6.38% which is still acceptable if the majority of patients have more than 180 hours of recordings per period.

Table 4. Variability of Proposed Gait Variables when averaged on 50h and 180h of recording

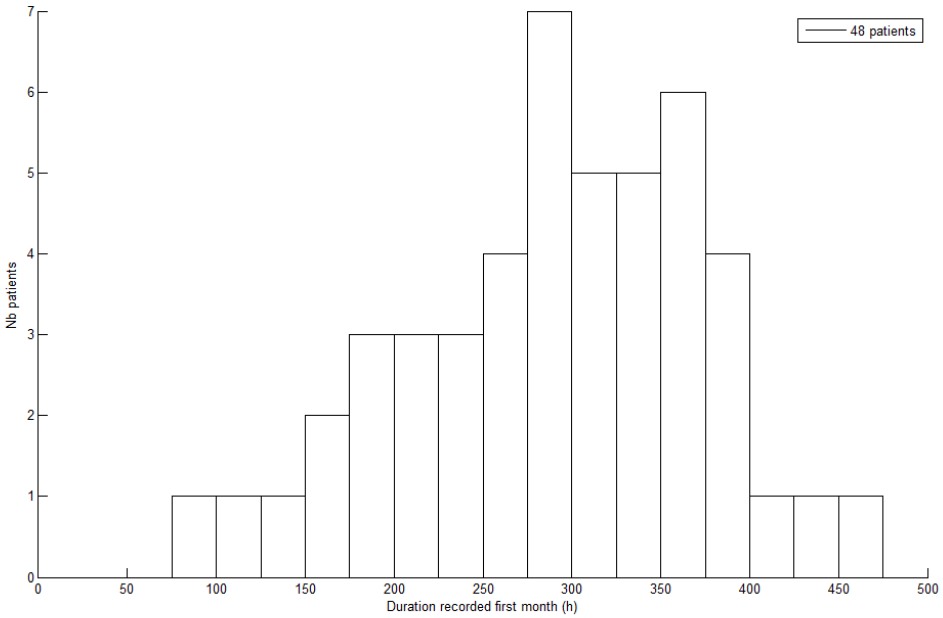
Proposed gait Variables	N	Mean (SD) variability at 50h of recordings	Mean (SD) variability at 180h of recordings
50th Percentile (median) stride length (m)	28	3.55% (1.05%)	2.24% (0.73%)
95th Percentile stride length (m)	28	3.40% (1.74%)	2.22% (1.34%)
50th Percentile (median) stride velocity (m/s)	28	5.31% (1.47%)	3.35% (1.24%)
95th Percentile stride velocity (m/s)	28	6.38% (2.60%)	4.41% (2.33%)
Distance walked/hour	28	26.27% (6.66%)	15.83% (5.77%)

Variability of Proposed Gait Variables at 50 hours and 180 hours of recorded data are given in Table 4.

The low variability of the Proposed Gait Variables can be explained by the identification of variables that are not dependent of social, familial or environmental factors. The weather or parental attitude may considerably affect cumulative variables like the distance walked or the number of steps in a day, but has a lower influence on stride length or stride velocity as shown in the variability results presented in Table 3. Figure 9 shows the histogram of the durations recorded during the first 30 days recorded. Of 48 DMD patients who have been equipped with the wearable device and system for at least one month, 43 patients (90%) had more than 180 hours of data recorded in the first 30 days of wearable device and system use and the other 5 patients (10%) had between 90 and 180 hours of data recorded.

There have been 39 patients who have reached the 6th months of study with the wearable device and system and in this group, 31 had more than 50 hours of data recorded. This represents a compliance rate of 79% in the 6th month.

Figure 9. Histogram representing the distribution of the wearable device and system use in hours for 48 patients during the first month of use



In order to determine the impact of fluctuations through the week, we compared the Proposed Gait Variables for 10 patients during week days and during week-ends. The selected the patients who were the most compliant and with at least 20 successive weeks of regular recording, and less than 10 days without any data in the period. We then calculated the variables using data from week days and data from weekends separately.

The Table 5 below shows the relative differences between week-end days and week days for the variables.

*Table 5. Difference in activity as measured by the Proposed Gait Variables measured by thewearable device and system between the week-end and the average over week days *: statistically significant at 0.05, **: statistically significant at 0.01*

	N	Mean	SD	p-value Wilcoxon
50th Percentile (median) stride length (m)	10	-3.85%	3.20%	0.012*
95th Percentile stride length (m)	10	-3.49%	4.79%	0.0593
50th Percentile (median) stride velocity (m/s)	10	-6.18%	5.18%	0.009**
95th Percentile stride velocity (m/s)	10	-7.34%	9.19%	0.0218*
Distance walked/hour	10	-21.4%	25.0%	0.047*

On average the patients seem to walk less in the weekends so the weekend effect is strongest on cumulative variables such as the distance walked but strides length and velocity are also affected. We recommend that patient use their device every day in order to acquire a representative image of their activity level and to smooth the day to day variability.

We have also studied the impact of fluctuations through the day by selecting mornings or afternoons only. For the 45 patients considered at baseline, the 95th percentile of stride speed for the entire day was 1.582 m/s with SD 0.378 m/s.

We isolated morning (8-12) and afternoon (2-6 PM) recording periods, and found no significant differences (mean 1.564 m/s and SD 0.384 m/s) and (mean 1.600 m/s and SD: 0.387 m/s) respectively. The mean difference between morning and afternoon session was 0.036 m/s with SD 0.215 m/s (Confidence interval: [-0.028, 0.1])

Measures to ensure data quality specific to continuous monitoring (e.g. whether the device is worn correctly) are through providing good training to both patients and the carers on the importance of capturing data. Commitment to use the device correctly will also be specified in the patient information sheet and consent process.

The risk that the patients accidently wears the ankle and wrist watches the wrong way around is low because the straps are different and the wrist watch remains attached to the unit for charging. Patients and carers are also given full instruction and training on how to wear both correctly before being discharged home.

It can happen that a patient removes the wrist band for example for cleaning leading to an inversion by mistakes. In that case, the software raises an alarm because too few strides are detected by the ankle sensor. Sensor inversion can therefore be detected and corrected during data analysis.

Whether the device is worn by someone other than the patients themselves is somewhat harder to monitor, and cannot really be verified but is mitigated trough good training, and clear instructions in the informed consent of the importance of good compliance to the end result of the trial.

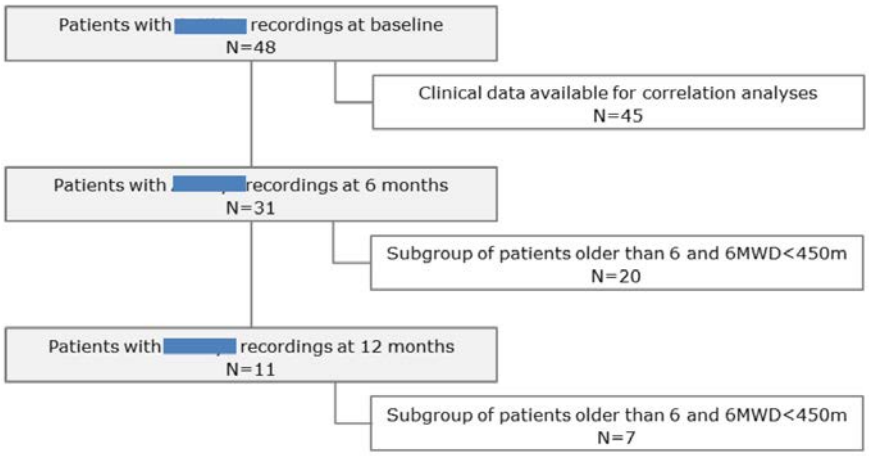
Question 3

Does the EMA agree that the variation on a 6 months and a one year period, and the standard deviation of this variation is compatible with clinical trials lasting six months or one year in the studied population?

Applicant's position

In order to determine the sensitivity to change of the Proposed Gait Variables, we explored the difference over a 6-months and a 12-months period. And to fit with current inclusion criteria for therapeutic trials in the DMD population, we investigated a subgroup of patients older than 6 years of age and walking less than 450 m in the 6MWT. The flowchart (Figure 10) gives a summary of the included and analyzed populations.

Figure 10. Flow chart representing baseline population



Month 1, month 6 and month 12 were evaluated for patients having more than 50 hours of wearable device and system data per month. Data for all patients and the subpopulation of patients older than 6 and with a with a 6MWD baseline value lower than 450 meters are presented in Table 6 and Table 7 respectively. Data from subjects older than 6 and with a 6MWD baseline value lower than 450 meters show a significant decrease of -2.4% for the 95th percentile of stride length, -4.7% for median stride velocity and -8.5% for the 95th percentile of stride velocity.

*Table 6. Longitudinal evolution for all subjects. *: statistically significant at 0.05, **: statistically significant at 0.01*

		N	Mean	SD	p-value Wilcoxon
6 month difference	50th Percentile (median) stride length (m)	31	-0.5%	5.8%	0.938
	95th Percentile stride length (m)	31	-1.7%	4.4%	0.092
	50th Percentile (median) stride velocity (m/s)	31	-2.9%	9.4%	0.060
	95th Percentile stride velocity (m/s)	31	-6.8%	8.3%	0.000*
1 year difference	50th Percentile (median) stride length (m)	11	-0.2%	6.8%	1.000
	95th Percentile stride length (m)	11	-2.8%	6.2%	0.155
	50th Percentile (median) stride velocity (m/s)	11	-3.3%	9.9%	0.286
	95th Percentile stride velocity (m/s)	11	-13.8%	10.4%	0.008*

*Table 7. Longitudinal evolution for subject older than 6 years old and with a 6MWD baseline value lower than 450 meters. *: statistically significant at 0.05, **: statistically significant at 0.01*

		N	Mean	SD	p-value Wilcoxon
6 month difference	50th Percentile (median) stride length (m)	20	-1.7%	6.1%	0.263
	95th Percentile stride length (m)	20	-2.4%	4.4%	0.030*
	50th Percentile (median) stride velocity (m/s)	20	-4.7%	9.4%	0.044*
	95th Percentile stride velocity (m/s)	20	-8.5%	7.9%	0.000**
1 year difference	50th Percentile (median) stride length (m)	7	-1.7%	7.0%	0.499
	95th Percentile stride length (m)	7	-4.4%	5.2%	0.091
	50th Percentile (median) stride velocity (m/s)	7	-5.6%	8.7%	0.176
	95th Percentile stride velocity (m/s)	7	-15.6%	7.9%	0.018*

Combination of age and 6 minutes walking test has been demonstrated repetitively to be a good predictor of patients' evolution (Mc Donald et al. Muscle and Nerve 2013; Goemans et al. Neuromuscular disorders 2013; Pane et al. PlOS One 2014).

Patients aged > 7 years and walking less than 350m during the 6MWT present a much higher risk of decline in the following year, in comparison with younger patients or patients better walking more than 350 m in the 6 MWT.

We investigated if 95th percentile of stride velocity could identify this subgroup, and if the decline of this population was significantly higher than in other groups.

Indeed, patients walking less than 350 m and aged > 7 years presented a 95th percentile stride velocity significantly lower than other groups, and presented a decline at least three times larger than in other subgroups. It must be noticed that all patients group do decline over a 6 months period, but patients older than 7 years and walking less than 350 m present a much higher rate of decline.

Table 8. Age and 6MWT as a predictor of patients' evolution

Group	nb patients	Mean age	Mean 6MWD	95 perc speed first month	Difference at 6 months 95 perc speed (%)
> 350 m and > 7yo	16	9.5	425.9 m	1.5335 m/s	**-5.70**
<= 350 m and > 7yo	5	8.9	285.6 m	1.1433 m/s	**-14.72**
> 350 m and <= 7yo	7	6.6	439.9 m	1.8177 m/s	**-5.51**
<= 350 m and <= 7yo	4	5.9	344.25 m	1.7821 m/s	**-2.34**

Question 4

Considering the low variability, the clinical relevance, and the sensibility of the methods, does the EMA agree to qualify the Proposed Gait Variables as measured by a valid and suitable wearable device as an endpoint to demonstrate efficacy in drug development clinical trials of ambulant DMD patients?

Applicant's position

The work done to date is with the ambition to transform patient monitoring during pivotal trials, enabling research to be moved from sterile hospital based assessments and to capture outcomes that are meaningful to patients and their families on a day-to-day basis.

The wearable device and system allows a continuous measure of DMD patients from 5 years of age to advanced non-ambulant stages. Work done to date validates its use in ambulant DMD patients over 5 years of age.

Future aspiration is to also validate it as a consistent monitoring approach across the full disease spectrum, and as a result filling the gap between different groups of patients targeted for clinical trials. Specifically, there are plans to explore work on the quality of walking, number of falls, patient sway, real-world (non-controlled) stair climbed and time to stand, as well as correlating to other indicators of patient well-being (e.g. patient reported outcomes). However, this work is very much in its infancy.

Sample size estimation in clinical trials

Based on work to date, we estimated the number of subjects that would be needed to power a new clinical trial in order to show a stabilization of the disease evolution. This is based on the data collected so far and presented here. We use the assessed sample size formula described previously (30) to calculate the sample size for a given randomized clinical trial with two independent groups.

$$n = 2 (Z_{\alpha/2} - Z_{\beta})^2 * \sigma^2 / D^2$$

where n is the sample size per group, Zα/2 and Zß are the type 1 and type 2 risks, σ the standard deviation of change and D the mean change.

The difference to detect was chosen as stabilization of the outcome in the treated group compared to the natural evolution of motor function in the placebo group; this was estimated based on natural history data presented here. The standard deviation was calculated as the standard deviation of differences at 6 months. The alpha risk was set at 5% and the power at 80%.

We estimated the number of patients required for a clinical trial to demonstrate a significant effect of a given intervention in stabilizing the disease over a six-month period. This estimation was performed for patients older than 6 years with a 6MWD lower than 450 meters. Standard deviation and mean are taken from the results summarized in Table 7 and the sample size that result are given in Table 9.

Table 9. Sample size per group to include in a clinical trial to detect a stabilization of motor function in 6 months for subjects older than 6 years old and with a 6MWD baseline value lower than 450 meters.

	Sample size per group
50th Percentile (median) stride length (m)	202
95th Percentile stride length (m)	53
50th Percentile (median) stride velocity (m/s)	63
95th Percentile stride velocity (m/s)	14

Considering that

- Our sample size calculation was computed on a group of patients that does not account completely for disease variability-the DMD population can present a lot of heterogeneity
- Some patients may present limited compliance that increase variability

We recommend including 30 patients per arm (rather than more than 100 in current trials) in a clinical study using the 95th percentile of stride speed as primary outcome measure to evaluate the stabilization of the disease by the IMP on a 6-month period. This is a significant improvement on the feasibility of recruiting into DMD clinical trials.

Work not done to date is to gain normative data in healthy age matched controls. The value of conducting such a piece of work to demonstrate the value of monitoring disease specific progression is an aspect to be considered further.

Another remaining gap considered to be more relevant is work to identify parameters that are predictive of motor milestones such as the loss of ambulation. Validation in non-ambulatory subjects is still to be completed.

One possible limitation of the wearable device and system is mainly related to patients' acceptability to wear the device. We have demonstrated (see infra) that 180 hours of recording (over a 2-weeks period) is optimal to get a minimal variation of the measure (about 2-4%). Shorter duration of recording keeps the measurement feasible, but increases its variability. 180 hours of recording over a 1-month period is considered to be very achievable by patients that take part in pivotal drug trials. Current effort is also being made to produce a more ergonomic version, based from user feedback.

The potential impact of the proposed method on regulatory guidelines is to match the different requirements listed in the guidelines and currently not met with standard measures. Indeed, current recommendations for clinical outcome measures in DMD trials imply endpoints that can validly and reliably assess function across a wide spectrum of symptoms and disease stages. Efficacy endpoints that can measure change of function over a wide range of deficits may offer a number of advantages in the development of drugs for dystrophinopathies. Such endpoints may increase the number of patients eligible for enrollment, and may decrease possible loss of information from floor and ceiling effects that occur. Endpoints that can assess function across different stages of the disease, for example, by combining measures of ambulation and upper body function, are encouraged for similar reasons. Endpoints should have the ability to detect improvement from baseline, as well as decline, to capture the spectrum of possible beneficial drug effects (4). Altogether, the wearable device and system may fulfill these different requirements. It may be used through a large spectrum of the disease phenotypes, from ambulant young patients to late non-ambulant, it captures reliably information that

is strictly correlated with patients real life-thus clinically significant- does not present floor nor ceiling effect, and is highly sensitive to change. The Proposed Gait Variables measured by the wearable device and system are related with motor activity, and should be used in conjunction with other efficacy endpoints based on function or respiratory and/or cardiac measures.

We are currently recording a cohort of 15 non-ambulant patients. Several variables have been identified in a controlled setting (3) the validation of these variables at home in a non-controlled setting is ongoing.

The wearable device and system has not been used in children younger than 5 years old. It is not technically impossible to record younger patients, but no data has been collected so far.

To date we do not have normative control data. We believe that gaining normative data and expressing patient's data as % of predicted value for age or height rather than as rough value will help to gain an understanding of the sensitivity to change, since values such as stride length are largely size-and thus age dependent. These data are currently being acquired in a study protocol conducted in the CRMN of Liege (PI : Dr Laurent Servais).

We also need to verify a drop-in stride speed that is predictive of significant motor milestone such as the loss of ambulation. A drop of 30m with 6MWD is considered clinically significant, it is equivalent to a 7.5% drop considering mean baseline 6WMT of 400 meters. Our results show a significant decline or 6.8% in 6 month which can therefore by comparison be considered as clinically significant. Ongoing data collection will determine how this drop in stride speed may predict loss of ambulation.

Another clinically significant outcome for ambulant DMD patients is the total number of falls which will also be further addressed in future studies, but is expected to entail a considerable amount of work which may take years to validate.

To summarise, although there are some remaining gaps in the demonstration of the value of the Proposed Gait Variables measured by the wearable device and system there is already enough evidence to demonstrate its strong value as a means to monitor ambulant DMD patients in clinical trials today.

Additional validation

Variables as measured with a suitable and valid wearable device vs optical motion capture

Test sequence

Eight healthy men volunteers (age: 25.6 ± 7.4 years; height: 1.77 ± 0.18 m) have been recruited to walk at several paces while being recorded by an optical motion capture system (OptiTrack®) installed in Sysnav facility. The test consisted in walking in the OptiTrack equipped room between two markers drawn on the floor and separated by approximately 4 meters. Prior to each test, the motion capture system was calibrated moving a wand with markers in the field of view of all cameras following OptiTrack® procedure. A solid rigid with fixed optical reflectors and the wearable device/was strapped to the volunteer's ankle to enable tracking by the motion capture system.

Some parts of the tests were not exploitable due to calibration issues with the optical tracking or due to misalignment between reflectors and the wearable device. A few recordings with low quality optical data were therefore excluded. Loss of calibration of the optical system can occur for example when a camera is unintentionally touched or when the proposed system recording device slides on the solid.

Each volunteer was asked to make 10 laps walking between the two markers with clockwise turns, 10 laps with anticlockwise turns and 10 laps alternating right and left turns (see illustration in Figure 11).

This sequence was repeated for slow, normal and fast paces so 30 laps were done for each pace. The tests performed are summarised in Table 10.

Table 10. Summary of the tests demanded to the volunteers

	Slow pace	Normal pace	Fast pace
Clockwise turns	10 laps	10 laps	10 laps
Anticlockwise turns	10 laps	10 laps	10 laps
Figure of eight	10 laps	10 laps	10 laps

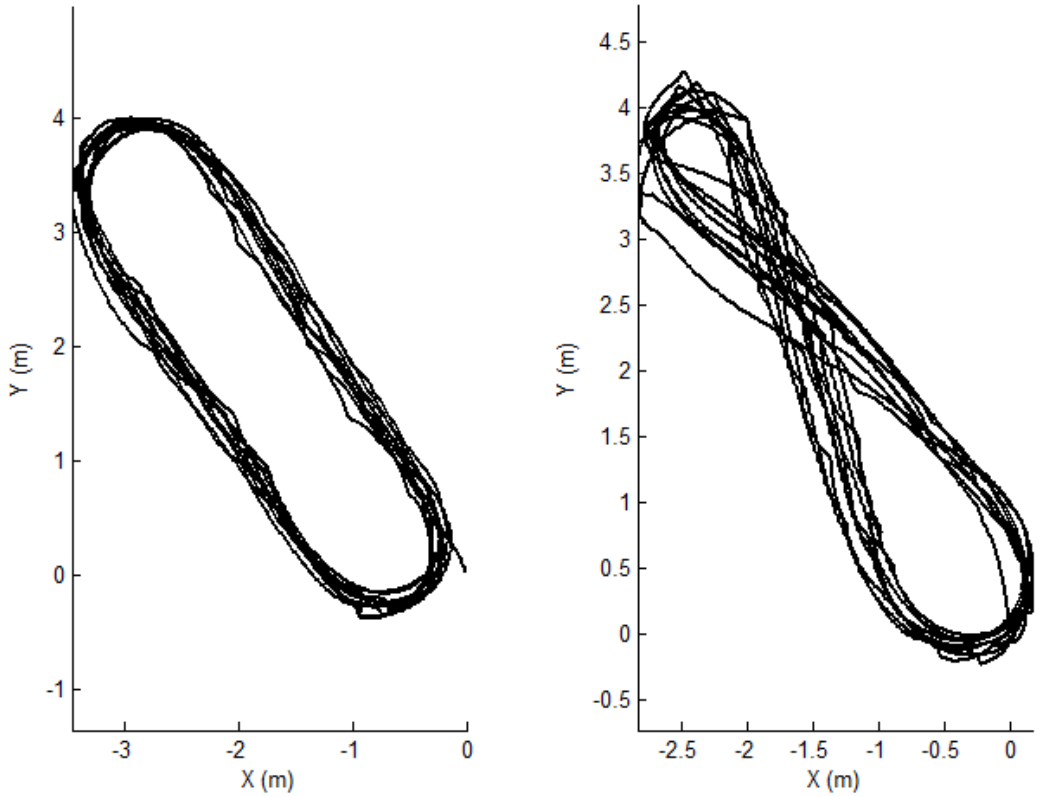


Figure 11. Examples of tests trajectories, 10 laps anticlockwise and 10 laps with figure of eight turns

In total more than 6000 strides have been recorded during these tests done by 8 volunteers.

Calibration and alignment

The optical motion system returns the trajectory of the rigid solid and the rotation between the solid and an inertial reference defined during the initial calibration. To make the comparison possible, the data need to be synchronised and the inertial measurement unit (IMU) need to be positioned relative to the optical reflectors. The IMU axes need to be aligned with the OptiTrack® reference frame defined arbitrary at system start-up.

Synchronization is achieved by finding the time offset that minimizes the difference between the norm of angular velocity measured by the gyro and derived from the optical reference. Alignment between IMU and the motion capture reflectors is achieved by finding the position that minimizes the difference between the speed computed by the wearable device and system algorithms and the speed derived from optical motion system. The rotation to pass from the OptiTrack® defined rigid solid frame to the

IMU axes is calculated by finding the rotation that minimizes the difference between angular velocity derived from optical system and rotated with the gyro measurements given in the IMU axes.

Motion capture reference

The OptiTrack® motion capture system returns a 3-dimension trajectory of the rigid solid. The vertical position of the rigid solid is used to identify the time that the foot takes off from the ground and the time it returns on the floor. This is used for automatic stride identification defining a reference for stride detection.

During the tests turns are made at every lap. A separate class is created for turning strides and all of the turning strides done in the tests at slow, normal, fast paces are set aside in a separate category. In this context a stride is considered as turning when there is more than 45° change of heading between the beginning and the end of the stride. All turning strides are grouped together regardless of the pace.

The proposed system algorithm calculates the gait parameters, length and velocity, for all the strides detected. For each of these strides the OptiTrack® trajectory is used to define a reference stride length using the proposed system algorithm segmentation.

Results strides detection

Using the optical reference, 6358 normal strides are identified during the slow, normal and fast walk tests. The wearable device and system algorithm finds 6274 of these and misses 84 strides. This makes an estimated detection rate for normal strides of 98.7%. The results for stride detection are summarised in Table 11.

Table 11. Stride detection using the wearable device and system vs Optical detection

	Strides detected	Strides not detected by optical
Optical reference	6358	
The wearable device and System	6274 (98.7%)	18 (0.29%)

Nearly all strides are detected in the context of this test and some of the errors are due to erroneous detection by the optical reference.

Strides length and velocity

The trajectory is calculated with the wearable device and system and the length and the velocity of each stride is derived from this trajectory. The length is defined as the distance in the horizontal plane between the position at the start and at the end of the stride. For each detected stride, the segmentation for start and end is given by the system detection algorithm. The velocity is calculated as the length divided by the duration of the stride that is the time elapsed between start and end of the stride. For every stride, the OptiTrack® trajectory is used to compute a reference length and velocity using the same segmentation.

Three types of comparison have been done.

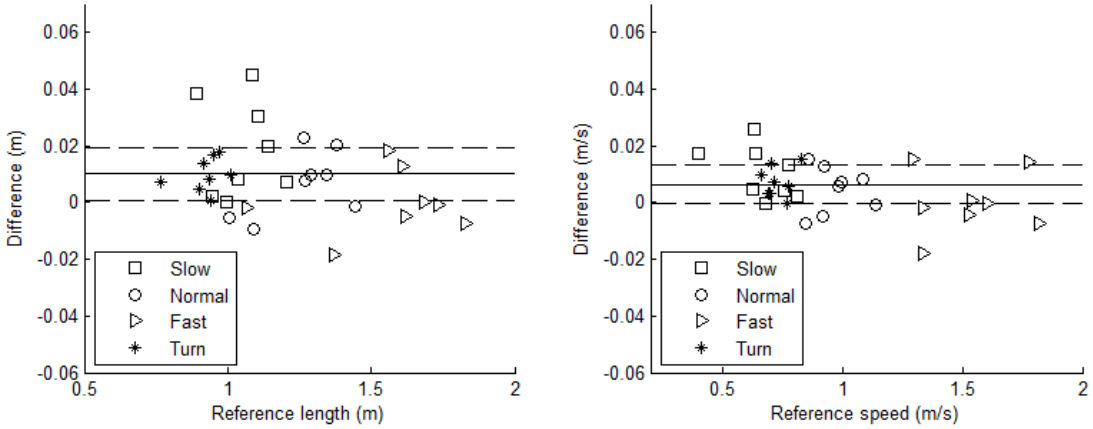
- First, we consider person per person and activity per activity in order to estimate the variability between individuals and as a function of the activity.
- Second, we consider all strides individually in order to estimate the variability between strides and as a function of the activity.

- And finally, we simulate the error of some outcome variables using all strides of each person in order to estimate the global error when calculating these variables.

Intra-individual variability

First, we compare person by person and separating by activity. The average difference between the optical reference and the wearable device and system is calculated for each patient separately and each class of activity. The results are plotted in Figure 12.

Figure 12. Average difference the wearable device and system vs motion capture for each pace and person



We can see that the length and velocity are correctly estimated at all paces and for all eight volunteers tested. On average, length and velocity are slightly underestimated. For all eight persons and at all paces the average error is always under 6 cm for length and 6 cm/s for velocity. In relative term, the error is under 5% for everybody at all paces.

The mean and RMS errors are summarised in Table 12 to Table 13 considering the persons tested individually for each activity. The average error and the root mean square error are under 1.5% globally and 2.5% at all paces tested.

Table 12. Stride length comparing Optical reference and Wearable device and System person per person

Comparison stride length Optical reference minus the wearable device and System					
	All normal	Slow	Normal	Fast	Turning
Mean	111.86 cm	105.03 cm	126.20 cm	155.83 cm	92.42 cm
Mean difference	1.02 cm	1.89 cm	0.69 cm	-0.01 cm	1.00 cm
Mean relative difference	0.88 %	1.82 %	0.50 %	-0.03 %	1.07 %
RMS difference	1.35 cm	2.49 cm	1.28 cm	1.07 cm	1.15 cm
RMS relative difference	1.16 %	2.43 %	1.00 %	0.72 %	1.22 %

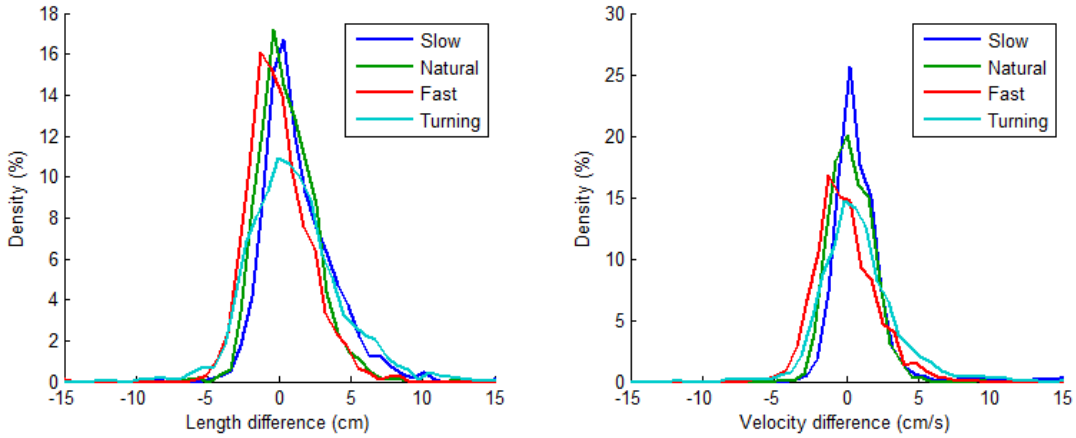
Table 13. Stride speed comparing Optical reference and the wearable device and System person per person

Comparison stride speed Optical reference minus *Wearable device and System*					
	All normal	Slow	Normal	Fast	Turning
Mean	87.72 cm/s	66.50 cm/s	96.89 cm/s	152.88 cm/s	73.07 cm/s
Mean difference	0.65 cm/s	1.06 cm/s	0.46 cm/s	-0.01 cm/s	0.73 cm/s
Mean relative difference	0.73 %	1.80 %	0.48 %	-0.02 %	0.99 %
RMS difference	0.90 cm/s	1.37 cm/s	0.90 cm/s	1.02 cm/s	0.88 cm/s
RMS relative difference	1.03 %	2.41 %	0.99 %	0.72 %	1.19 %

Average error considering individual strides and per activity

Here all strides are considered together not separated by person and classified by category. The density functions for the stride length and velocity is shown in Figure 13.

Figure 13. Density functions of length and velocity difference compared to reference



The standard deviation may not be the best metric to quantify the performance of the stride measurements as just a few outliers can have a disproportionate effect. What matters is to have as many strides as possible with a small error. To address this issue, the threshold that include 68.27% of the strides with an error under this threshold has been calculated.

Table 14 and Table 15 summarise the results of these comparisons for all strides and for each stride category. The relative values given in percentage are calculating by dividing by the average length or velocity of the stride category.

Table 14. Stride length comparing Optical reference and wearable device and System

Comparison stride length Optical reference minus *the wearable device and System*					
	All	Slow	Normal	Fast	Turning
Average length (cm)	111.37	103.67	123.49	156.17	92.71
Mean difference (cm)	0.95 (0.86%)	1.78 (1.72%)	0.55 (0.45%)	-0.09 (-0.05%)	1.00 (1.08%)
Std difference (cm)	3.69 (3.3%)	4.28 (4.1%)	2.70 (2.2%)	2.25 (1.4%)	4.02 (4.3%)
Limit 68.27% error (cm)	2.37 (2.1%)	2.41 (2.3%)	1.94 (1.6%)	2.04 (1.3%)	2.84 (3.1%)

Table 15. Stride velocity comparing Optical reference and wearable device and System

Comparison stride velocity Optical reference minus *wearable device and System*					
	All	Slow	Normal	Fast	Turning
Average velocity (cm/s)	87.64	66.15	95.71	152.72	73.21
Mean difference (cm/s)	0.60 (0.68%)	0.98 (1.49%)	0.36 (0.38%)	-0.08 (-0.05%)	0.72 (0.99%)
Std difference (cm/s)	2.73 (3.1%)	2.59 (3.9%)	2.10 (2.2%)	2.27 (1.5%)	3.21 (4.4%)
Limit 68.27% error (cm/s)	1.77 (2.0%)	1.44 (2.2%)	1.49 (1.6%)	1.96 (1.3%)	2.23 (3.0%)

The mean error considering all strides is around 0.6 and 0.9% for stride length and stride velocity. So, on average the algorithm tends to underestimate slightly the stride length. When considering the average error category by category, the average error is always under 1.5%. And considering the threshold that contains 68.27% of the strides, the error is under 3.5% for all paces of walk.

Outcome variables considering all strides per person

The median and the 95th percentile of the length and of the velocity have been computed for each patient using all strides recorded during walking tests. The variables are also calculated using the optical reference. The difference between the wearable device and System and reference is plotted as a function of the reference for each patient in Figure 14. The mean difference and the RMS are given in Table 16.

Figure 14. Average difference of outcome variables motion vs Proposed System

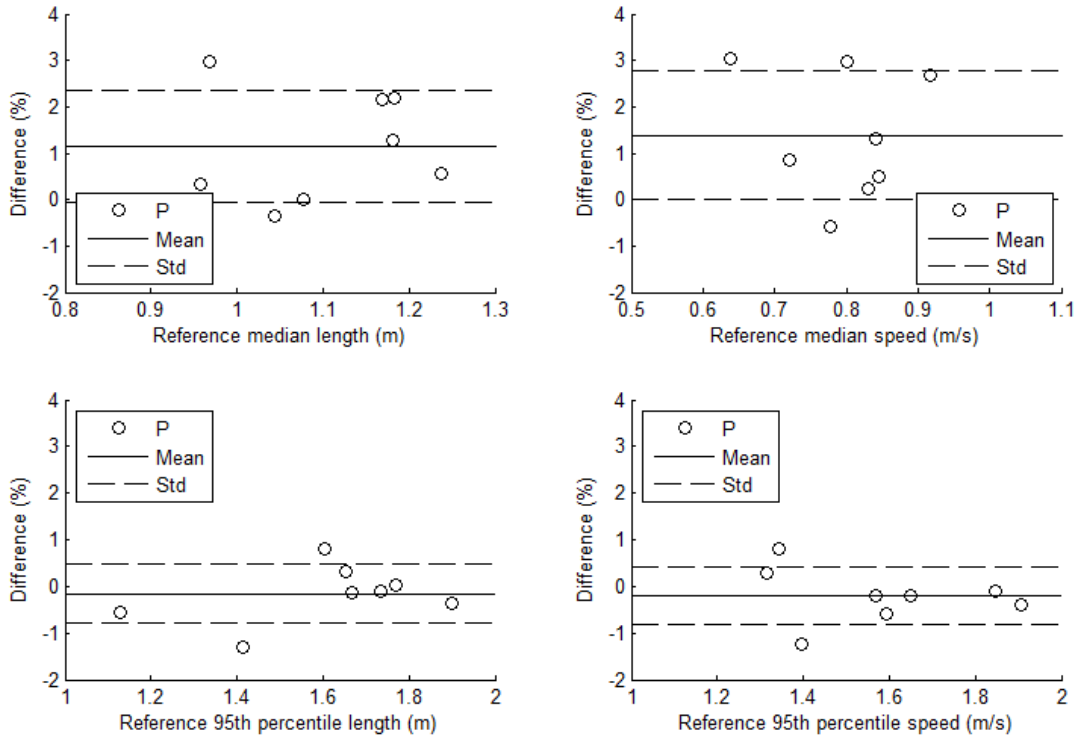


Table 16. Comparison optical reference and the wearable device and System

	Median length	Median speed	Percentile 95th length	Percentile 95th speed
Mean	110.20 cm	79.66 cm/s	160.83 cm	157.71 cm/s
Mean difference	1.27 cm	1.09 cm/s	-0.20 cm	-0.35 cm/s
Mean relative difference	1.15 %	1.38 %	-0.16 %	-0.20 %
RMS difference	1.75 cm	1.49 cm/s	0.89 cm	0.87 cm/s
RMS relative difference	1.60 %	1.89 %	0.60 %	0.60 %

The mean relative difference and the RMS error are under 2% for the four variables.

Longitudinal comparison with 6MWT

The 6MWT distances measured along the test are available for 23 patients of the population. The evolution of the 6MWT distances for these patients is plotted in Figure 15. The evolution of all patients equipped with the wearable device and System is plotted in Figure 16. Of the 45 patients available at baseline, one patient is excluded of the plot because he had back pain and injuries during the test period.

Figure 15. Evolution of the 6MWT distance as a function of age

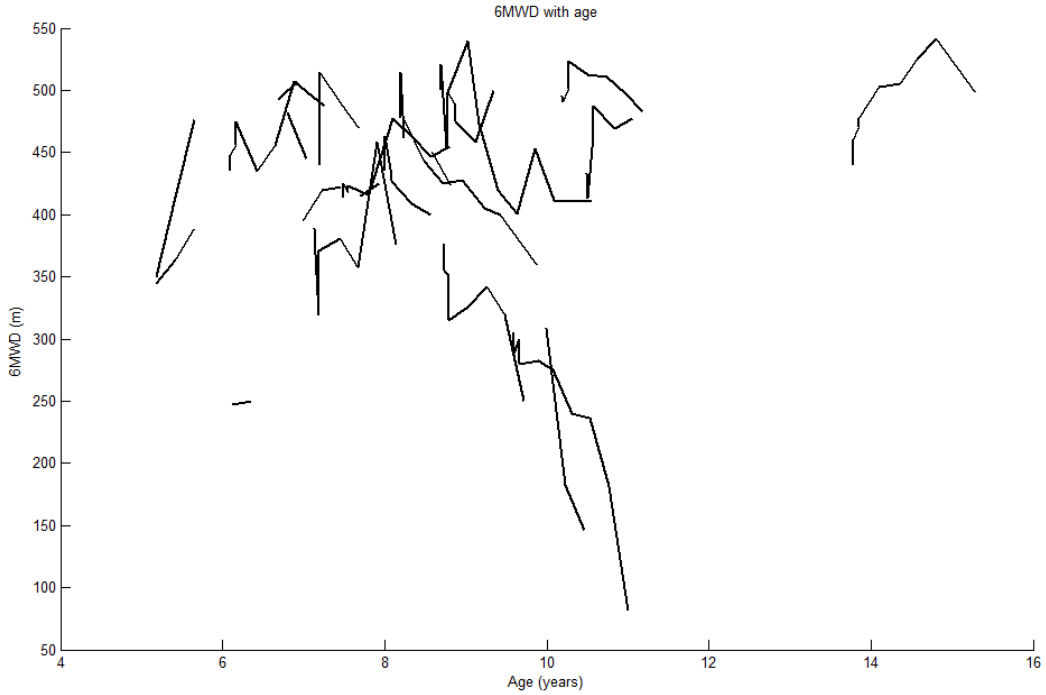
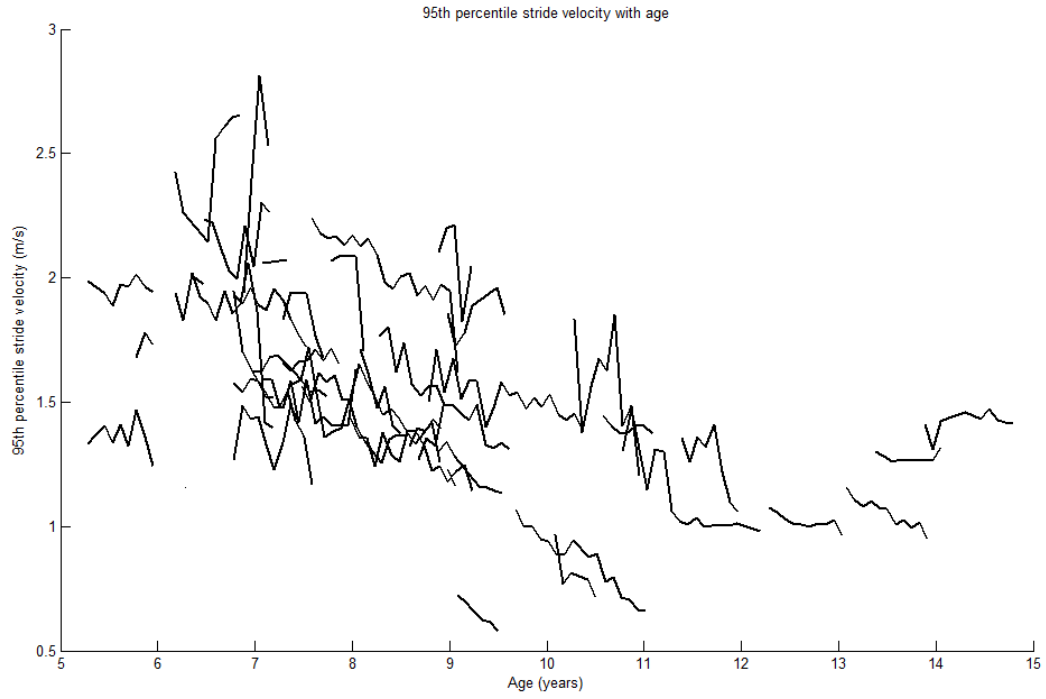


Figure 16. Evolution of the 95th percentile of stride velocity as a function of age



A correlation between 95th percentile of stride velocity and 6MWT distances has been done at 6 and 12 months when possible. The criteria for the comparison is that there is a 6MWT done within 45 days of the middle of the first, of the sixth and of the twelfth month of the recording period. There are 16

patients meeting these criteria at 6 months and 5 patients meeting these criteria at 12 months. The mean and standard deviation of the changes at 6 months are given in Table 17.

Table 17. Evolution at 6 months for the patients with 6MWT and 95th percentile of stride velocity measured by the wearable device and system

		N	Mean	SD	p-value Wilcoxon
6-month difference	6MWT	16	0.37%	18.34 %	1.4305
	50th Percentile (median) stride velocity (m/s)	16	-7.08%	9.14%	0.013

The Figure 17 shows the mean relative change at 6 months (16 patients) and 12 months (5 patients) for the 6MWT distance in black and for the 95th percentile of stride velocity in red. The vertical bars represent the standard error of the mean of the population for the 6-month change.

The correlation at 6 months between the 6MWT distances and the 95th percentile of stride velocity is given in Table 18 and shown in Figure 18.

Table 18. Correlation at 6 months between 6MWT and the 95th percentile of stride velocity measured by the wearable device and system

	6MWT				
	N	ρ	p-value	r	p-value
95th Percentile stride velocity	16	0,515**	0.044	0, 0.673**	0.004

Figure 17. Evolution of the 6MWT and 95th percentile of velocity at 6 and 12 months with standard error of the mean

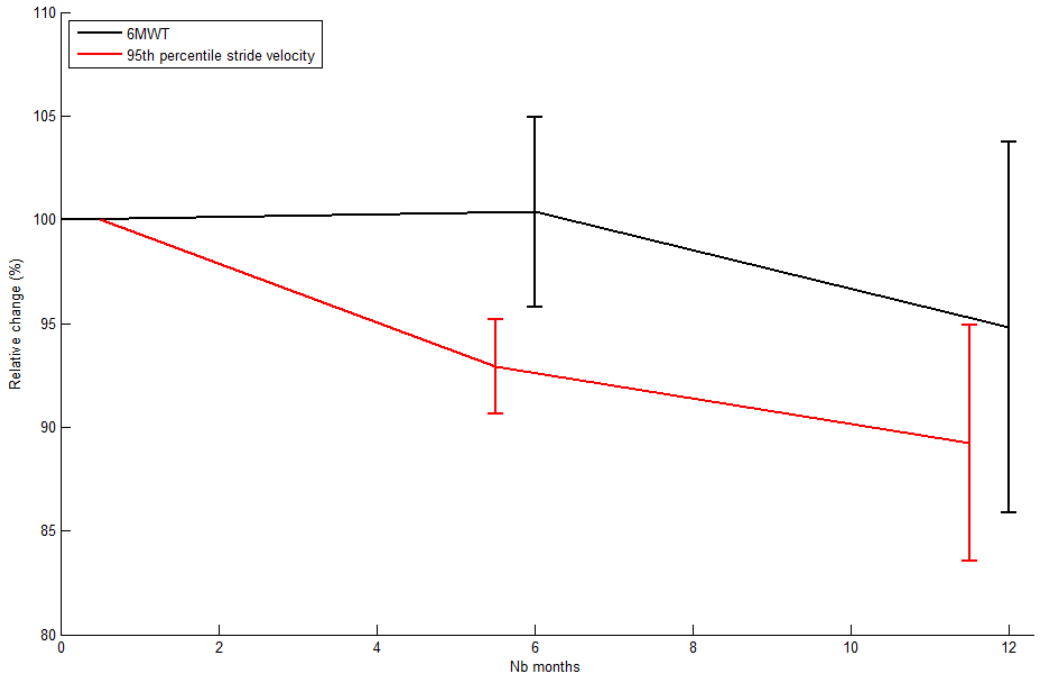
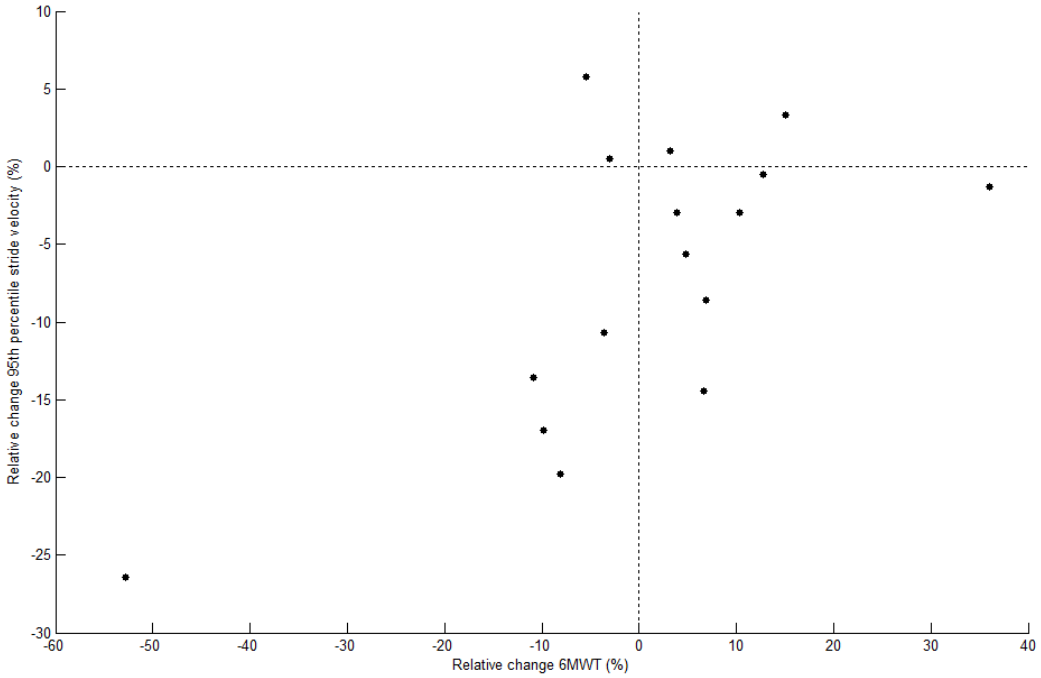


Figure 18. Correlation at 6 months between relative change of 6MWT and of 95th percentile of velocity measured by the wearable device and system



Applicant's Responses to initial request for clarification in writing

The following comments were given regarding the qualification procedure of the Proposed Gait Variables. The dossier has been modified accordingly and a brief answer is given in blue below for each comment.

- Context of use (CoU)

A section Context of use section of the briefing document has been added to clarify this topic.

- Elaborate on the clear advantages of the Proposed Gait Variables over current Primary endpoints in this indication.

The sensitivity of the 95th percentile of stride velocity calculated with the wearable device and system is higher than current primary endpoints. The sensitivity is given in Tables 6 and 7 of the briefing document.

- Elaborate on work in progress on quality of walking, fall, sway, real world (non-controlled) stairs, time to stand, and correlation with patient well-being.

It is planned to investigate these more deeply in the future as stated but there is no specific results or data on these variables at the moment.

- For the 6MWT vs 180hrs recording with the proposed system, elaborate on how potential confounding covariates have been adjusted for, and whether there is any bias given the extending duration of recording.

All patients have been used for the correlation at baseline, the selecting criteria being to have more than 180 hours of recording during the first 2 months of wearing the system. The table 2 at of the briefing document has been updated to include correlations with age and height.

- For the 180 hours data, describe the distribution of data recording, possible patterns (AM/PM/every day, whether it is meaningful to simply aggregate the hours of recording data, or whether approaches such as modelling/stratification have been looked into.

For the statistics on variability shown in figure 8 of the briefing document, all data have been concatenated together regardless of the pattern of use. Separately we looked at the difference

between week days and weekends using the 10 most compliant patients and found as summarized in table 5 that the variables are on average lower on weekends.

We have also added in this version of the document some statistics to compare AM/PM pages 21 and 22.

- Describe the gyroscope derivation bias (p15)

The description has been reformulated to clarify.

- Provide retest data in relation to recent PLoS One publication.

There is no additional data on the PLoS One publication. However, for the Proposed gait variables, a test retest has been calculated using the two first periods of 15 days, the results are presented in table 3 of the briefing document.

- Explain why individual calibration is not needed. Please explain whether low magnetic field or other interference could impact on the properties of the device. Please explain if errors from device (i.e. fixed Orange led) are recorded?

A section has been added to explain how the algorithm works and justify why there is no need for individual calibration.

- Describe the CE status, and evolution of the device throughout the validation studies. Explain why bridging data are not needed. Tabulate and discuss any reported safety issues with the device.

A section on the regulatory status has been added to the briefing document.

- Summarise and also annex the validation in healthy controls.

The results of the validation tests done on healthy controls are presented in annex to the briefing document.

- For each study: outline the design in relation to the validation objective and also provide the protocol of validation study and study reports as annexes, discuss the strengths and weaknesses of the validation study designs, and present and discuss the results.

Given the fact that none of these three studies are published yet, it is difficult to provide all protocols so we share anonymised patient level data without indicating which study they come.

- Discuss compliance and patient burden in general. Discuss the missing data in the validation studies and the factors that contributed to these. Base any statements on data.

Statistics on compliance are given in figure 9.

- Regarding evolution at 6 and 12 months; when discussing results, consider the impact of small numbers and bias. Discuss confounding by age, height and steroid regime.

Statistics and comments have been added; see table 8 to differentiate according to age and height.

- Provide a summary of patient slopes data and corresponding figures.

The figure 16 shows the evolution of the 95th percentile of stride velocity as a function of the patient's age.

- Please provide a re-analysis of data to see if the proposed= methods discriminate between more or less severe baseline groups, and those with or without steroids, at baseline, and also if possible, longitudinal changes in these groups. Please try to ensure that the data are corrected for prognostic variables e.g. with a multivariate analysis adjusting for e.g. genetic mutation (exon 45 mutation boys vs others), steroid regime (weekend dosing, 10 days on 10days off VS every day AND prednisolone vs deflazacort)).

The data regarding steroid regime and the mutation has been included in the attached file but the low number in some of the subgroups make it difficult to draw significant statistics on them. Evolution and severity are analyzed based on baseline 6MWT distance.

- You have done the correlation between the proposed gait variable with 1-2 months recording and baseline 6MWT, and calculated longitudinal changes in the Proposed Gait Variables. Can you correlate

the changes in 6MWT and changes in the Proposed Gait Variables, and provide these results and discuss.

The longitudinal correlation between 6MWT and the Proposed Gait variable is given in annex to the briefing document.

- Please describe how software will be validated for the proposed data analysis

Software development follows EC 62304 as explained page 10.

- Please describe measures to ensure data quality that are specific to continuous monitoring (e.g. whether the correct person is wearing the device) or why those are not needed

Precisions are added

- Please provide a general comment regarding data privacy and protection and how this will be handled.

Precisions have been added.

Applicant's Responses to CHMP's issues for Discussion

Please discuss plans to generate normative data in healthy age-matched controls.

To gain not only more patients' data, but also normative controls is a work in progress. The protocol "ActiLiège" (Sponsor: Centre de Reference des Maladies Neuromusculaires, PI: Prof. Laurent Servais), supported by parents advocacy group Action Duchenne currently includes DMD patients and controls. All together, we plan to include 130 controls (100 children and 30 adults). The following table reports controls included so far according to age and gender (n=68, age range 6-84 years).

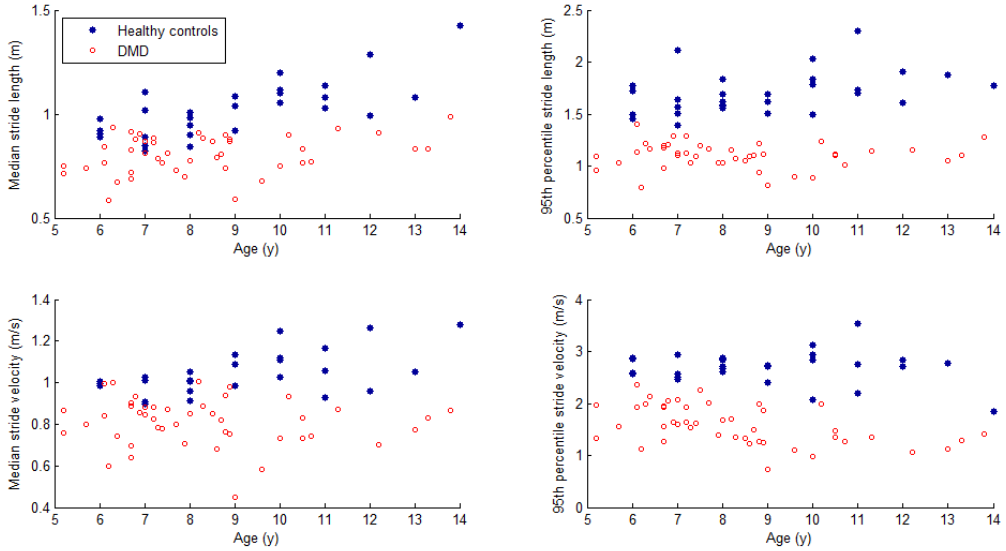
Age	Gender	Inclusion Date
47	F	05/07/2017
34	F	05/07/2017
7	M	25/07/2017
40	F	22/08/2017
14	M	29/08/2017
25	F	29/08/2017
30	F	29/08/2017
25	F	12/09/2017
46	M	25/09/2017
9	F	27/09/2017
11	F	27/09/2017
6	F	27/09/2017
6	M	27/09/2017
8	F	17/10/2017
61	M	17/10/2017
6	F	25/10/2017
35	F	25/10/2017
41	F	30/10/2017
10	F	30/10/2017
42	F	31/10/2017
9	M	31/10/2017
65	M	31/10/2017
13	M	03/11/2017
11	F	03/11/2017
12	M	03/11/2017
8	M	03/11/2017
11	M	03/11/2017
7	M	02/11/2017
8	F	02/11/2017
11	F	02/11/2017
84	F	08/11/2017

Age	Gender	Inclusion Date
75	F	08/11/2017
10	F	15/11/2017
8	F	22/11/2017
11	F	22/11/2017
8	M	06/12/2017
10	M	06/12/2017
39	F	06/12/2017
8	F	26/12/2017
10	F	26/12/2017
8	M	26/12/2017
8	F	26/12/2017
9	M	27/12/2017
6	F	27/12/2017
8	M	27/12/2017
12	M	27/12/2017
7	F	28/12/2017
6	F	28/12/2017
7	F	29/12/2017
9	F	29/12/2017
11	M	29/12/2017
9	F	02/01/2018
7	F	02/01/2018
6	F	02/01/2018
10	M	04/01/2018
6	M	04/01/2018
18	M	12/02/2018
8	F	12/02/2018
18	M	12/02/2018
10	F	13/02/2018
8	F	13/02/2018
11	M	13/02/2018
7	F	14/02/2018
9	M	14/02/2018
11	F	14/02/2018
9	F	16/02/2018
8	F	16/02/2018
6	M	16/02/2018

Last control first visit is scheduled by July 2018, and last patient last visit (all controls have 2 visits 1 year apart each other) by July 2019. Full age normative longitudinal data will be available for November 2019. We have attached the protocol ActiLiège.

Interim analysis to date demonstrates that stride length and stride velocity are clearly different in patients and controls. The 95th percentile variables seem to discriminate more between DMD and controls than the median for the same variable. Plots are shown below.

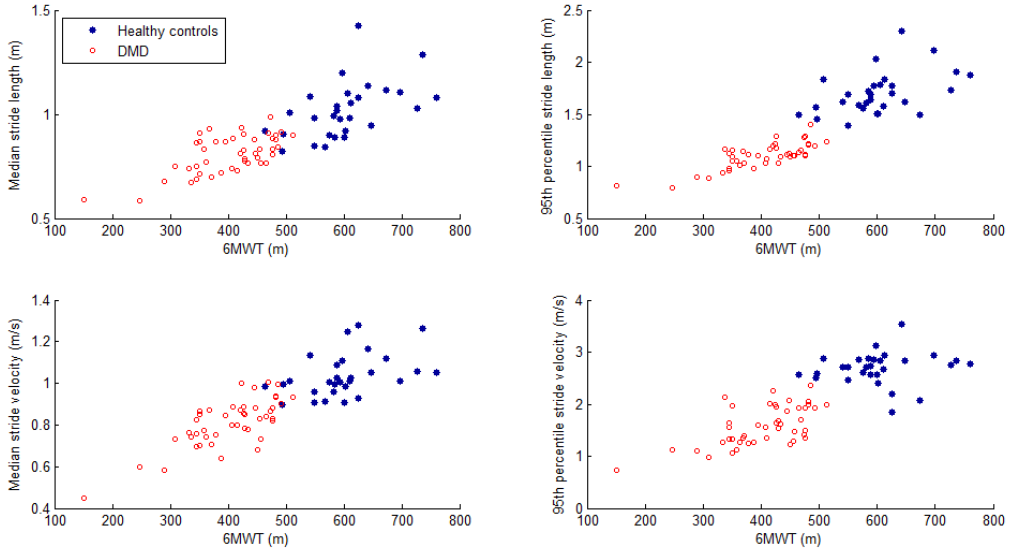
Figure 19: Proposed Gait variables measured by the wearable device and system as a function of age for DMD and healthy controls.



Interestingly, 95th percentile stride speed and stride length are much less related with age and height than corresponding median value.

In controls, as in the Duchenne population, stride velocity and stride length are moderately correlated with 6MWT.

Figure 20: Proposed Gait Variables measured by the wearable device and system as a function of the 6MWT for DMD and healthy controls.

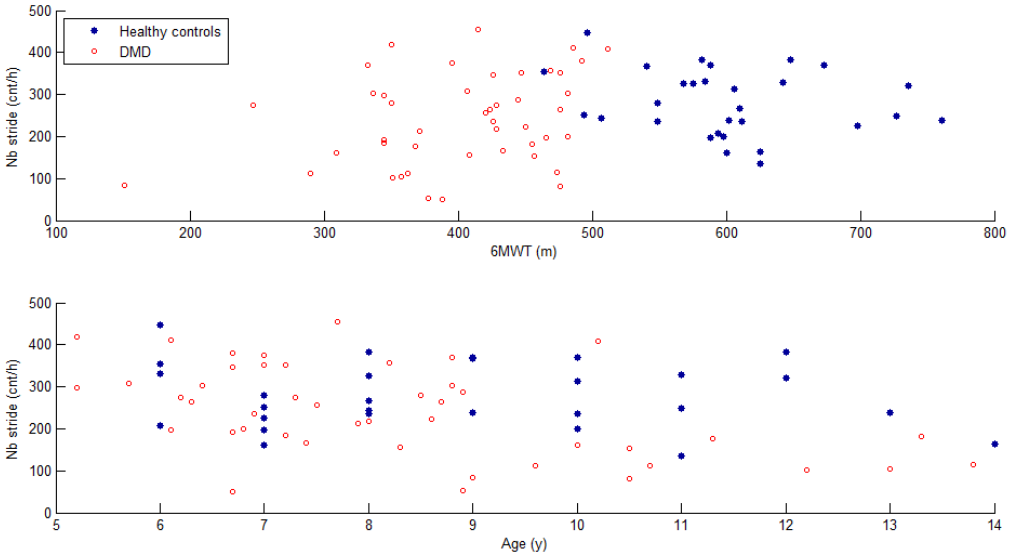


Descriptive variables, such as stride speed and stride length descriminate between controls and DMD accurately, especially when expressed as 95th percentile.

Another approach that can be achieved with a simple podometer or a GPS is to compute the number of stride or meters per day, as an indicator of patients activity, which constitutes “cumulative data”.

These cumulative data do not discriminate between patients and controls, except for patients with advanced disease, after the age of 10 years. This is probably due to the high social variability of these outcomes. Through all the analysis performed, cumulative data appeared to be highly variable, poorly discriminant and non sensitive to change.

Figure 21: Normalized stride count as a function of the 6MWT and age for DMD and healthy controls.



These preliminary data in the control study show that age-matched controls present faster and longer stride than DMD, and that in both populations, these parameters are correlated with 6MWT.

More controls patients are being included in the following weeks, and longitudinal data in controls will be acquired starting July 2018.

The influence of compliance on variability, on stride length and stride speed as recorded by the wearable device and system requires further clarifications. The method for the results in the compliance needs to be described as well as how the non-activity, non-recording periods were accounted for. In addition, the Applicant is kindly asked to discuss the feasibility of a standardised method to measure the compliance rates.

Compliance can be calculated for each recording period considered. In a period, data are supposed to be recorded daily and the sensors are recorded in the time between unlocking and locking the sensors on the docking station and a file created every time. All the files that belong to the same recording period are then analyzed together to compute the variable reported. In ambulant DMD, we propose 30 days periods in order to ensure that enough data (sufficient compliance) is generated during a period for almost all patients. Indeed, as illustrated in Figure 8, variability of all measures decreases exponentially with the time during which the measure is averaged. This decrease becomes nearly flat after 180 hours, and is still acceptable between 50 and 180 hours. The duration of 30 days insure at least 180 hours of recording in patients wearing the device at least one every two days (12 hours/day).

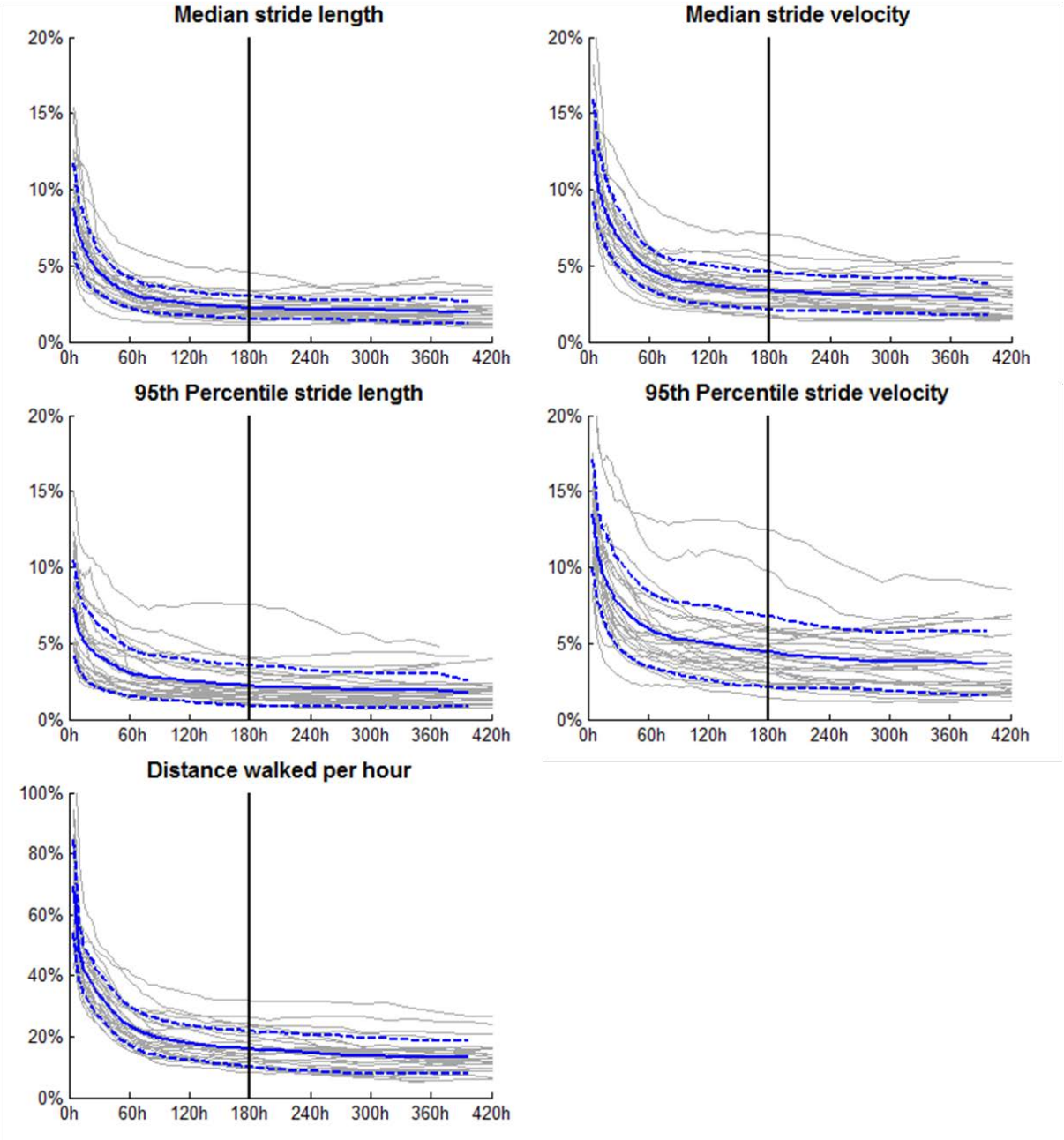
All recordings periods are analyzed individually for each patient. If no steps are detected on the ankle sensors, and if no movement is recorded, the individual recording file is discarded (Fig 4). Then, the sum of the durations of all files recorded in the period is computed to evaluate the compliance.

Figure 22: Compliance calculation decision tree for each file of a recording period

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. We propose to consider the data as missing.

These thresholds are based on the variability calculated with DMD patients as shown in Figure23:

Figure 23: Variability plot for the Proposed Gait Variables measured by the wearable device and system as related to the number of hours of recorded data. Blue line indicates mean curve and dashed line mean+/- SD.



This demonstrates that non-systematic noncompliance is acceptable as long as at least a total of 50 hours is available for analysis.

The effect of systematic non-compliance has also been analyzed:

1. Morning vs Afternoon

We studied the impact of fluctuations through the day by selecting mornings or afternoons only. For the 45 patients considered at baseline, the 95th percentile of stride velocity for the entire day was 1.582 m/s with SD 0.378 m/s.

We isolated morning (8-12AM) and afternoon (2-6 PM) recording periods and found no significant differences (mean 1.564 m/s and SD 0.384 m/s) and (mean 1.600 m/s and SD: 0.387 m/s) respectively. The mean difference between morning and afternoon session was 0.036 m/s with SD 0.215 m/s (Confidence interval: [-0.028, 0.1])

2. The weekend vs the days of the week

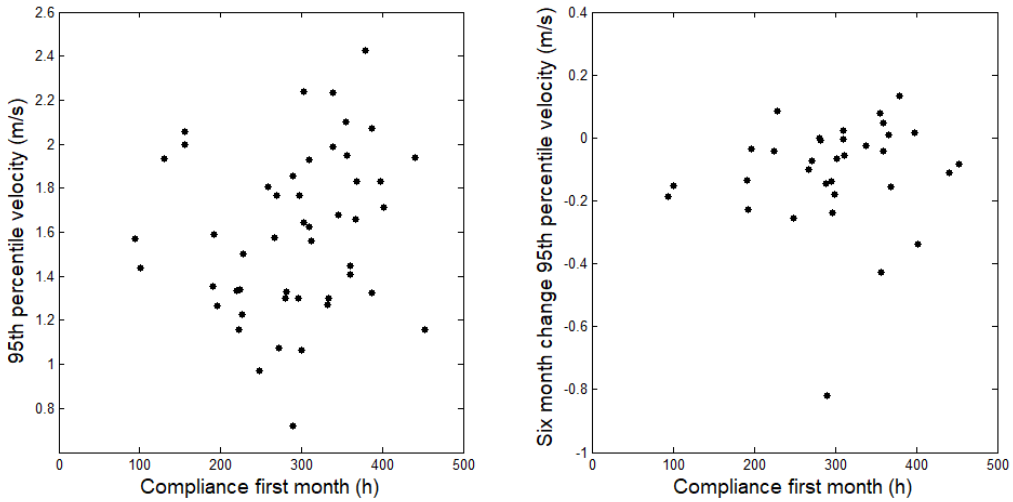
	N	Mean	SD	p-value Wilcoxon
50th Percentile (median) stride length (m)	10	-3.85%	3.20%	0.012*
95th Percentile stride length (m)	10	-3.49%	4.79%	0.0593
50th Percentile (median) stride velocity (m/s)	10	-6.18%	5.18%	0.009**
95th Percentile stride velocity (m/s)	10	-7.34%	9.19%	0.0218*
Distance walked/hour	10	-21.4%	25.0%	0.047*

Difference in activity as measured by the wearable device and system between the week-end and the average over week days *: statistically significant at 0.05, **: statistically significant at 0.01

In DMD patients, there is a significant difference between week days and week end days. Even if this difference account for a variability lower than in classical outcomes measures. For future studies this will be explained to patients (and carers) and the instruction will be to wear the device during week days and weekends.

In order to ensure that the level of compliance has no influence on main parameters, such as 95th percentile stride speed and stride length, we correlated the number of hours recorded during 30 days and Stride length and stride speed (Fig 6). We found no correlation, which demonstrates that level of compliance has no influence on patient's performance.

Figure 24: Absence of correlation between compliance and performance

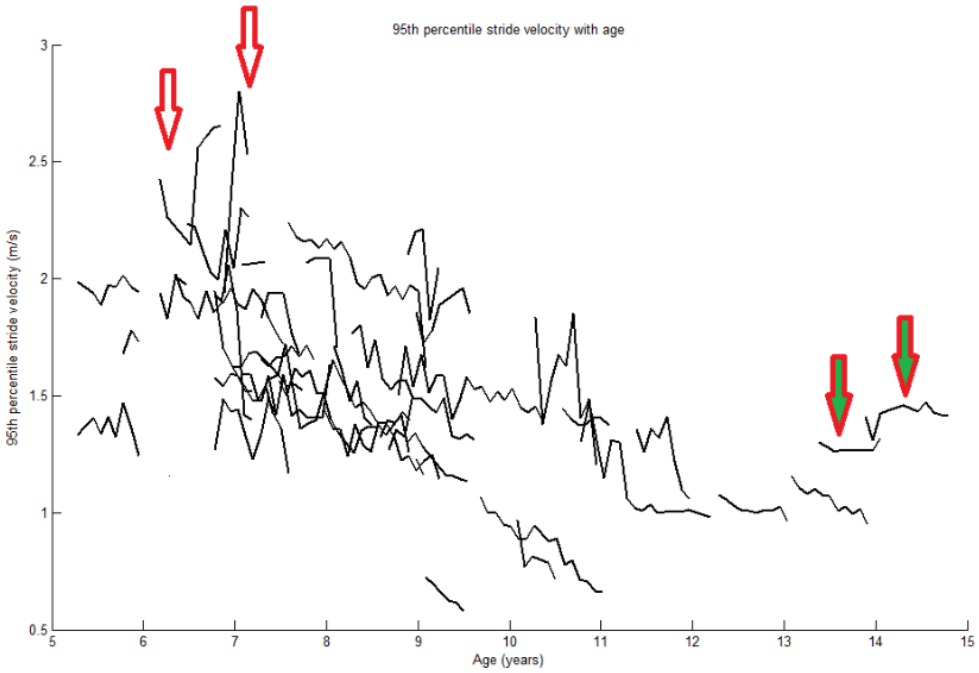


Please discuss the potential influence of outliers on the 95th percentiles of stride length and velocity.

The phenotype of patients with DMD is large, with some patients losing ambulation as early as 6 years, and other patients not losing ambulation until around 15 years of age.

In our studied population, we identified two kinds of outliers illustrated with arrows in Figure 25.

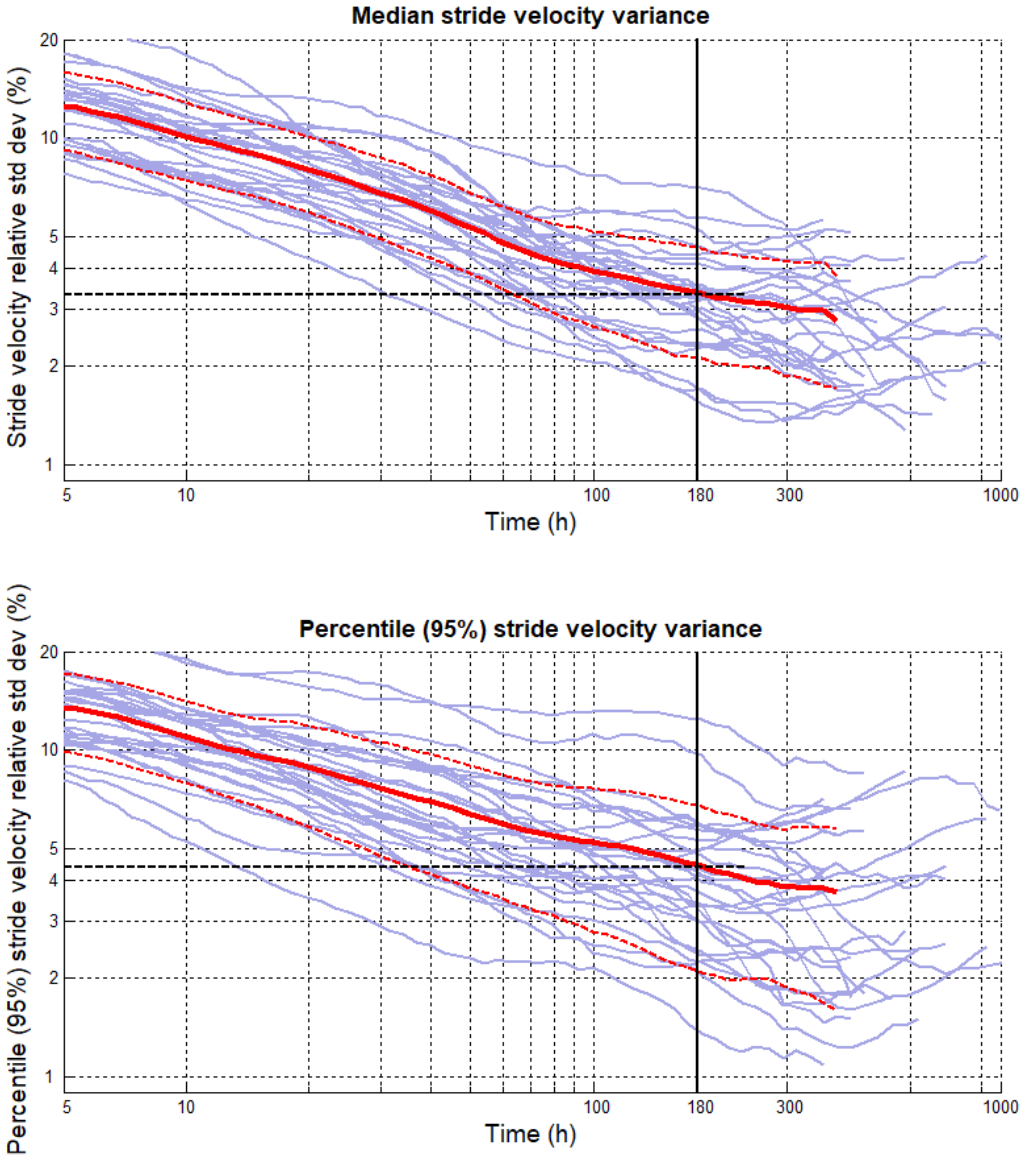
Figure 25: Evolution of 95th percentile of stride velocity measured by the wearable device and system as a function of age



- Two patients with well-preserved ambulation at the age of 14 (Red/Green arrow) have 6MWT of 455 m and 473.5 m at baseline, which strongly demonstrates a well-preserved ambulation. These two patients present a rather stable evolution at a 1-year period
- Two patients with a large variability (RED/WHITE arrow) at 1-year period. In these patients, the variability occurs much more clearly in the top performance (95th percentile) and is not present in the 50th percentile evolution (Median).

When considering the whole group of patients, the variability related to the use of the 95th percentile value of stride speed and stride length reach 4.5% rather than 3.2% when using the median for the same variables.

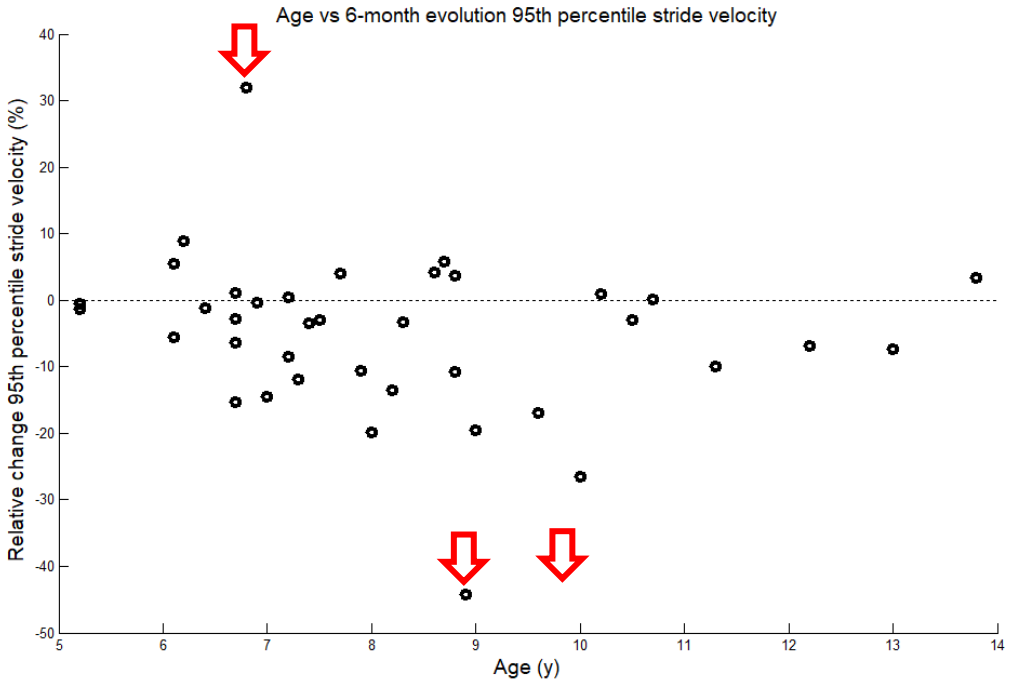
Figure 26: Variability plot for the median and 95th percentile velocity measured by the wearable device and system related to the number of hours of data. Red line indicates mean curve and dashed line mean+/- SD.



Yet the 95th percentile presents a slightly higher variability at baseline when compared to the median of the same variable, its sensitivity to change is much higher. The combined effect of both parameters still results in an improvement of the effect/size when using the 95th percentile value.

The figure below illustrates the distribution of 6 months change. From this figure, it appears that 2 patients present an evolution which is outside the range of other patients which represent 5 % of patients.

Figure 27: 6-month evolution of 95th percentile of stride velocity measured by the wearable device and system as a function of age



Two patients are clear outlier, one was losing ambulation, the other was described by parents and doctor in charge as “very much improving”

Together, it appears that there are an acceptable number of outliers, either related to their mild phenotype or to their variability. They have been included in the analysis and impact only moderately the effect size that remains excellent.

Please discuss how changes in stride velocity will be linked to a clinically relevant effect.

There are several ways of estimating MCID. In the application, we used the methods applied by Craig Mc Donald et al. (2010) to estimate to 30 meters the MCID of 6MWT. Using the same methods, we found a MCID of 0.1 m/s for the 95th percentile stride speed, which corresponds (*360) to 36 m/6 min at top speed.

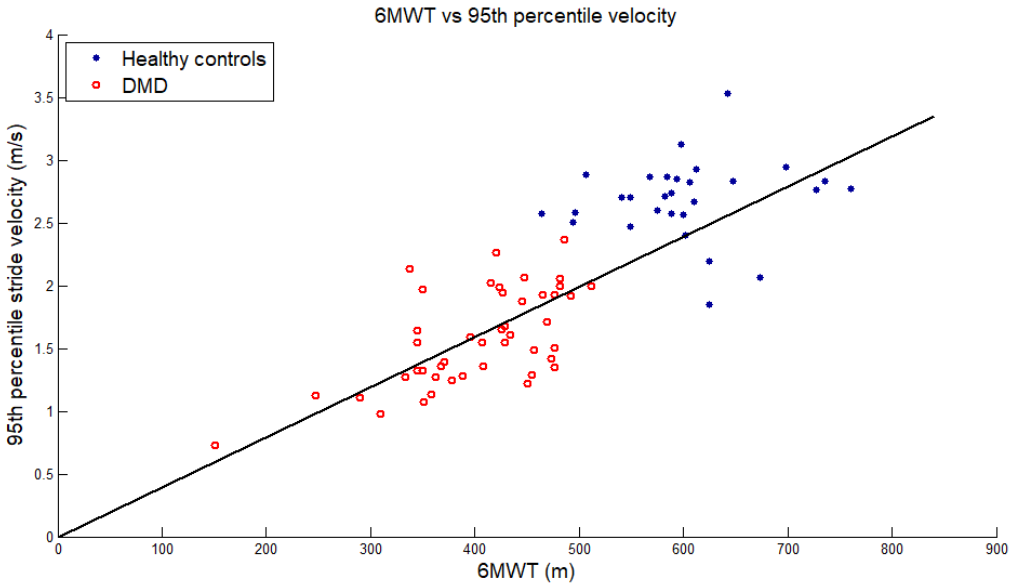
To gain further understanding of what a change of 0.1m/s on the 95th percentile stride speed means, we tried to estimate how many meters in the 6 minutes walking test and how many points on the NSAA it represents.

Since 95th percentile stride speed is linearly correlated to 6MWT (in DMD as well as in controls), we estimated the number of meters in the 6MWT that corresponds to this MCID

The slope of the linear correlation between the 95th percentile of stride velocity and the 6MWT is 0.42 m/s per 100 m of 6MWT (Fig9). It means that a delta of 0,1m/s in the 95th percentile stride speed is correlated to a delta of 23 m in the 6MWT. In addition, 0.1m/s for the 95th percentile stride speed corresponds to 24 meters during 6 minutes at maximum speed.

McDonald CM, Henricson EK, Han JJ, Abresch RT, Nicorici A, Elfring GL, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve. 2010;41(4):500-10.

Figure 28: Correlation between 95th percentile stride velocity measured by wearable device and system and 6MWT for DMD patients



Other approaches to estimate MCID would be to demonstrate the relation between a drop in the 95th percentile stride speed and a probability to lose ambulation. We are currently following a cohort of patients using the wearable device and system, and measuring the Proposed Gait Variables. This data, as well as future trials and follow up will help address this issue in more clarity. However, this will require a significant number of patients and years to generate the necessary data. Indeed, the age at loss of ambulation does not only depend on the pace of disease evolution: Loss of ambulation may occur after a fracture or a strain and is also dependent upon patient and caregivers motivation to preserve a minimal ambulation. In addition, steroids treatment or contracture management adjustment, including treatment interruption, may significantly interfere with the age of loss of ambulation, which is a major manifestation in DMD. In addition, improvement in standard of care as well as new therapeutics will add to uncontrolled variables that significantly interfere with the prediction for loss of ambulation.

Thus, any methods, as sensitive and clinically relevant it can be, will only predict the age at loss of ambulation up to a certain extent, and the robustness and clinically relevance of this prediction will always require very large number of patients, given the number of uncontrolled variables.

Therefore, relying on age at loss of ambulation prediction for new outcome will be increasingly difficult, and will require larger and larger cohort, precluding the use of innovative and expensive new technologies.

This constitutes the rationale of the different methods used in this application to evaluate the MCID, using the commonly accepted 30 meters difference in 6MWT as a currently accepted 'gold-standard' comparator.

Please outline your plans to generate more comparative data to conventional ambulation endpoints. The discussion should include the most appropriate parameter for comparison.

The wearable device and system is currently being used in new DMD phase III and phase I studies with [redacted] which demonstrates the interest of pharmaceutical companies in these new outcomes. Since these studies include placebo controls, they will allow not only to evaluate sensitivity to positive

change-as long as the drugs are effective-but will also contribute to the natural history dataset. However, the “last patient last visit” is scheduled more than two years from now for [redacted], so patients group allocation-and thus data use, cannot be scheduled before, but should not be considered as a reason not to adopt this data source as a meaningful insight already.

The study “Actiliège”, (Sponsor: CRMN Liège, Co-Funder Action DMD), also allows the inclusion of DMD patient and thus present the opportunity of gaining more results.

The increasing number of studies in DMD means that conducting natural history studies is now more and more difficult, and the cost of technology makes it difficult to sustain if data cannot also be used during interventional studies.

Qualification by EMA at this point would greatly help to demonstrate the value of this approach in data generation, and as a result gain more trust and buy-in amongst other stakeholder groups (e.g. pharmaceutical companies, clinicians and patients) which then ultimately supports the on-going generation of much more data and thus gaining increasing robustness and confidence in the definition of MCID.

Regarding the conventional outcome for comparison, we believe that the 6MWT and the four stair climbing test are the most appropriate for the short-term evaluation, and the loss of ambulation for a much longer term comparison goal. The 95th percentile of stride speed and stride length measure patient’s top ambulation performance during home assessment. The more direct comparison is achieved with patient’s ambulation top performance during hospital assessment.

The wearable device and system has also the potential to record stairs climbing at home, which may constitute a valuable outcome in younger patients, still able to climb stairs. The 95th percentile of stair climb velocity will be best correlated with the four stairs climbing test, that represent also the top velocity in climbing stairs-but in a controlled environment and during a single assessment.

In summary, predicting loss of ambulation will require not only much more time, but also much more patients, and will be more and more difficult for new outcome, given the large numbers of interfering variables between a measure a time T and the event “Loss of ambulation” three years later (change in steroids treatment, contracture management, new therapeutics, occurrence of fracture or strain….) and the increasing number of patients included in trials. In addition, 6MWT and FSCT represent primary outcome frequently used in pivotal trials in DMD, and as such considered adequate.

Please discuss further validation plans in interventional clinical trials with respect to the adequate measurement period in randomized controlled trials; sensitivity to change.

Most studies in DMD run for a 1 year period, but given the poor sensitivity of current outcome, a general trend is to design them for longer (NCT03218995, NCT2500381, NCT02851797….), which raises major ethical challenges, especially when placebo groups are included. As we have demonstrated, the Proposed Gait Variables measured by the wearable device and system appear to capture a change within 6 months even with a limited group size of patients. As such we are confident that the duration of the study is far long enough to observe a clinically meaningful significant change if it occurs.

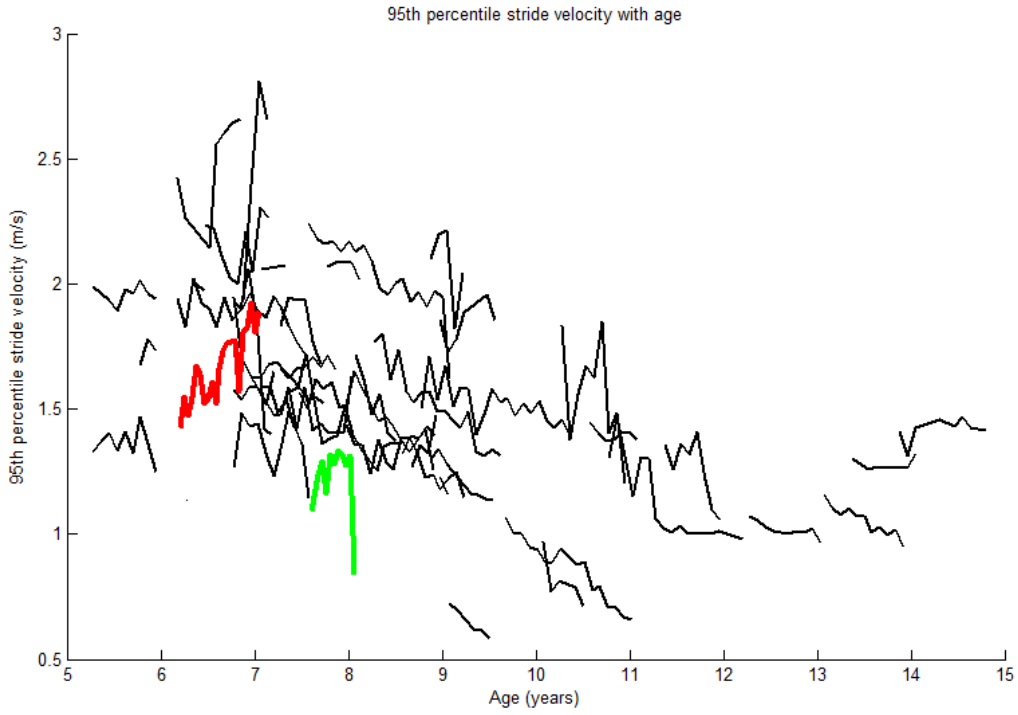
The current recommended use of the wearable device and system is either to record continuously either to record during pre-specified time period of at least 1 month with periods of “holidays” in order to decrease patients burden. In trials for which the Proposed Gait Variables measured by the wearable device and system are to be used as the primary outcome, a baseline period of 180 hours (to be

acquired during screening and baseline) would be defined, and patient randomized to treatment or placebo after this period has been recorded.

Through the currently ongoing therapeutic studies using the Proposed Gait Variables measured by the wearable device and system, we will also be able to verify this and better define the optimal period of recording if required for patient feasibility/ burden and/or data quality as necessary, while still maintaining minimal criteria to ensure comparative data sets.

However, this will have to be suited to the protocol design and to the expect mode of action of the drug. Indeed, for drug where a rapid effect is expected, as in steroids, continuous measure should be encouraged. We have two cases (more are planned) of patients who starts steroids during recording use, and their evolution within the first weeks and months of treatment is markedly different that the standard DMD evolution after stable steroids, which indicates that continuous measurement is clinically valuable and can be justified in those scenarios too.

Figure 29: Evolution of 95th percentile of stride velocity as a function of age for DMD patients highlighting two patients who started steroid treatment



The patients in red and green are patients who started a steroid treatment while being given a device. The first point corresponds to data recorded before starting steroids treatment. Patient in green was rapidly declining, and parents decided to try steroids to manage their son rapid deterioration. Parents reported rapid improvement during the first weeks of treatment, then the patient presented with rapid deterioration. Patient in red can be seen to be markedly different after starting steroids compared to other patients on stable steroids.

In contrast to drugs that present rapid effect, like steroids, a phase 3 trial with an exon skipping drug that restore a limited amount of dystrophin could certainly accommodate a block of one-month use to capture a minimum of 180 hours every 3 or 6 months.

Qualification of the device by EMA would certainly help to include the device in more studies, and thus being able to better target its use to these methodological questions assessed by the different studies and the different mechanism of action.

Please outline your plans of validation in non-ambulatory or younger DMD patients and other indications.

Work is ongoing to validate variables measured by the wearable device and system in both younger and older non-ambulant population

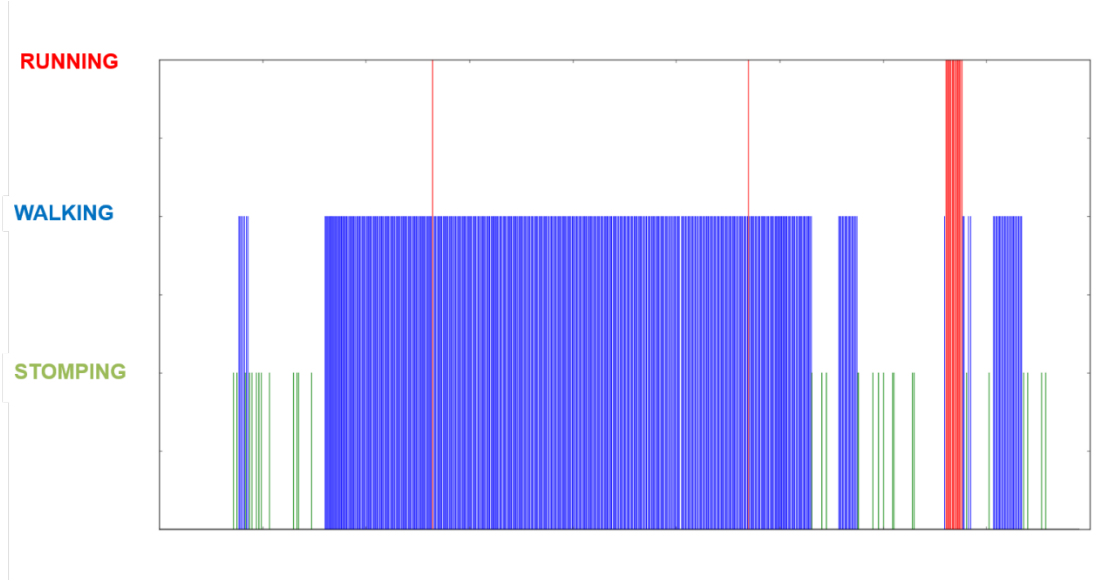
In younger DMD patient (less than 5 years of age)

Younger DMD present a double challenge, on the hardware and software aspect of the device

Hardware challenge: The device today is not suited for children below the age of 5 years because of its size. Adaptation of the hardware to make it lighter and more importantly a smaller device is needed and planned in order to be able to assess this population.

Software challenge: Climbing stairs velocity, running and falls seem to be promising outcome in this age group. Current work is ongoing to individualize these motor activities through machine learning approaches.

Figure 30: Classification of running and walking strides in a controlled environment for DMD during a 6MWT and a running exercise



1. In older non-ambulant patients.

The device was originally designed for non-ambulant patients, and first data already published in this population (Le Moing et al PlOS One 2016). Currently, data are available in 12 DMD patients.

First data have been presented recently at the World Muscle Society (Seferian et al. https://doi.org/10.1016/j.nmd.2017.06.503)

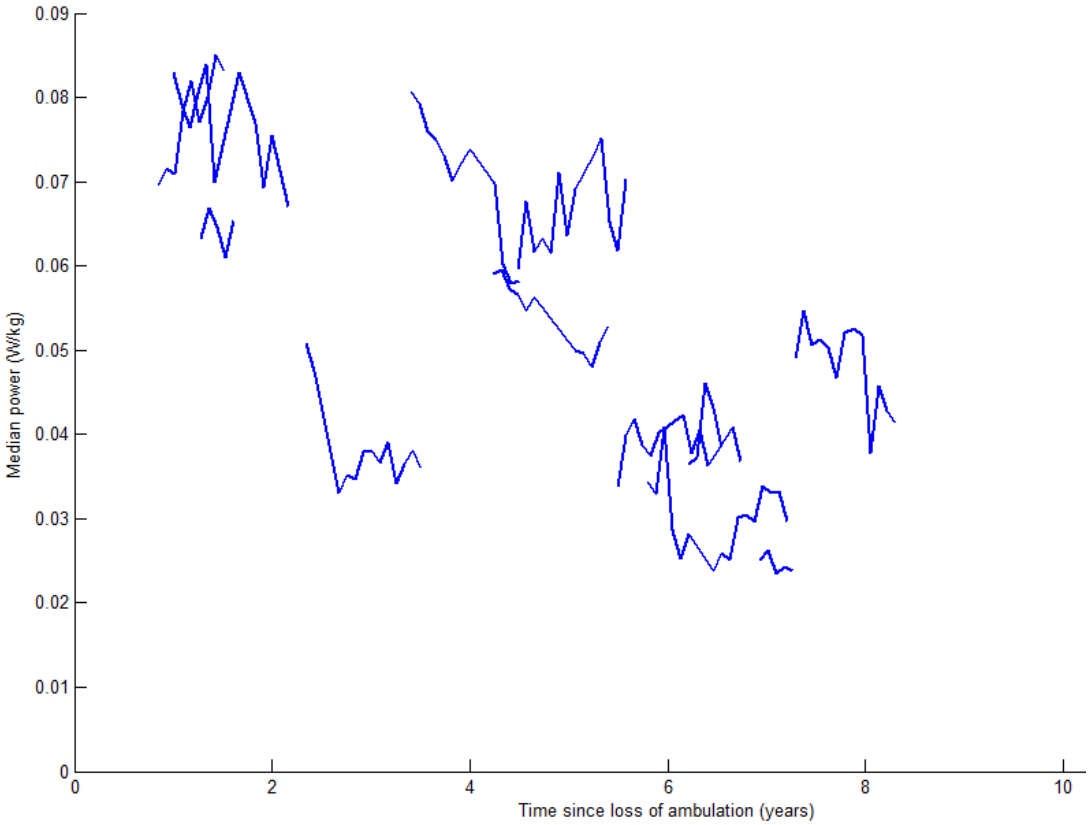
Further validation plan is as follows:

1. Evaluate variability and optimal period of recording of the variables initially described (Le Moing et al.) with the sensor placed on the wrist and on the wheelchair: Vectorial norm of gyroscope signal (Median), Vectorial norm of accelerometer signal (Median), Proportion of movements including an anti-gravitational component, Power developed by the forearms
2. Evaluate correlation with Brooke score, Hand grip, Vital capacity

3. Evaluate sensitivity to change and effect size

Initial data on sensitivity to change seem very promising, as shown in example below:

Figure 31: Non-ambulant variables, longitudinal evolution



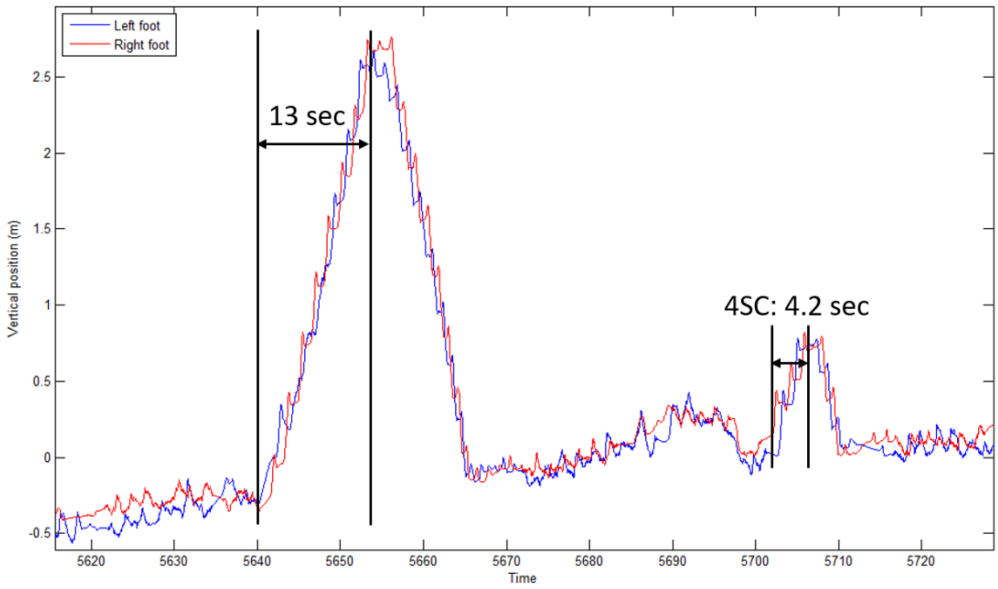
It appears that the sensors the wearable device and system can record additional data apart from stride length and stride velocity which could potentially provide information on gait pattern, the quality of walking, falls, sway, climbing stairs and time to stand. The Applicant is kindly requested to clarify this.

Additional endpoints related to gait are currently being investigated. The trajectory of the foot during walk is calculated so using this trajectory additional variables could be extracted possibly estimating the quality of walk and sway.

Active research is ongoing to detect episodes of falls, stairs climbing running using machine learning techniques.

Preliminary data are very encouraging, but the robustness has not yet reached the stage of robustness focusing primarily on control environment achieved in stride length and stride speed analysis.

Figure 32: Example of stairs detection with measurement of height climbed and time to climb



The results and the validation data will be presented when they are available and are estimated to be another 2 years away.

The impact of magnetic disturbances has been evaluated for the wearable device and system. Have the devices (docking station and sensors) been tested for electrical, radio or WIFI interferences?

The calculation of gait variables is based on the accelerometer and gyro measurements. These sensors are sensitive to movements, acceleration and angular velocity but not to magnetic field. Therefore, the measurements are not sensitive to magnetic disturbances.

The electronic components used in the sensors devices and in the station are standard components not sensitive to electromagnetic disturbances also used in appliances designed for home or industrial environments such as mobile phone, car electronics, etc. Additionally, the system (station and sensors) has passed electromagnetic compatibility tests required for CE marking.

Applicant's response to 2nd list of written questions

The Applicant used the methods applied by Craig Mc Donald et al. (2010) to estimate to 30 meters the MCID of 6MWT. Using the same methods, a MCID of 0.1 m/s for the 95th percentile stride speed, which corresponds to 36 m in 6 min at top speed, was found. The number of meters in the 6MWT that corresponds to this MCID was estimated based on a linear correlation between the 95th percentile stride speed and the 6MWT. The slope of the linear correlation between the 95th percentile of stride velocity and the 6MWT is 0.42 m/s per 100 m of 6MWT It means that a delta of 0,1m/s in the 95th percentile stride speed is correlated to a delta of 23 m in the 6MWT. In addition, 0.1m/s for the 95th percentile stride speed correspond to 24 meters during 6 minutes at maximum speed.

Questions and answers

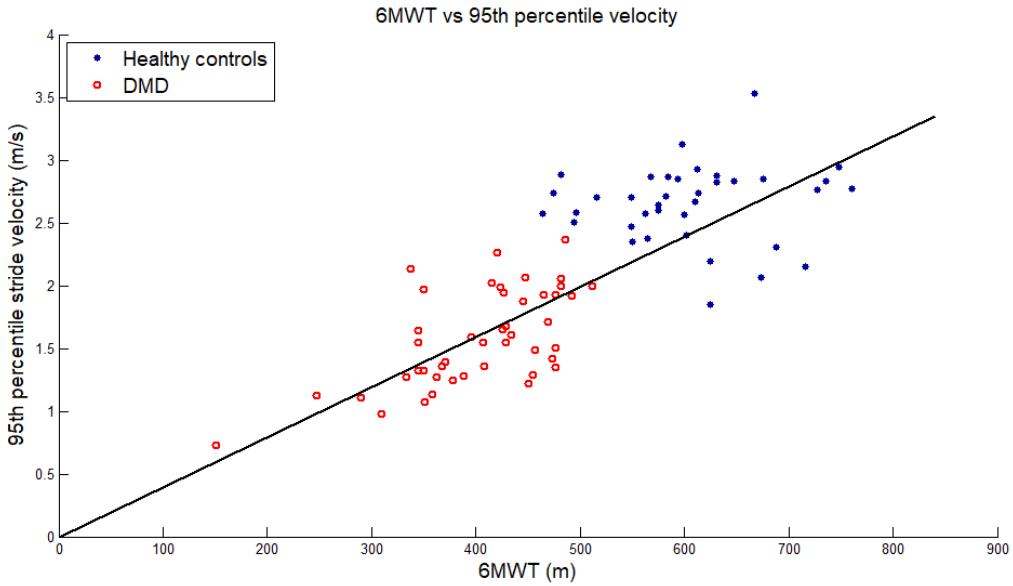
Can you explain mathematically the working out of how you got the 24 m as this is not clear.

The correlation at baseline between 6MWT and 95th percentile stride speed is:

		Pearson		Spearman	
	N	*r*	*p-value*	*ρ*	*p-value*
DMD	*45*	*0.616*	*0.0000*	*0.542*	*0.0001*
All (DMD and healthy controls)	*82*	*0.799*	*0.0000*	*0.811*	*0.0000*

So assuming a proportionality between 6MWT and 95th percentile stride speed, the slope is 0.42m/s per 100m of 6MWT when considering all DMD and healthy control under the age of 18 years (37 healthy controls and 45 DMD), see figure below:

Figure 33 Correlation between 6MWT and 95th percentile stride speed for children (37 healthy controls and 45 DMD)



It means that 0.1m/s corresponds to 100/4.2 = 23.8 m

1. ***If you confirm this number, please comment on the differences between the 36m, (distance at MCID 95CSV), 23m (distance in 6MWT from correlation) and 24m (distance in 6MWT from correlation) and 30m (distance at MCID 6MWT) - and how this all can be put together / interpreted not just that these are in the same order of magnitude?***

We defined the MCID using the same distribution-based method that the one used by Mc Donald et al.,

$MCID = SD * \sqrt{(1-R)}$

The other formula proposed by the same authors: MCID = 0.3333 SD considers that R ~ 0.88, so it is a simplification of the formula. This simplification underestimates MCID for methods with low reliability.

Using the non-simplified formula, we found an MCID of 0.0985 m/s. This corresponds to 35,46 m/6min. We approximate conservatively to 0.1m/s

The most straightforward way to understand this value is to consider that both 95th percentile stride speed and 6 MWT measures the same patients top velocity. The difference between the two measures

is that 6MWT is performed during 6 minutes in a controlled environment, and that there is a huge motivational factor that raised uncertainty on the measure. Considering that 95th percentile stride speed and 6MWT measure the top velocity, 0.1 m/s = 36 m/360s. So, 0.1 m/s is more conservative than 30m/6min.

We then compared this top velocity with the top velocity measured by the 6MWT using the correlation at baseline. We found that 0.1 m/s corresponds to 24 m at baseline for the 6MWT. This comparison was performed just to ensure that both measures were in the same order of magnitude. However, this way of comparing is much less precise, since the slope of correlation is influenced by the motivation of the patients to perform the 6MWT.

Altogether, using the same complete formula than the one which led to the commonly accepted 30 m MCID for 6MWT, we found 0.0985m/s that we conservatively approximate to 0.1m/s, which corresponds to 36 m/6min. This is in the same order of magnitude than the MCID of 6MWT.

2. ***The 30m MCID for the 6MWT- from the McDonald paper this was 28, or 31m depending on the different distribution methods. Please comment on the 30m MCID in this regards.***

Mc Donald et al. proposed two formulas, one is a simplified version of the other.

Initial population-based formula is

$MCID = SD * \sqrt{(1-R)}$

The other formula proposed by the same authors: MCID = 0.3333 SD, so it considers that R ~ 0.88. It is so just a simplification of the initial formula. This simplification underestimates MCID for methods with low reliability.

3. ***Please briefly describe the evidence around the 30m MCID and association with loss of ambulation. We noted your comments in the written answers.***

A 10% decline in ambulation over 12 months is associated with significantly greater likelihood of lost ambulation over the next 4 years (Mc Donald et al. 2012) and, given a typical baseline 6MWD of 350 m, a 30-m change to 320 m (which approaches a 10% change) places patients below a threshold level of function where they become at risk of losing ambulation. (Mc Donald et al. 2013)

4. ***Do you have any further data on longitudinal correlation with NSAA, 4SC, the MCIDs of these (you mentioned in the discussion meeting?), or can you confirm detailed plans for collecting these data.***

We ran a similar MCID comparison for NSAA than we did for 6MWT. Since NSAA and 95th percentile stride speed measure two different parameters, we estimated at baseline to how many points of NSAA correspond 0.1 m/s change in the 6MWT

The correlation slope between 95th percentile stride speed and non-linearized NSAA (scored on 34) is 0.04295 m/s per 1-point NSAA. It means that 0,1m/s on the 95th percentile stride speed is correlated with 2,32 points on the non linearized North Star, which corresponds approximatively to 7 point in the linearized North Star. This is considered as the MCID for NSAA (Mayhew et al.)

5. ***Can you please send us the substudy protocols for the studies below dealing with the wearable device and system, data collection and analysis that you presented***

The studies used for the analyses presented are [Redacted for commercial confidentiality]. The protocols are detailed in the attached document to the submission.

The analyses done using data from these protocols and presented in the dossier are:

- Validation of the stride measurements by comparing the 6MWT distance measured by the wearable device and system and by a physiotherapist
- Validation of the stride measurements using an optical motion tracking room as reference for healthy controls (7 adults and one child)

- Baseline correlation between the Proposed Gait Variables and the references variables (6MWT, North Star Ambulation Assessment and 4 stairs climbing)
- Variability as a function of time recorded for the patients with more than 1800 hours of data recorded
- Comparison between weekends and week days and between mornings and afternoons
- Change of Proposed Gait Variables between the first month and the 6^{th} or 12^{th} month
- Correlation between the Proposed Gait Variables evolution at 6 and 12 months with the 6MWT evolution for the patients available
- Calculation of MCID comparing 95^{th} stride speed and 6MWT
- Duration of proposed system recordings during in the 30 days following the start of use

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