Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000103: ActiMyo®
Letter of Intent

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

NAME	*EMPLOYER*	*STATUS*	*LABORATORY*	E-MAIL
David Vissiere	Sysnav	CEO	R&D	david.vissiere@sysnav.fr
Marc Grelet	Sysnav	Engineer	R&D, medical device division	marc.grelet@sysnav.fr
Laurent Servais	Association Institut de Myologie (AIM)	MD, PhD	I-Motion – platform for pediatric clinical trials	l.servais@institut-myologie.org
Amélie Moraux	Association Institut de Myologie (AIM)	Engineer	Neuromuscular physiology and evaluation laboratory	a.moraux@institut-myologie.org
Andreea Seferian	Association Institut de Myologie (AIM)	MD	I-Motion – platform for pediatric clinical trials	a.seferian@institut-myologie.org
Erwan Gasnier	Association Institut de Myologie (AIM)	PhD	I-Motion – platform for pediatric clinical trials	e.gasnier@institut-myologie.org
Serge Braun	Association Française contre les Myopathies (AFM)	Advocacy group	Scientific Director	sbraun@afm-telethon.fr
Fiona Lawrence	Duchenne UK	Advocacy group	Director of Research and Clinical Development	fiona@duchenneuk.org
Mónica Fernández Moret	Asociacion Duchenne parent project Espana	Advocacy group	Coordinator of the Research Department	investigacion@duchenne-spain.org

Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities)

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 medication(1), leading to FDA refusals, 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) or the 4-stair climbing test are unsatisfactory. They are highly dependent on patient motivation at the time of assessment. They represent a single time point evaluation in a controlled environment, where the patient must often travel long distances to be assessed, which not only interfere with family, social and school life but also with the assessment itself, as the patient may be tired because of the travel to the research centre or distracted from missing school / social activities. At best, they represent discrete peak motor performance of the patients at a given time, but are partially subjective and assessor-dependent. This is especially true for scales or for short timed test.

The sensitivity to change also remains poor. Minimal clinically significant change for North Star Ambulatory Assessment (NSAA) score is about 8 units per year, which implies large cohorts of patients, or very long studies, to reach this threshold(2).

In contrast, monitoring the patients' real life would allow a continuous and completely objective assessment of daily circumstances, and a much more clinically relevant and powerful outcome measure for clinical trials. Indeed, such measure 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. One of the problems is of technological nature: in order to precisely evaluate movements, sensitive and highly stable recording devices and adapted software are required.

In order to tackle this issue, we produced a sensor based on magneto-inertial technology, the ActiMyo®, able to capture very precisely all linear acceleration and velocity and angular velocity, allowing precise qualification and quantification of patient activity, in non-controlled environment.

Targeted labeling or promotional claim(s) based on the COA to be developed (i.e., proposed wording)

Continuous monitoring of patients with neuromuscular disorders movement using magneto-inertial technology.

COU for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups)

Duchenne muscular dystrophy (DMD) is a devastating childhood pathology, affecting 1 in 5000 boys (3). This disease causes progressive and unyielding muscle weakness with survival up to the 3rd and 4th decade. Loss of ambulation occurs generally around the age of 12.

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(4). However, this measure 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 a 1 year period. 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.

Six minutes walking distance has also been used in other neuromuscular diseases, such as facioscapulohumeral dystrophy and spinal muscular atrophy type 3.

The currently used assessment tools for upper limb function in non-ambulant DMD patients include observer-rated performance in a controlled environment and self-reported questionnaires (5-9). Collaborative efforts among medical doctors, physiotherapists, and patients have led to development of a novel scale for assessing performance of upper limbs (10), a stereo camera-based reachable workspace analysis system (11, 12) or a skeletal tracking system (13, 14).

These different approaches aim to quantify peak patient performance in a controlled environment, and do not reflect meaningful real-world outcomes that matter to patients.

ActiMyo® is designed to be used from the age of 5 years until very advanced stage of the disease, when the Brooke score is 5 (i.e. when the patient is able to carry a pencil).

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*)**

ActiMyo® is designed to be used in ambulatory and non-ambulatory subjects. Work done to date using the ActiMyo® have identified several measures that are robustly measureable in ambulant patients and that are clinically relevant in the context of neuromuscular diseases. These include the 95th Percentile of the stride speed (primary), the median stride speed, the 95th Percentile and the median stride length (secondary), and distance walked/recorded hour (tertiary). Validation of variables relevant to non-ambulatory subjects is still ongoing.

To validate relevant measures for ambulatory subjects, the following work has been done:

1. Demonstrate that foot trajectory of ambulant patients as assessed by the magneto-inertial sensor correspond to the real distance as manually measured. In this purpose, we have measured simultaneously the distance performed during 6MWT using the ActiMyo® and using the classical method in 31 tests performed by 23 different patients within a large range of clinical conditions.

2. Measure the reliability of these variables: 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 Allan Variance.

3. Cross validate these measures: We have studied the relation in 45 DMD patients between stride speed, stride length, distance walked per hour and 6MWT, + North star ambulatory assessment for DMD.

4. Study the sensitivity to change: We have studied 31 patients over 6 months and 11 patients over 1 year to capture the mean change in a 6 month and 1 year period.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***
- ***Other study setting specifics (e.g., inpatient versus outpatient)***

ActiMyo® 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 autonomy and feasibility of the device use (15). 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. 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.

Since then, world leading research centres have equipped patients with ActiMyo® during international natural history clinical trials in: University College London, UK for the natural history of Duchenne Muscular Dystrophy; the National Institute of Health, USA for congenital muscle dystrophy. The system has been purchased by several prestigious sponsors, such as Genethon (NCT 01385917), Valerion Therapeutics (NCT 02057705), Sarepta Therapeutics (NCT 02310906), AtyrPharma (NCT 02579239) and the Association Institut de Myologie (NCT 01611597, NCT 02780492 and NCT 02391831).

Currently, 173 ActiMyos® have been used in 10 countries (France, UK, Italy, Denmark, Romania, USA, Spain, Germany, Belgium and The Netherlands), used in 7 different protocols in 6 diseases (DMD, SMA, FSH, LGMD2D, X-MTM and Parkinson), and purchased by 5 different sponsors. There is a user manual with validated translation in French, English, Spanish, German, Dutch, Romanian, Italian, Polish, Portuguese, Turkish and Chinese. Further discussion is also ongoing with several sponsors to include ActiMyo® as a secondary outcome measure in upcoming trials.

ActiMyo® data of patients currently recorded in European clinical trials has provided extensive feedback from physicians, physiotherapists and patients.

COA Type: Digital Monitoring Clinical Outcome Assessment

ActiMyo® is a wireless wearable device for continuous recording of patient's movements, containing a tri-axial accelerometer, gyroscope, magnetometer and barometer that record the linear acceleration, the angular velocity, the magnetic field in all directions and the elevation. The device is light (38g; 43/33/20mm) and can be worn as a watch/ bracelet. The battery allows for 16 hours of data capture recording. A set comes with a docking station and two devices, one to be worn at the wrist and one around the ankle or on the wheelchair. The generated raw data are downloaded to the docking station and stored on an internal USB memory or sent via the internet to a platform for analysis. Accelerometry data is computed using specific software and algorithms.

Compared to conventional actimetry devices, one novel feature of the ActiMyo® system is the capability to reconstruct trajectories using a patented and validated technology. This allows precise measurements of variables such as stride length, stride speed, distanced covered, and number of falls (for ambulant patients) to be captured continuously. For non-ambulant patients, we have also developed several variables such as a computed power of the upper limb that corresponds to the mechanical power necessary to move the forearm or the elevation rate of the forearm (for non-ambulant patients) (15).

References

1. Bushby K, Finkel R, Wong B, Barohn R, Campbell C, Comi GP, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. Muscle Nerve. 2014;50(4):477-87.
2. Ricotti V, Ridout DA, Pane M, Main M, Mayhew A, Mercuri E, et al. The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. J Neurol Neurosurg Psychiatry. 2016;87(2):149-55.

3. Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. Neuromuscul Disord. 2014;24(6):482-91.
4. McDonald CM, Henricson EK, Han JJ, Abresch RT, Nicorici A, Atkinson L, et al. The 6-minute walk test in Duchenne/Becker muscular dystrophy: longitudinal observations. Muscle Nerve. 2010;42(6):966-74.
5. Berard C, Payan C, Fermanian J, Girardot F, Groupe d'Etude MFM. [A motor function measurement scale for neuromuscular diseases - description and validation study]. Rev Neurol (Paris). 2006;162(4):485-93.
6. Connolly AM, Malkus EC, Mendell JR, Flanigan KM, Miller JP, Schierbecker JR, et al. Outcome reliability in non ambulatory boys/men with duchenne muscular dystrophy. Muscle & nerve. 2014.
7. Hiller LB, Wade CK. Upper extremity functional assessment scales in children with Duchenne muscular dystrophy: a comparison. Archives of physical medicine and rehabilitation. 1992;73(6):527-34.
8. Mazzone E, Vasco G, Sormani MP, Torrente Y, Berardinelli A, Messina S, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology. 2011;77(3):250-6.
9. Servais L, Deconinck N, Moraux A, Benali M, Canal A, Van Parys F, et al. Innovative methods to assess upper limb strength and function in non-ambulant Duchenne patients. Neuromuscul Disord. 2013;23(2):139-48.
10. Mayhew A, Mazzone ES, Eagle M, Duong T, Ash M, Decostre V, et al. Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy. Developmental medicine and child neurology. 2013;55(11):1038-45.
11. Han JJ, Kurillo G, Abresch RT, Nicorici A, Bajcsy R. Validity, Reliability, and Sensitivity of a 3D Vision Sensor-based Upper Extremity Reachable Workspace Evaluation in Neuromuscular Diseases. PLoS currents. 2013;5.
12. Kurillo G, Han JJ, Abresch RT, Nicorici A, Yan P, Bajcsy R. Development and application of stereo camera-based upper extremity workspace evaluation in patients with neuromuscular diseases. PLoS One. 2012;7(9):e45341.
13. Lowes LP, Alfano LN, Crawfis R, Berry K, Yin H, Dvorchik I, et al. Reliability and validity of active-seated: An outcome in dystrophinopathy. Muscle Nerve. 2015;52(3):356-62.
14. Lowes LP, Alfano LN, Yetter BA, Worthen-Chaudhari L, Hinchman W, Savage J, et al. Proof of concept of the ability of the kinect to quantify upper extremity function in dystrophinopathy. PLoS Curr. 2013;5.
15. Le Moing AG, Seferian AM, Moraux A, Annoussamy M, Dorveaux E, Gasnier E, et al. A Movement Monitor Based on Magneto-Inertial Sensors for Non-Ambulant Patients with Duchenne Muscular Dystrophy: A Pilot Study in Controlled Environment. PLoS One. 2016;11(6):e0156696.