Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000106: Actibelt® in Multiple Sclerosis
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.

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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)

"A change in real-world walking speed in diseases where mobility is a concern measured by a mobile accelerometer for seven consecutive days for use as primary endpoint to determine efficacy of a drug of investigation in pivotal clinical trials.

The change in real-world walking speed, that is considered clinically relevant:

- For Multiple Sclerosis: 0.1 m/s
- For recovery after surgical treatment of hip fracture: 0.1 m/s
- For Sarcopenia: 0.1 m/s

The threshold value of 0.1 m/s is proposed as a threshold that Trium believes would translate into a clinical meaningful change in real-world walking speed across the above listed conditions and beyond, where impaired mobility forms the major burden of disease. Trium believes that mobility and gait speed, being a central facet of independence and quality of life, has far wider relevance, and the universality of the proposed threshold should be investigated for specific severities or subpopulations in other mobility impaired indications."
(from EMA Briefing Book, Intended use, p 10).

Provide a conceptual framework for the COA(s)

Mobility is a broad term describing our ability to move freely within our environment, however, we believe that the most important aspect of mobility, and the focus of this Briefing Book, is walking. We further divide this into "walking ability" and "walking behavior".

Walking ability is what a person is capable of doing and a person's walking ability is indicative of their quality of life as it is considered to being essential for most activities of daily living (Tudor-Locke 2001;

Winter 2010). Strictly speaking, walking ability does not necessarily reflect actual habitual behaviors seen in normal daily life routines, i.e. walking behavior. Walking behavior is how a person normally walks in their daily life. For example, a person typically walks at a moderate pace to work and back home (walking behavior) but may be able to walk much faster or even run if motivational influences prompts them (walking ability).

Walking ability is multifactorial and encompasses endurance, speed, power, balance, and poise. It is well known that walking ability is not only affected by MS, hip fracture and sarcopenia, but is also modified by obesity, asthma, COPD, diabetes, heart insufficiency, hypertension, stroke, Parkinson's disease, Alzheimer's disease, and other neuromuscular and neurodegenerative diseases, as well as by aging and age-related frailty (WHO fact sheet 2016, WHO Recommendations 2010, Cesari 2011). For Parkinson's disease, e.g., difficulties in walking are among the first early symptoms that indicate the onset of disability (Shulman 2008). In Alzheimer's disease, gait speed declines before cognitive deficits become symptomatic (Verghese 2014). A person's walking ability determines their independence at home, capacity to achieve self-actualization and to function in society, and is therefore a clinically relevant target. However, a true and direct measurement of a patient's walking ability is difficult due to motivational factors, white coat effect" and limited space and time during clinical interactions.
The limitations of current methodologies have motivated our efforts to find a pragmatic substitute for walking ability and to find or develop tools to measure it (Helmerhorst 2012). Such limitations include the inability of short-term clinical tests to assess true walking ability or capture fluctuations and exacerbations in performance, as well as self-reported activity questionnaires yielding incomplete, insensitive and/or variable results.

A pragmatic substitute for walking ability should:
1. Have an obvious link to a patient's quality of life.
2. Be quantifiable with current technology with sufficiently low signal-to-noise ratio to allow for manageable sample sizes.

Walking behavior fulfills the first requirement. In disabled patients, long-term real-world walking behavior is strongly linked to walking ability, since it can be expected that patients will frequently reach the limits of ability in daily life. For example, in the United States the ability to walk at least 1.32 m/s is considered to be the lower threshold for safe street crossing (Salbach 2013). We therefore consider real-world walking behavior, measured continuously, as a potentially reliable endpoint for use in clinical trials and as a reasonable surrogate to estimate a person's walking ability as well.

Walking behavior, in contrast to walking ability, has another substantial advantage: there is a strong body of evidence that walking is critical for a person's health. This notion is supported by epidemiological data and more recently by studies uncovering the molecular basis for the beneficial effect of walking exercise on muscles action via anti-inflammatory, neuroprotective and neurodegenerative qualities (Pedersen 2009, Handschin 2008, Safdar 2016). Therefore, actual walking behavior indicates the use of large muscle groups which is linked to the production of myokines and exerkines. Walking ability alone does not trigger this effect. Therefore, the link from actual walking behavior to a patient's quality of life is extending to the future.

A reliable quantification of real-world walking behavior can now be achieved using the actibelt. We are able to instruct patients to wear the device in their normal daily life routines to gather detailed recordings of their true daily walking behavior, thereby fulfilling the requirements formulated by Pearson et al (Pearson 2004) that a "gold standard "for measuring ambulatory mobility in neurological disorders should be the total ambulatory activity undertaken by an individual in their usual environment in performing their usual range of daily activities. From a patient's recordings, bouts of daily walking can be extracted and the corresponding durations, distances and speed can be measured. Other aspects linked to realworld

walking behavior include gait variability, gait asymmetry, gait instability, including stumbling and falls, and the statistical distribution of sequences of steps in a row. Accurate estimates for the number of steps per day obviously need high daily wearing times; estimates for mean daily walking speed are more robust.

It is obvious that real-world walking speed, as element of real-world walking behavior is of particular importance and therefore is a valuable measurement from a clinical perspective in patients with walking disturbances. From an evolutionary perspective, inability to walk or run fast enough was linked to low fitness and survival (Bramble 2004; Lieberman 2015).

In summary real-world walking behavior as a multidimensional variable is a pragmatic substitute for walking ability, consisting of:
The daily pattern of walking for an individual (e. g. walking in the home, walking the dog to the park and back twice a day 7x per week, walking to a shop and back 2x per week etc.), Quality of walking (gait variability, gait asymmetry, gait instability, including stumbling and falls), and the speed of walking during each of the specific walking bouts."

(From EMA Briefing Book p 10-13).

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)

"It is well known in the literature and in the medical community that walking ability is clinically relevant for many types of diseases where mobility restriction or impairment is an issue (see for example (Del Din 2016) for Parkinson's disease). The limitations of currently used short term clinical tests to capture walking ability, include the inability to assess true walking ability or capture fluctuations and exacerbations in performance, as well as self reported activity questionnaires yielding incomplete, insensitive and/or variable results. Long term real-world walking behavior is strongly linked to walking ability, since it can be expected that disabled patients will frequently reach the limits of ability in daily life. Ability sets a ceiling on behavior, but more importantly, as ability declines, behavior declines even more as symptoms such as fatigue, shortness of breath, or dizziness limit behavior at a fraction of ability. Real-world walking speed, as element of real-world walking behavior is a particularly important parameter and is seen as a valuable clinical measurement in patients with walking disturbances. Not only is walking speed itself linked to mortality and falls in the elderly but habitual walking speed is sufficiently stable that it can be estimated with shorter observations than total walking activity (which requires continuous monitoring) (Studenski 2011)."
(From EMA Briefing Book, 2.1.2, p 25ff).

We had originally proposed to EMA a universal usage of the outcome "per se", but were advised to first focus on selected disease areas. In the EMA briefing book we have focused on MS, recovery after hip fracture and sarcopenia. However, we believe that the outcome will be similarly useful in diseases like Parkinson's disease, Huntington's disease, Lupus, IBD, Rheumatoid Arthritis, COPD etc.

***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*)**

Design: Placebo/ active control compared to treatment group or cross over design. Statistics: Demonstrate statistically significant change in real world walking speed with a clinically meaningful minimal threshold of 0.1 m/s.

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***

  There is no obvious limitation w.r.t. language/culture groups. (Experience so far in Europe, North and South America, Russia, Japan, Taiwan, South Korea).

- ***Other study setting specifics (e.g., inpatient versus outpatient)***

  Patients have to be sufficiently mobile to allow to measure real world walking speed. (Secondary outcomes such as step numbers etc. can replace real world walking speed in some indications/phases of the treatment).

COA Type: Other