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Executive Director

Letter of support for Mobilise-D digital mobility outcomes as monitoring biomarkers

On 04 October 2019 the Applicant McRoberts B.V., on behalf of the IMI consortium Mobilise-D, requested qualification advice for Digital Mobility Outcomes (DMO).
This initial qualification is part of the Mobilise-D's wider objective to establish acceptable DMOs (derived from suitable mobile wearable devices and associated algorithms) as biomarkers for clinical benefit (i.e., as surrogate, primary or key secondary endpoints) in pivotal clinical trials for treatment of diseases or health conditions that impact upon mobility. An incremental approach is being taken, with qualification of monitoring biomarkers in Parkinson's Disease (PD), as the initial stage.

During its meeting held on 09 – 12 March 2020, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on 23 – 26 March 2020, the CHMP adopted the advice to be given to the Applicant.

Mobilise-D is a consortium funded and run under the Innovative Medicines Initiative (IMI) (https://www.mobilise-d.eu/). The consortium consists of a multidisciplinary combination of international research partners at leading universities and pharmaceutical / medtech companies.

The overall purpose of this application is to obtain qualification advice on the steps required for the outcomes derived from suitable mobile wearable devices and their associated algorithms to be accepted as biomarkers of clinical benefit (i.e., as surrogate, primary or key secondary endpoints) in pivotal clinical trials for diseases or health conditions where mobility is a concern.
Due to the complexity of this request for qualification advice, the Mobilise-D consortium is pursuing an incremental approach. In this first submission, the consortium seeks qualification advice on the use of DMOs as monitoring biomarkers of disease status (show relationship with changes in the degree or extent of the disease) in patients affected by PD. In a subsequent submission the consortium plans to seek qualification advice on the use of DMO's as monitoring biomarkers of disease status in multiple diseases, including Parkinson's Disease (PD), Chronic Obstructive Pulmonary Disease (COPD), Multiple Sclerosis (MS), and outcome of a Proximal Femur Fracture (PFF).
The applicant intends to pursue regulatory qualification for a new methodology to quantify mobility performance continuously over a week in real world settings, using a multi-sensor wearable device and associated algorithms that compute the various DMOs by analysing the raw signals recorded by the device. The Consortium intends to use this measurement as an additional monitoring biomarker to account for mobility performance in assessing the efficacy of new treatments for Parkinson's Disease (PD) patients. This approach is complementary to those already in use, that account only for patient's perception of mobility (patient reported outcomes, PRO's) and mobility capacity (performance related outcomes, PerfO's, such as 6-minute walk distance).

The applicant proposes that Digital Mobility Outcomes can be used as biomarkers in PD in addition to the movement disorders society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) components II and III. The MDS-UPDRS-II provides a measure of the patient's perception of mobility, and the MDS-UPDRS III provides a clinician rated measure of mobility capacity during brief tests performed during the visit. The Mobilise-D DMOs will quantify in addition mobility performance measured continuously in the real-world. To demonstrate the validity of the DMOs, the applicant will evaluate their construct

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validity, predictive capacity, and ability to detect change. The applicant intention is to qualify DMOs as secondary endpoints, complementary to the MDS-UPDRS II and III.
In order to demonstrate the validity of this biomarkers, the consortium plans to perform an extensive technical validation, and a large scale observational clinical trial. The technical validation will verify the accuracy of the device and algorithm to measure a range of different DMOs. The design of the study is based on a metrology approach where state of the art human movement analysis lab is used to quantify the accuracy and precision of a multisensory wearable instrumentation, expected to be one order of magnitude more accurate than the wearable sensors. This instrumentation is then used to quantify the accuracy and precision of the wearable sensors in real world conditions, on small cohort of healthy volunteers and of patients affected by PD.
In a second stage, clinical validation will be obtained in an observational multicentre clinical trial involves a longitudinal 24 months cohort study (with 6 monthly follow-up) in patient cohorts for each disease of interest, where disease progression is monitored from a clinician's and patient's perspective using the accepted gold standards in each disease. The Mobilise-D consortium also plans to use the Later-Life Function & Disability Instrument (LLFDI) as a disease-independent outcome of mobility disability, to validate the use of DMO's across all the target diseases. At each six-month assessment each patient will be asked to wear the device continuously for seven days. The raw data from the device will be collected through a secure digital infrastructure, and analysed with the Mobilise-D analytical software, that calculates a number of DMOs for each patient. The clinical and patient-reported outcomes will be used to assess construct validity, predictive capacity, and ability to detect change for each DMO.

Summary of the Qualification Advice

The EMA supports the general objective of the Mobilise-D consortium to pursue the qualification of DMOs as biomarkers of mobility performance in regulatory drug trials.

Utility of real-world mobility quantification

It is agreed that digital measurement of mobility can be an aid to assess treatment response, to complement other measures that quantify efficacy.
Digital quantification of mobility cannot, at this stage, be considered a primary endpoint, as a full validation of a complex tool is needed.
EMA considers that the incremental approach outlined thus far is reasonable, and standardised quantification of real-world mobility and respective digital mobility outcomes are useful to complement existing functional tests and PROs to inform regulatory decisions in drug development.
The proposal to standardise real world data using continuous measurements of digital mobility is welcomed as a complement of other tests and PROs.

Technical Validation Approach

Mobilise-D approach to validation of DMOs will cover criterion validity, construct validity, predictive capacity (their ability to predict clinically relevant outcomes) and ability to detect change (their ability to change in relation with clinically relevant changes in related constructs or to change after clinically relevant events), in the clinical validation study. The approach to the technical validation of the DMOs is acceptable.

Clinical validation in Parkinson's Disease

The Mobilise-D consortium hypothesises that mobility *performance*, measured over a week in real world conditions, is a further important dimension to evaluate mobility, in addition to patient's mobility perception and mobility capacity.
To confirm this, the consortium plans to demonstrate construct validity of a Digital Mobility Outcome (DMO) obtained with the MOBILISE-D measurement protocol by showing that they are a valid measure of the construct "mobility", they correlate with related constructs, they distribute differently across known groups of PD patients expected to have different mobility performance, and do not correlate with constructs that are not correlated with mobility. Predictive capacity will also be tested against the MDS-UPDRS. The ability to detect change will be evaluated by assessing the longitudinal validity against therapy changes; calculating the minimal important difference (MID) using MDS-UPDRS-II, MDS-UPDRS-III and other constructs relevant to patients or clinicians as anchors; responsiveness of the DMO will be tested in relation to interventions that are known to be effective.
EMA considers this approach acceptable.

The biomarker letter of support is issued on the basis of this qualification advice.

Yours sincerely,

Guido Rasi

Executive Director