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

Procedure

On 04 October 2019 the Applicant McRoberts B.V., on behalf of the IMI consortium Mobilise-D, requested qualification advice for the use of Digital Mobility Outcomes (DMO). On 12 June 2020 it submitted a second related request for qualification advice.

The initial qualification was part of Mobilise-D's overall purpose to establish acceptable DMOs (derived from suitable mobile wearable devices and associated algorithms) as biomarkers of mobility capacity 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 has been taken, with an initial qualification of monitoring biomarkers in Parkinson's Disease.

During its March 2020 meeting, the SAWP agreed on the advice to be given to the Applicant. Subsequently, during its March 2020 meeting, the CHMP adopted the advice, and a letter of support was issued in November 2020 (Letter of support for Mobilise-D digital mobility outcomes as monitoring biomarkers).

Following this first advice, McRoberts B.V., on behalf of the Mobilise-D Consortium, submitted a second request for qualification advice in June 2020 the procedure for which started during the SAWP July meeting. With this follow-up qualification advice, the Mobilise-D consortium sought EMA's feedback on the clinical concept to validate disease-specific and disease-independent DMOs as monitoring biomarkers, on the observational study to validate DMOs in four diseases (Parkinson's Disease (PD), Chronic Obstructive Lung Disease (COPD), Multiple Sclerosis (MS) and Proximal Femoral Fracture (PFF)), and on the clinical concept to validate DMOs as surrogate endpoint, predictive of clinical outcome.

During its October 2020 meeting, the SAWP agreed on the advice which was subsequently adopted by the CHMP at its December meeting.

Mobilise-D is a consortium funded and run under the Innovative Medicines Initiative 2 (IMI2) (https://www.mobilise-d.eu/). The consortium includes international and multidisciplinary research partners at leading universities and pharmaceutical / MedTech companies.

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The proposal

Due to the complexity of the request for qualification advice, the Mobilise-D consortium is pursuing an iterative approach. In a first submission, the consortium sought qualification advice on the use of DMOs as monitoring biomarkers of disease status (to show relationship with changes in the degree or extent of the disease) in patients affected by PD. The Applicant intended 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. In a second advice request, the consortium intended to use the DMO as an additional biomarker to monitor mobility performance that can be used to assess efficacy of new treatments for COPD, MS, and outcome of a PFF, in addition to PD which was subject of the first advice request. The Applicant proposed that DMOs can be used as an additional parameter to measure mobility (or mobility disability) continuously in the real-world. To demonstrate the validity of the DMOs, the Applicant intends to evaluate their construct validity, predictive capacity, and ability to detect change. The Applicant intends to qualify DMOs as secondary endpoints, complementary to the established secondary endpoints (e.g., EDSS and T25-FW in MS).

For clinical validation of the DMOs, the Applicant proposed an observational multicentre clinical trial as a longitudinal 24 month 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 (PRO) will be used to assess construct validity, predictive capacity, and ability to detect change for each DMO.

Finally, the consortium proposed a concept to validate DMOs as surrogate endpoints predictive of clinical outcome. Therefore, comparison of DMOs to established endpoints is foreseen such as falls in PD and MS, and admission to care home in case of PFF to position them as secondary endpoints in the context of an MAA, i.e., to support relevant claims to be included in the product information but without establishing an wholistic impact on the disease.

Summary of the Qualification Advice

The EMA supports the overall clinical validation concept. It is agreed that the construct 'mobility performance' could provide valuable additional information about mobility disability in the diseases in focus: MS, COPD, PFF and PD. It should be noted that, since mobility performance is an outcome that has not been evaluated so far, there is thus no gold standard to be used, the observations may or may not correlate to other known mobility outcomes such as mobility capacity or mobility perception.

The observational clinical study

The study will enrol 2400 subjects (600 in each cohort) in the four different disease cohorts: PD, COPD, MS and PFF. Each participant will be followed up every 6 months for a total duration of 24 months. For the qualification procedure, the intention is to focus the evaluation on single DMOs and each DMO will be tested for the ability to monitor disease status over time vs. disease specific endpoints (such as SPPB in PFF, and EDSS and T25-FW in MS).

EMA considers the observational multicentre clinical trial as an exploratory trial and as an important step in the validation of DMOs. The 24-month follow-up is considered appropriate for the specific diseases. In addition, EMA agrees that the observational trial may be adequate to demonstrate the ability to detect

change which will allow to identify the most appropriate DMO per disease, as long as a minimal clinical important difference of disease specific outcomes is justified. While this approach is in principle acceptable, it is also recommended to consider combining DMOs which may increase predictability.

For further clinical evaluation, it is acknowledged that evaluation of responsiveness would need randomised clinical trials.

Clinical validation in COPD, MS, PD and PFF

The first qualification advice (EMEA/H/SAB/104/1/FU/1/2020/SME) focused on use of the DMO in Parkinson's Disease and the letter of support (EMA/234828/2020) issued in 2020 by EMA, hypothesised that additional diseases may be targeted. The use of the DMO to measure mobility performance over a week in real world conditions may provide an additional dimension of mobility, in addition to patient's mobility perception and mobility capacity across the four diseases. To confirm the value of DMOs in this setting, the consortium plans to demonstrate construct validity of DMOs obtained with the Mobilise-D measurement protocol by showing that they are valid measures of the construct "mobility", they correlate with related constructs, they distribute differently across known groups of 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 relevant endpoint (e.g. SPPB score and EQ-5D in PFF, occurrence of moderate-to-severe exacerbations in COPD, and EDSS and T25-FW in case of MS).

In principle, comparing observed with expected correlations between DMOs and clinical endpoints for evaluation of convergent and discriminant validity could be endorsed. The proposed disease specific endpoints are standard and commonly used for the assessment of disease status and disease progression in the various diseases of interest (e.g., EDSS, T25-FW and MSWS-12 for MS, MDS-UPDRS III and II for PD, FEV_1, 6MWT and exacerbations for COPD).

The ability to detect change will be evaluated by assessing the longitudinal validity against therapy changes calculating the minimal important difference (MID) and other constructs relevant to patients or clinicians as anchors. In this context, EMA agrees that for PFF validation, admission to long-term care home or other form of assisted living setting could be acceptable provided that the criteria are sufficiently standardized across regions. In addition, for COPD, exacerbations may be an acceptable link but experience with this endpoint with respect to mobility outcomes is not available and FEV_1 levels as a widely accepted clinical endpoint need to be recorded and correlated at all visits, too. Last, for MS disability, progression as measured by EDSS may be more appropriate as anchor than fall frequency as falls are not an accepted primary endpoint in MS as well as in PD.

Clinical validation of a disease-independent DMO

Beyond the planned evaluation for the four specific diseases, disease-independent (across cohort) assessment of predictive capacity for decline in LLFDI and assessment of longitudinal validity based on general change events is planned. However, for validation of disease-independent DMOs LLFDI is only used when multiple DMOs perform similarly across diseases. In such a situation, the LLFDI will be utilized to compare DMOs in order to identify the best performing DMO across diseases.

The plan to use the LLFDI only if multiple DMOs perform similarly across diseases can be accepted.

While the LLFDI is a well-validated and frequently used patient-reported outcome for older adults, additional justification is needed that this tool is also validated and adequate for younger patients, e.g., MS patients or younger patients with COPD. Consequently, further data would be needed (i.e., validation of LLFDI in PD and MS, and in patients younger than 45 years) to justify the current approach, i.e., validation of LLFDI as disease-independent PRO/biomarker in the planned observational study. As long as these data are not available it is recommended to focus on the validation of disease-specific biomarkers.

Use of DMOs as surrogate endpoints

Provided that established endpoints for the four diseases are used to validate DMOs, EMA agrees that, if the study results are supportive, DMOs may be positioned as secondary endpoints in the context of an MAA; i.e., to support relevant claims to be included in the product information.

Yours sincerely,

Emer Cooke

Executive Director