



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Executive Director

Letter of Support for the development of Patient-Reported Outcomes tools for use as an endpoint in Inflammatory Bowel Disease (IBD) clinical trials

On 9 March 2017 the Applicant Roche Products Limited requested qualification advice for two Patient-Reported Outcome (PRO) tools to evaluate the effects of treatment on patient-reported Ulcerative Colitis (UC) and Crohn's disease (CD) signs and symptoms in UC and CD clinical trials.

During its meeting held on 27 - 30 November 2017, the SAWP agreed on the Qualification Advice to be given to the Applicant. During its meeting held on 22 – 25 January 2018, the CHMP adopted the Qualification Advice to be given to the Applicant.

On the basis of the qualification advice, the Agency is issuing this letter of support to encourage data sharing and to facilitate studies aimed at eventual qualification for the novel methodology under evaluation in line with the intentions of the applicant to make the instrument publicly available for use through Evidera and to non-commercial users (e.g. academic and research institutions) free of charge.

Background and context of use of the novel methodology

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal (GI) tract, which presents clinically as either UC or CD. The aetiology of IBD is complex, and many aspects of the pathogenesis remain unclear. UC is a mucosal inflammation of the colon and CD is a chronic transmural inflammatory disease with the potential to affect any part of the entire GI tract. UC is typically characterised by diarrhea that may be associated with blood. The clinical presentation of CD is more varied and can include abdominal pain, diarrhea, weight loss, fatigue, strictures, and fistulae. While both conditions may necessitate surgery, CD patients can require multiple surgeries due to recurrence. Both UC and CD are associated with an increased risk for malignancy of the GI tract.

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There is growing interest in better assessing different aspects of IBD, such as clinically derived signs, symptoms, and/or clinical tests. Although endoscopy is available to clinicians to visualise GI tract inflammation, there is currently no reliable and validated PRO measure to comprehensively assess the meaningful signs and symptoms of UC or CD for the purpose of assessing treatment benefit in clinical trials.

Clinically, UC is monitored through signs and symptoms of disease activity and periodic objective assessment (e.g., endoscopy) to evaluate mucosal inflammation. In clinical trial settings, the Mayo Clinic Score (MCS) historically has been used to assess disease activity. The MCS combines endoscopic findings, a physician-rated global assessment, and patient reported stool frequency and rectal bleeding into a single total score. Both the EMA and the FDA have recently released guidelines specific to clinical trials of UC, noting the importance of including an adequately validated PRO to assess symptomatic relief as a primary outcome measure in pivotal clinical trials of UC (FDA 2016; EMA 2016).

CD is also clinically monitored through signs and symptoms of disease activity and periodic objective assessment (e.g. endoscopy, imaging, or measurement of biomarkers) to evaluate disease activity. In clinical trial settings, the Crohn's Disease Activity Index (CDAI) score (Best et al. 1976) had been used to assess disease activity, combining patient-reported signs and symptoms (loose/liquid stools, abdominal pain, general well-being) with clinical assessments (i.e., complications, presence of abdominal mass, change in weight, haematocrit levels, use of antidiarrheal agents), with use of a weighted scoring algorithm. Recent guidance from both the EMA and FDA discourage the use of the CDAI for future clinical studies, and instead recommend that signs and symptoms and inflammation be evaluated independently (EMA 2016; FDA 2009, GREAT I 2012, GREAT II 2013, GREAT III 2015). The guidelines state that the signs and symptoms of CD are best reported directly from the patients themselves through use of a reliable and valid measure fit for this purpose.

The UC-PRO/SS and CD-PRO/SS have been developed and validated with the purpose of addressing this unmet measurement need in IBD clinical trials. The UC-PRO/SS and CD-PRO/SS have been designed to comprehensively assess meaningful signs and symptoms of IBD reported by patients. These tools could be used either as a secondary signs/symptoms endpoint or as a co-primary signs/symptoms endpoint along with an objective marker of disease activity, e.g. endoscopy.

Available data

The Agency considered the methodology for establishing the content validity and psychometric properties of the UC-PRO/SS and CD-PRO/SS to be acceptable. The validation work conducted was thorough, of a high-standard and is endorsed by the Agency.

The UC-PRO/SS and CD-PRO/SS measures were developed to standardise the quantification of signs and symptoms of IBD in clinical trials through direct patient ratings. Based on the currently available preliminary set of data, the instruments can be regarded to have potential to provide valid, and reliable daily diary tools to facilitate gathering data on meaningful IBD signs and symptoms directly from the patient. The UC PRO/SS and CD-PRO/SS complement and extend information provided by endoscopy in understanding treatment effect.

The UC-PRO/SS and CD-PRO/SS were developed based on a review of the literature, clinical input, and in depth interviews with IBD patients. The currently available evaluation of psychometric properties, demonstrated that both instruments possess good measurement properties (reliability and validity).

Continuing and future investigations

The Agency recommends further investigation and development of the UC-PRO/SS and CD-PRO/SS in patients with IBD is encouraged to (1) provide information on the relationship between patient-reported signs/symptoms and objective markers of disease activity (e.g. endoscopy), (2) assess the longitudinal measurement properties, and (3) define a threshold for meaningful change. The Agency encourages further collaboration with research groups to generate additional data to support a final qualification of the PRO tools in the future.

Sincerely,

Guido Rasi
Executive Director

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