15 February 2022
EMADOC-1700519818-776978
Executive Director

Letter of support for intermediate Age-Related Macular Degeneration (AMD) biomarker and novel clinical endpoint development

On June 13th, 2016, the Applicant Bayer AG requested a qualification advice on behalf of the MACUSTAR Consortium for intermediate Age-Related Macular Degeneration (iAMD) biomarkers. On May 3rd, 2021, it submitted a second related qualification advice to the EMA.

The initial qualification was part of the MACUSTAR project the overall purpose of which is to develop novel clinical endpoints for Clinical Trials in patients with intermediate AMD. It also aims to characterise visual impairment in iAMD and its progression, as well as to identify risk factors for progression to late-stage AMD.

The advice was given in the framework of an EMA FDA HTA parallel advice procedure. During its meeting held on April 18 – 21, 2017, the CHMP adopted the advice to be given to the Applicant and a letter of support was issued on February 15, 2018 (Letter of support for intermediate Age-Related Macular Degeneration (AMD) biomarker and novel clinical endpoint development).

Following this first advice, Bayer AG on behalf of the MACUSTAR consortium filed a second request for qualification advice in April 2021 which started during the SAWP meeting of July 2021. With this follow-up qualification advice, the consortium aimed to present the results of the cross-sectional analysis of the MACUSTAR clinical study, discuss the indication iAMD by defining a development path and explore the strategy for the evaluation of progression from iAMD to late AMD.

A discussion meeting with the Applicant took place on 30 August 2021. On 28 October 2021, the SAWP agreed on the advice to be given to the Applicant. On 11 November 2021, the CHMP adopted the advice to be given to the Applicant.

The MACUSTAR Consortium is a public-private research project funded by the European Initiative for Innovative Medicines (IMI2) with a 5-year funding period which started on September 1, 2017. The goal of the MACUSTAR project is to develop a toolbox of clinical endpoints acceptable for clinical trials in iAMD with a regulatory and patient access intention. The background, proposed context of use as well as a description of the objectives of the MACUSTAR clinical study have been described in detail in the publicly available Letter of Support for intermediate Age-Related Macular Degeneration biomarker and novel clinical endpoint development (15 February 2018).

European Medicines Agency's feedback on the MACUSTAR project and the presented results of the cross-sectional part

In the follow up qualification advice, the Applicant presented the results of the cross-sectional part of the study which focused on the technical evaluation of functional, structural and patient-reported candidate outcomes. The Agency supported the Applicants' interpretation of the proposed measures to quantify the reproducibility of structural, functional and patient-reported outcome (PRO) measures to be overall in a reasonable range to allow their use in future interventional clinical trials. It was agreed that (according to the Bland-Altman plots) there is no obvious dependency of test/re-test discrepancy on the level of the measures and no systematic differences between those measures taken 7 to 21 days apart.

Furthermore, the agency agreed that the extent of visual impairment varied between individuals with iAMD diagnosed by structural criteria based on retinal imaging (Beckman classification, Ferris et al., 2013). They considered the definition of a new treatment indication for functional impairment in iAMD as primary endpoint in phase 3 for proof of efficacy to be in principle acceptable. Remaining open questions were discussed with the Applicant, including agreement between visual impairment detected by functional tests, external validity of the proposed thresholds to define normal/abnormal and the specific goal of such a qualification (prevention of progression versus treatment of a subpopulation with an immediate medical need). The further evaluation of the iAMD subcohort with visual impairment in the larger longitudinal study was endorsed. It was further noted that presence of visual impairment in individuals with iAMD would gain strong support by establishing a link to progression to late AMD.

In this context, the Applicant was encouraged to proceed with the ongoing validation of a new patient-reported outcome measure for AMD (Vision Impairment in Low Luminance, VILL questionnaire). They were advised to address the minimally important difference of VILL questionnaire scores and change in response to intervention for a full validation of the instrument.

The Agency considered the structural sample characteristics of the cross-sectional part of the MACUSTAR study at least largely comparable to the populations investigated in previous studies and thus in principle generalizable for iAMD. However, the external validity of the results within the small early AMD subset was discussed. The Agency suggested accounting for the different risk of progression of participants in the analyses. Additionally, external validation of the results of the longitudinal part of the MACUSTAR clinical study was encouraged.

In summary, the Agency supported the further conduct of the MACUSTAR study and encouraged the ongoing validation of functional, structural and patient-reported endpoints in AMD.

Letter of support for intermediate Age-Related Macular Degeneration (AMD) biomarker
and novel clinical endpoint development
EMADOC-1700519818-776978   Page 2/2