06 December 2024
EMADOC-1700519818-1790091
Executive Director

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

On 23/10/2023, the Applicant Bayer AG requested scientific advice relating to biomarkers and novel clinical endpoint development in intermediate Age-Related Macular Degeneration (AMD), pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

On 16/05/2024, the SAWP agreed on the advice to be given to the Applicant.

On 30/05/2024, the CHMP adopted the advice to be given to the Applicant.

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

Context

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. 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. On April 21, 2017, the CHMP adopted the advice to be given to the Applicant and a letter of support was issued on February 15, 2018.

Following this first advice, Bayer AG on behalf of the MACUSTAR consortium filed a second request for qualification advice, starting 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 and explore the strategy for the evaluation of progression from iAMD to late AMD. On 11 November 2021, the CHMP adopted the advice to be given to the Applicant.

On 23/10/2023, the Applicant Bayer AG requested a third qualification advice on behalf of the Macustar consortium relating to biomarkers and novel clinical endpoint development intended for use in intermediate Age-Related Macular Degeneration (AMD). On 30/05/2024, the CHMP adopted the advice to be given to the Applicant.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

The MACUSTAR Consortium is a public-private research project funded by the European Initiative for Innovative Medicines (IMI2) with a 5-year funding period that started on September 1, 2017, which has recently been extended by involved consortium partners.

Age-related Macular Degeneration (AMD) is a major health problem in a globally aging population. AMD affects almost 30% of the older population and progresses from early AMD to intermediate AMD (iAMD) and ultimately to late-stage AMD with severe and frequently irreversible visual loss (Li et al, 2020). Population aging will lead to a considerable increase in AMD prevalence. Today, late-stage AMD is the leading cause of blindness among the elderly in industrialised countries and affects more than 2.5 million patients in the EU (Colijn et al., 2017, Finger et al., 2011).

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). Progress and advice concerning the assessment of the cross-sectional data was available in the Letter of Support dated 15 February 2022.

Scientific discussion

In this third advice, the consortium presented data from additional 417 iAMD patients at baseline and also longitudinal data obtained from the total MACUSTAR longitudinal cohort after a median follow up period of 3.5 years. This longitudinal cohort consisted of 619 individuals with early AMD (n=34) and iAMD (n=585) from the MACUSTAR study cohort, in which participants undergo functional, structural and patient-reported outcome assessments in a 6-monthly interval. During this observation period 84 individuals progressed from iAMD to late AMD, including both geographic atrophy (GA) and neovascular AMD (nAMD). The longitudinal part of the study is not yet complete. The Agency tentatively agreed that the cross-sectional and longitudinal MACUSTAR cohorts appear largely comparable at baseline.

The aim of the scientific advice was to discuss enrichment criteria for iAMD study populations as well as the indication of iAMD, and explore further strategies for the evaluation of progression from iAMD to late AMD.

CHMP provided responses to the questions and supporting documentation submitted by the Applicant, and in the light of the current state of the art in the relevant scientific fields.

The CHMP agreed in principle with the presence of heterogeneous visual function deficits in one or more tests present in a large proportion of subjects with iAMD at baseline. It was noted that the visual impairment varies within iAMD and that only a fraction of iAMD subjects suffer from visual impairment across the majority of tests. Given the functional heterogeneity, the CHMP overall considered that the current iAMD classification (based on structural changes only) might need to be revisited.

CHMP agreed that the data presented support the hypothesis of an association between visual function deficits in iAMD and the conversion to late AMD (based on deviating from a non-AMD cohort) notably in best-corrected visual acuity, low-luminance visual acuity, Moorfields Acuity (MAT) and microperimetry-based endpoints in iAMD, making these deficits or a combination thereof potential enrichment factors prognostic for disease progression. These associations were strengthened with an increasing number of baseline deficits taken into account simultaneously. However, some important limitations were noted to exist: The observation period and thus the number of conversions to the different subsets of late AMD (GA and nAMD) were limited. A longer follow-up is needed in order to better determine whether the prognostic associations are of similar relevance for both subsets of late AMD. Further, functional reference limits are based on a non-AMD group with a limited sample size. A larger non-AMD group is necessary to establish reliable reference limits. Thus, it remained unclear for now to what extent the observed baseline deficits can identify a subgroup at higher risk of progression to late AMD.

Accordingly, further work on determining relevant reference limits as prognostic biomarkers for conversion to late AMD relative to normal age-related function and its decline over time is encouraged.

While the existence of a slow and variable decline of function observed within the iAMD MACUSTAR cohort was agreed, it was noted that the relationship to age-related changes remained unclear from the dataset due to the lacking normative age-matched control group.

The CHMP agreed with the prognostic value of structural and functional biomarkers, notably the presence of reticular pseudo-drusen (RPD) and mesopic microperimetry pattern standard deviation (PSD), as a continuous variable in the context of the risk of progression from iAMD to late AMD in MACUSTAR. CHMP acknowledged the independent confirmation of findings from the LEAD study. These were agreed as enrichment criteria for patients at higher risk of progression to late AMD for use in future phase II and/or phase III trials in iAMD. However, the main analysis did not differentiate between progression to neovascular AMD or GA. Thus, it remains unclear whether the proposed enrichment factors, presence of RPS and PSD, have prognostic value for both progression to neovascular AMD and GA. Pending longer-term data, this needs attention and should be considered when planning future intervention studies. The patient burden of microperimetry testing is recognised; however, it should be feasible in a setting of a clinical trial. In addition, as PSD was evaluated as a continuous measure, it remains unclear how this measure may be used for an enrichment strategy and how a cut-off could be determined.

Hyperreflective foci also appear to be a significant risk factor for progression to late AMD and may therefore also be suitable as a future parameter for the identification of high-risk patients.

Finally, CHMP appreciated the development of a new patient related outcome measure, and the Vision Impairment in Low Luminance (VILL) is a promising measure for future trials. The minimally important difference (MID) of the VILL questionnaire requires further confirmation based on longitudinal data. It was endorsed to introduce a patient-reported anchor to derive the VILL questionnaire's MID. The CHMP considered use of the VILL as a secondary endpoint in a future iAMD interventional study to be in principle acceptable but noted that the VILL would need to be further evaluated in exploratory trials before proceeding to confirmatory trials. Finally, for a full validation, data regarding the responsiveness to an intervention is lacking. In this context, it is acknowledged that currently no approved therapy exists for the treatment of iAMD.

Considering different options for future interventional trials in AMD, i.e. to slow or halt the progression from intermediate to late AMD (with the event-related endpoint 'progression to late AMD'), or slow or halt the development of visual function deficits or improve visual function in subjects with iAMD, at the current development stage of MACUSTAR development, the planning of studies aimed at investigating the ability to delay/prevent progression to late AMD appears the most straightforward.

Conclusion

In conclusion, the CHMP supported the goals and further research to develop trial enrichment criteria, and trial endpoints for subjects with iAMD.

Yours sincerely,

Emer Cooke Digitally signed by Emer Cooke
Date: 2024.12.06 14:27:28 +01'00'

Emer Cooke

Executive Director