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

On June 13, 2016, the Applicant Bayer Pharma AG requested a qualification advice on behalf of the MACUSTAR Consortium for intermediate Age-Related Macular Degeneration (iAMD) biomarkers pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council. The procedure started during the SAWP meeting held on January 9 – 12, 2017, and the advice was given in the framework of an EMA FDA HTA parallel advice procedure.

The multi-stakeholder meeting, including the EMA, FDA, HTA and the MACUSTAR Consortium, took place on April 3, 2017. During its meeting held on April 3 – 6, 2017, the SAWP agreed on the advice to be given to the Applicant. During its meeting held on April 18 – 21, 2017, 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 starting 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.

Background and proposed context of use

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 (Lim et al[i]., 2012). 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 (Augood[ii] et al., 2006, Finger[iii] et al., 2011b).

Until recently, focus in drug development was mainly on one late-stage manifestation of AMD, i.e. neovascular AMD. However, there are other phenotypic variants of AMD that present with visual impairment for which to date no treatment options exist: patients with intermediate AMD (iAMD) show a generally progressive visual impairment mostly in low luminance and low contrast situations. Also, no biomarkers are available to identify iAMD patients at high risk of progression to late stages of AMD, i.e., progression to neovascular AMD and/or geographic atrophy (GA).

The MACUSTAR project targets development of clinical endpoints for iAMD in the categories of functional, structural, and patient-reported outcomes (PROs), to provide a toolbox of endpoints for different stages of drug development from first-in-human, over proof-of-concept (POC/Phase 2) to Phase 3 trials. It is intended to link these candidate outcome measures to AMD disease biology and to the natural course of the disease. The goal of the clinical validation is to have functional and/or structural biomarkers validated for their use as primary endpoints in future (exploratory and confirmatory) clinical trials. PROs are intended to be used as secondary clinical endpoints.

Although pilot research has been conducted in iAMD to date, it remains to be investigated which combination of biomarkers would successfully achieve full clinical validation. Two key factors are expected to drive acceptability of clinical outcomes to regulators and HTA bodies:

1. Establishment of visual impairment beyond high contrast BCVA in iAMD in functional assessments and patient-reported outcomes (PRO)s. Based on preparatory work of the members of the MACUSTAR consortium and of other researchers it is expected that visual function in iAMD is most affected under low-contrast and low luminance conditions. Accordingly, a PRO work stream to create and validate a novel PRO Measure (PROM) containing relevant items for iAMD will be part of the MACUSTAR research project. If the correlation of functional endpoints with a PRO could be supported by study data from the MACUSTAR clinical study and demonstrate sensitivity to change in an interventional setting, it is expected that functional clinical endpoints could be used as primary endpoints. Correlation with imaging biomarkers would add further robustness to the functional endpoint(s). The PRO could be used as a secondary endpoint to support the efficacy information of primary endpoints.

2. Correlation of structural biomarkers with progressive functional impairment during the progression of iAMD to late stage AMD (i.e., neovascular AMD or GA). If the correlation of imaging biomarkers is positively correlated both with functional endpoints and with a PRO to support clinical meaningfulness (as well as demonstrating a sensitivity to change), it may be expected that also structural clinical endpoint(s) could be used as primary endpoints. Biomarkers capturing structural changes and progression could have potential for clinical studies on therapeutic prevention of this progression but the predictivity and clinical meaningfulness of any change in terms of delay to significant visual impairment will remain to be established.

Endpoint validation in the MACUSTAR Clinical Study: To achieve this goal, the MACUSTAR project will implement the following specific objectives:

- Establish and conduct a clinical study (the MACUSTAR clinical study) with a total of 750 subjects with two parts: (a) a cross-sectional part b) a longitudinal part with follow-up assessments: see below.
- Assess the relationship between functional and structural outcome measures as endpoints and their relationship to the PROM using data from the clinical study.
- Candidate outcome measures will be anchored against progression to neovascular AMD or to GA
- Develop a PROM to be tested in the MACUSTAR clinical study to evaluate the patient-relevant impact of iAMD and the impact of progression to late AMD.
- Develop a utility instrument for iAMD that will allow conduct of health economic assessments for new therapies.

After this first scientific advice, the Consortium intends to apply for the first follow-up scientific advice with the results of the cross-sectional part and another follow-up with the long-term follow-up of iAMD patients for progression and conversion to late-stage AMD.

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The MACUSTAR clinical study

MACUSTAR will generate data on the visual impairment and decline in iAMD and its impact on patients' lives, as well as data on functional, structural and patient-reported outcomes (PROs) with progression from iAMD to late AMD.

Different functional tests and multimodal retinal imaging will be employed to evaluate different relevant aspects of patient-reported functioning.

This multimodal approach to outcome assessment will be implemented in the MACUSTAR clinical study with a two-part study design. The two parts have different objectives but will be combined into one study for operational synergies.

- The cross-sectional part: with a total of 300 subjects comprising 50 patients with early AMD, 50 patients with late AMD manifesting as geographic atrophy (GA), 50 age-matched, normal controls, and 150 patients with intermediate AMD. The main objective of this part is to assess the discriminatory properties of each outcome measure employed, i.e., their ability to discriminate between the different stages of disease in AMD. The cross-sectional part comprises a first visit and a repeat visit within 7-21 days to assess variability and test-retest reliability of all outcomes measures.
- The longitudinal part: The main objective of this part is to assess the course of outcome measures in a cohort of 600 patients with iAMD (150 iAMD participants from the cross-sectional part plus 450 additional subjects) for three years to assess deterioration of iAMD and progression of iAMD to late AMD. Clinical data are captured in 6-monthly intervals to assess longitudinal changes in function, retinal structure and reported PROs against progression to late AMD. Also, risk factors and prognostic biomarkers for the progression from iAMD to late AMD will be assessed.

Target patient population of iAMD patients for the biomarker evaluation will be defined as patients with
- iAMD in the study eye and
- iAMD or iAMD with extrafoveal GA in the fellow eye.

AMD staging will follow the recently published Beckman Classification (Ferrisiv et al., 2013). The inclusion of patients with extrafoveal GA in the fellow eye will be allowed to enrich the population for progression events in the study, as these patients are known to be at high risk to progress to central GA (Schmitz-Valckenbergv et al., 2016). Eyes with no AMD or normal aging changes will only be included in the cross-sectional analysis as controls.

Candidate biomarkers:

A number of potential outcomes/candidate biomarkers for which there is more or less support that different stages of AMD can be distinguished have been defined for assessment in the MACUSTAR project:

- Tests of visual function, which include Microperimetry (scotopic), Low Luminance Acuity (LLA), Moorfields Acuity Test (MAT; Vanishing Optotypes), Dark Adaptation, Contrast Sensitivity, and obviously ETDRS BCVA.
- Performance based tests (PBTs) (functional vision): International Reading Speed Texts (IReST), Navigational PBTs (the Pedestrian Accessibility and Mobility Laboratory (PAMELA), London and Streetscape, Paris).
- Retinal imaging and automated analysis: multimodal imaging approaches including colour fundus photography (CFP), spectral-domain optical coherence tomography (SD-OCT), OCT angiography (OCT-A), blue and green confocal scanning laser ophthalmoscopy (cSLO) fundus autofluorescence (FAF), near-infrared cSLO reflectance (NIR) imaging with automated and semi-automated computerised quantification of imaging biomarkers
- Patient reported outcomes mean change from baseline in patient-reported low luminance visual functioning, as measured by a novel PROM and change in utility index from baseline as measured by a PROM utility index will be included.

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European Medicines Agency's feedback on the MACUSTAR project

The Agency supported exploration of markers that address both how the patient functions and how the patient feels and that the correlation between structural and functional markers/PROs will be evaluated. Overall, it is agreed with the Consortium that it is important to create a dataset of functional, structural and PRO assessments also in patients with impaired central vision (BCVA 20/40-20/200).

All imaging and technical measurements should be standardized and results should be confirmed by a central reading centre. The Consortium should carefully consider how psychosocial factors such as learning effects and the level of alertness or technical factors such as instructions for tools application might impact test results. Continuation of the early AMD cohort into the longitudinal part for at least one additional follow-up visit, e.g. at the end of the 3-year period was recommended.

Two important limitations of the project were discussed with the applicant:

The MACUSTAR clinical study is designed as a fully explorative study. Hence, the results and the conclusions of the study will have to be confirmed, either by splitting the study population in exploratory and confirmatory sub-cohorts (following the TRIPOD statement [vi], which may have the risk of too low numbers of progression events to late stage AMD or by a truly confirmatory external dataset, e.g. applying the principle of cross-validation with data from other similar natural history studies or from interventional studies in subjects with wet AMD or GA assessing similar biomarkers to support discrimination of disease states over time.

Secondly, the study is aimed to investigate the prognostic but not the predictive value of the biomarkers due to the lack of any interventional comparison. Hence, no claim will be possible on the usefulness of any intervention in the subjects that are classified as those that will likely progress to late AMD. Considering this limitation, a prognostic tool is regarded as a valuable starting point but no assertion on the usefulness of the tools to asses a given therapy will be possible without further interventional studies.

The proposed plan for the repeated interactions using the biomarker qualification advice procedure, e.g. after the results of the cross-sectional part of the study become available, is supported. Extension of the longitudinal study beyond 3 years may be needed.

In summary, to reduce the significant burden of late AMD, novel interventions that stop or delay progression from iAMD to late AMD will need to be developed (Holz et al., 2014[vii]). To achieve this goal, acceptance of fully validated, clinical endpoints by regulatory agencies is needed. Specifically, there is a need to develop new endpoints that can best capture visual impairment in iAMD and its impact on patient´s lives and that are sensitive to change.  Currently, such validated and accepted clinical endpoints do not exist for clinical trials in iAMD. The proposed approach to develop functional and/or structural biomarkers towards validation as primary endpoints of future clinical trial endpoints in intermediate AMD with PROs are intended to be used as secondary clinical endpoints is supported. Sharing of relevant data where appropriate and feasible to support validation is strongly encouraged.

Sincerely,

Guido Rasi
Executive Director

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