



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Executive Director

## Letter of support for reading speed and functional reading independence (FRI) index in geographic atrophy

On 16 February 2015 the applicant Roche Registration Ltd requested scientific advice for use of reading speed and functional reading independence (FRI) index pursuant to Article 57(1)(n) of regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 05 – 08 October 2015, the SAWP agreed on the advice to be given to the applicant. During its meeting held on 19 – 22 October 2015, the CHMP adopted the 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.

### *Background and context of use of the novel methodology*

Geographic atrophy (GA) is a non-exudative form of advanced age-related macular degeneration (AMD), characterised by a progressive loss of choriocapillaris, retinal pigment epithelium (RPE), and photoreceptors. In the natural history of the disease, atrophic lesions typically develop in the macula surrounding the fovea, and grow over time; they may not directly involve the foveal centre until later stages of the disease. There are no approved treatment options for patients with GA secondary to AMD. Therefore, GA secondary to AMD is a serious disease with a significant unmet medical need.

Atrophic lesions represent areas of retinal tissue loss where the retina does not function. The assessment of visual function endpoints in clinical trials is essential to support prognostic value and clinical significance of observed changes in anatomical lesions. However best-corrected visual acuity (BCVA), as measured using high contrast black and white letters on standardised eye charts, may not capture the full extent of visual function loss or its progression in GA, due to the phenomenon of foveal sparing. Visual acuity charts assess the function of the foveal region, and do not adequately measure macular sensitivity, which is of relevance to everyday visual function. The nature of GA progression implies that trials are necessarily lengthy, further adding to the challenges in developing new medicines in this indication. In the earlier stages of GA, patients may experience deficits in visual function, caused by loss of macular functioning, such as difficulties with reading and recognising faces, giving rise to a loss of independence. For example, it is estimated that more than half of patients with



GA experience profound reduction of reading function in everyday life, despite having relatively good BCVA under test conditions.

Thus the following two evaluations have been proposed as potential functional secondary endpoints to capture treatment effects in trials of new medicines in geographic atrophy based on measures of reading function

1) Reading speed, and 2) the Functional Reading Independence Index (FRI Index).

#### *Reading speed*

Reading speed tests provide a direct, objective measure of a patient's ability to read continuous text, measured monocularly or binocularly, determining average maximum reading speed, critical print size and reading acuity. The Minnesota low-vision reading test (MNREAD) and the Radner reading charts are valid and reliable reading speed tests widely reported in published literature. Additional evidence of validity for the MNREAD test, used binocularly, is available from a phase 1b/2 clinical trial of lampalizumab in GA.

The importance of reading speed is recognised among the scientific community and supported by a number of publications cited by the applicant. Reading speed could therefore be used as one tool to support the clinical meaningfulness of a treatment effect on GA progression although further data from ongoing randomised controlled trials and epidemiological studies in GA, will be needed to address some remaining uncertainties. Issues such as the impact of variability, lesion location, confounding factors, potential learning effects, adequacy of standardisation, consistency with other functional measures, and comparability of the different charts need to be thoroughly explored.

The definition of a clinically meaningful change for maximum monocular reading speed should be justified. To better understand the reading speed data, exploring the cut-points commonly used in the scientific literature where maximum reading speed of 40 words per minute is considered non-fluent reading, 80 words per minute is considered minimum fluent reading and 160 words per minute is considered high fluent reading is a good starting point.

#### *The functional reading independence index (FRI index)*

The functional reading independence index (FRI index) is a new patient-reported outcome measure developed specifically for use in GA patients. The FRI index evaluates the level of independence patients have in performing everyday activities that require reading, such as writing a cheque or reading a prescription. Scores derived from the index range from 1 (unable to do) to 4 (total independence), and may be analysed as either categorical (which is preferred from a regulatory perspective) or continuous variables. The FRI index has explored evidence of content validity based on qualitative research with GA patients, and provided evidence of quantitative validity and reliability based on data from a phase 1b/2 study of lampalizumab in GA.

The concept of functional reading independence may provide information on aspects of vision-related functioning that are not captured by other outcome measures, although further data from ongoing trials and studies will be needed to further support sensitivity to change, to examine precision, and to explore the impact of the better seeing eye in addition to the features mentioned above with reading speed. In principle, there are no objections against an instrument that does not capture the degree of difficulty subjects have performing reading-related activities where the questionnaire is to be used in conjunction with other measures like the VFQ-25. Broader awareness and use of the FRI index is

encouraged; the FRI index is available for use through Mapi Research Trust for both academic and clinical research (proinformation@mapi-trust.org).

*Summary*

The further use and development of the FRI index and reading speed in patients with GA, both to provide information on the relationship between GA lesion size and reading function, and to explore the potential effect of treatment on reading function is supported.

Sincerely,

Guido Rasi  
Executive Director