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An observational study to understand markers indicating disease progression in dry age-related macular degeneration

Submission date 20/12/2023	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 24/09/2025	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 24/09/2025	**Condition category** Eye Diseases	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
This is a prospective, observational study in two cohorts of participants with intermediate age-related macular degeneration (iAMD) or geographic atrophy (GA) or GA in one or both eyes. It aims to recruit 200 eyes with iAMD and GA (100 in each cohort) to study endpoints on multimodal imaging and visual function tests. The study will consist of an observation period of 1 year (~52 weeks) for participants with visits at baseline, 3 months, 6 months and 12 months. The participants will be recruited from Moorfields clinics or the diagnostic hub, from the hospital database or optometry referrals. Patients who have participated in a completed observational study and are willing to participate in this study will be invited as well. A new baseline will be captured and follow-up data will be analysed for structural and functional progression markers.

Who can participate?
Patients with iAMD or GA aged 50 – 90 years old

What does the study involve?
Along with a collection of demographics, relevant medical and ocular history, VA acuity assessments (BCVA/LLVA) and detailed ocular clinical examination, all patients will undergo multimodal imaging assessments at all 4 visits. These would include spectral domain optical coherence tomography (SD-OCT), OCT angiography (OCTA), near-infrared reflectance (NIR), fundus autofluorescence (FAF), colour photographs and FAF and Enhanced depth imaging OCT (EDI-OCT). Additional visual function tests – dark adaptation (DA) for rod intercept time (RIT) and microperimetry (MP) will be done at baseline, 6 and 12 months only.

What are the possible benefits and risks of participating?
There will be no direct benefit, but patients will be contributing to science and there may be a benefit to the future development of healthcare provision. This study is being carried out to observe changes in the eye only. The information we get from this study may help to improve the future treatment of people with AMD.

Where is the study run from?
Moorfields Eye Hospital's Clinical Research Facility (UK)

When is the study starting and how long is it expected to run for?
October 2023 to October 2025

Who is funding the study?
Boehringer Ingelheim (Germany)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
330679

Protocol serial number
CPMS 58287, IRAS 330679

Study information

Scientific Title
A Prospective, Observational study for identification of biomarkers of disease progression in Intermediate Age related Macular Degeneration and Geographic Atrophy (PROBE-IGA)

Acronym
PROBE-IGA

Study objectives
AMD is a major public health burden, but disease mechanisms remain unknown resulting in several failures in drug development including inconclusive trials for this condition. Choosing new onset GA as an endpoint for the prevention of the progression of intermediate age-related macular degeneration (iAMD) trials will likely require outcome trials with long follow-ups. There is an unmet need to find an imaging biomarker that is a precursor to new onset GA. Similarly, novel imaging biomarkers that predict the growth rate of GA will be valuable in identifying the GA phenotype with fast progression.
The major issues of new treatment development are:
(a) Complexity of disease mechanism: The primary structure that is affected in GA is not yet identified. It is also unclear whether GA is driven by a single pathogenesis. Questions remain whether GA is caused by primary RPE failure or photoreceptor layer or choriocapillaris are affected first before RPE cell loss. Deciphering the differences in various GA phenotypes may result in fewer drug failures.
(b) Lack of potential surrogate markers: To test potential new interventions in AMD, we urgently need new robust early end points that occur before overt GA. The Classification of Atrophy Meeting group (CAM), defined the sequence of events that occurs in GA in an attempt to redefine AMD with more granular stepwise progression criteria. This would identify biomarkers that could act as potential surrogate endpoints for clinical trials. However, conversion from one stage to another has not yet been studied in prospective cohorts.
(c) Anatomical versus functional clinical outcomes: The United States Food and Drug Administration (FDA) has approved fundus autofluorescence as a primary endpoint for GA trials, but visual function remains the key endpoint for the European Medicines Agency (EMA). Therefore, more work is required for structure-function correlations in iAMD and GA.
(d) Challenges in clinical trial design: Although the subtype of macular atrophy has been defined by the CAM group, the definitions such as iRORA and cRORA need to be simplified further to identify the earliest changes that could help design trials with shorter follow-ups.

Ethics approval required

Ethics approval required

Ethics approval(s)
approved 26/09/2023, London - City & East Research Ethics Committee (Research Ethics Committee Centre, 2nd Floor, 2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048171; approvals@hra.nhs.uk), ref: 23/LO/0755

Study design
Prospective observational study in two cohorts

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Age-related macular degeneration - intermediate AMD and geographic atrophy

Interventions
This is a prospective, observational study in two cohorts of participants with intermediate age-related macular degeneration (iAMD) or geographic atrophy (GA) in one or both eyes. It aims to recruit 200 eyes with iAMD and GA (100 in each cohort) to study endpoints on multimodal imaging and visual function tests. The study will consist of an observation period of 1 year (~52 weeks) for participants with visits at baseline, 3 months, 6 months and 12 months. The participants will be recruited from Moorfields clinics or the diagnostic hub, the hospital database or from optometry referrals. Patients who have participated in a completed observational study and are willing to participate in this study will be invited as well. A new baseline will be captured and follow-up data will be analysed for structural and functional progression markers.
Along with the collection of demographics, relevant medical and ocular history, VA acuity assessments (BCVA/LLVA) and detailed ocular clinical examination, all patients will undergo multimodal imaging assessments at all 4 visits. These would include spectral domain optical coherence tomography (SD-OCT), OCT angiography (OCTA), near-infrared reflectance (NIR), fundus autofluorescence (FAF), colour photographs and FAF and Enhanced depth imaging OCT (EDI-OCT).
Additional visual function tests – dark adaptation (DA) for rod intercept time (RIT) and microperimetry (MP) will be done at baseline, 6 and 12 months only.

Intervention Type
Other

Primary outcome(s)
1. For intermediate age-related macular degeneration (iAMD) group, time to conversion from iAMD to nGA/iRORA/cRORA/ hypoautofluorescense evidence of GA measured using imaging modalities below from baseline up to 1 year
2. Conversion from nGA/iRORA to cRORA/GA measured using imaging modalities below from baseline up to 1 year
3. For GA, change from baseline in disease progression measured using imaging modalities below from baseline up to 1 year

Imaging modalities:
Spectral domain optical coherence tomography (SD-OCT), OCT angiography (OCTA), near-infrared reflectance (NIR), fundus autofluorescence (FAF), colour photographs and FAF and Enhanced depth imaging OCT (EDI-OCT), dark adaptation (DA) for rod intercept time (RIT) and microperimetry (MP).

Abbreviations:
nGA: Nascent geographic atrophy, iRORA: incomplete retinal pigment epithelium and outer retinal atrophy, cRORA: complete retinal pigment epithelium and outer retinal atrophy, GA - geographic atrophy

Key secondary outcome(s))
1. Change from baseline in choroidal thickness at 3, 6 and 12 months.
2. Change from baseline in choroidal choriocapillaris flow deficits at 3, 6 and 12 months.
3. Slope of change from baseline in square root transformed GA lesion area
4. Change from iRORA to nGA and relation to functional parameters.
5. Change from baseline in area and linear measure of EZ/ELM/RPE loss at 3, 6 and 12 months.
6. Change from baseline in mean and point to point retinal sensitivity on microperimetry at 3, 6 and 12 months.
7. Change from baseline in Rod intercept time in minutes at 12 months
8. Change from baseline in Low Luminance Deficit at 3, 6 and 12 months
9. Change from baseline in drusen volume measured as RPE-BM thickness at 3, 6 and 12 months
10. Difference in choroidal flow metrics in eyes with subretinal drusenoid deposits (SDD) versus those without SDD.

Imaging modalities:
Spectral domain optical coherence tomography (SD-OCT), OCT angiography (OCTA), near-infrared reflectance (NIR), fundus autofluorescence (FAF), colour photographs and FAF and Enhanced depth imaging OCT (EDI-OCT), dark adaptation (DA) for rod intercept time (RIT) and microperimetry (MP).

Abbreviations:
EZ- ellipsoid zone, ELM - External limiting membrane, RPE - retinal pigment epithelium, SDD : subretinal drusenoid deposits, RPE-BM: Retinal pigment epithelium - Bruchs membrane.

Completion date
30/10/2025

Eligibility

Key inclusion criteria
Inclusion Criteria – intermidiate AMD
1. Subjects of either sex aged 50 – 90 years old
2. Diagnosis of iAMD (defined by Beckmann Classification) at least in one eye
3. Visual acuity of Snellen 6/18 or better in at least one eye with media clarity, pupillary dilation, and subject cooperation sufficient for adequate imaging and functional tests

Inclusion Criteria – GA
1. Subjects of either sex aged 50 – 90 years old
2. Diagnosis of hypoautofluorecence in at least one eye, either foveal or extrafoveal in location
3. Media clarity, pupillary dilation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
50 years

Upper age limit
90 years

Sex
All

Key exclusion criteria
The following exclusions apply to the study eye:
1. Co-existent ocular disease: Any other ocular condition that, in the opinion of the investigator, might affect or alter the visual acuity, for example, amblyopia.
2. A substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (eg. a cataract would be reducing acuity to 6/12 or worse if the eye was otherwise normal).
3. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within the prior 3 months or anticipated within the next 6 months following enrolment.
4. Concurrent or history of retinal laser photocoagulation or anti-vascular endothelial growth factor (anti-VEGF) treatment for exudative MNV, diabetic macular edema, retinal vein occlusion, or proliferative diabetic retinopathy
5. Previous participation in interventional clinical trials for GA or early stages of AMD, except for vitamins and minerals, regardless of the route

Date of first enrolment
30/10/2023

Date of final enrolment
31/01/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

NIHR Moorfields Clinical Research Facility
162 City Road
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Sponsor information

Organisation
Moorfields Eye Hospital NHS Foundation Trust

ROR
https://ror.org/03zaddr67

Funder(s)

Funder type
Industry

Funder Name
Boehringer Ingelheim

Alternative Name(s)
Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, BI, BIPI

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available because NHS data under GDPR regulations will not be made publicly available.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	19/09/2023	05/01/2024	No	Yes