ISRCTN22122298 https://doi.org/10.1186/ISRCTN22122298

Using direct observation of dying retinal cells technique to predict the likelihood of macular atrophy developing in newly diagnosed wet macular degeneration patients

Submission date
21/04/2022

Recruitment status
Recruiting

Registration date
14/09/2022

Overall study status
Ongoing

Last Edited
14/01/2026

Condition category
Eye Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Wet age-related macular degeneration (AMD) remains the leading cause of sight loss in the developed world with numbers set to rise in line with the aging population. Injections into the eye such as ranibizumab and aflibercept (intravitreal treatments) are the mainstay of treatment for AMD in the UK but there has been increasing concern that long-term intravitreal treatment may lead to macular atrophy (MA) associated with irreversible vision loss. Studies suggest that this occurs in up to a third of wet AMD patients receiving intravitreal treatment within 24 months. Detection of Apoptosing Retinal Cells (DARC) technology involves the use of a fluorescent dye ANX776 to identify sick or dying retinal cells on a retinal scan. To date 131 patients have received ANX776 as part of Phase I and II clinical studies, which have demonstrated good safety and tolerability. This study aims to investigate if DARC can predict the onset of macular atrophy in patients undergoing intravitreal treatments using retinal scans taken at the start of the study and after 3, 6 and 12 months.

Who can participate?
Patients aged 50 years and over with newly diagnosed wet AMD will be recruited from the Western Eye Hospital and Central Middlesex Hospital's medical retina clinics. Eligible patients will have no evidence of macular atrophy and are listed for needing standard of care intravitreal treatments, comprising three monthly injections (loading phase), followed by a combination of monitoring and treatment visits, the frequency of which will depend on patient response.

What does the study involve?
On average, patients are expected to attend seven clinic visits including the loading phase over a 12-month period. In order to avoid extra visits to the hospital site, study visits will be coordinated such that they fall on the same day as the regular care visits. The primary objective will be to see if the DARC scores at the start of the study and after 3 and 6 months are predictive of macular atrophy as defined by current gold standard imaging at 12 months.

What are the possible benefits and risks of participating?
As with all clinical research studies, participation often involves risks, some of which are known and some unknown. The risks associated with the study procedures are listed below. Patients will be asked to focus on looking into a camera and sit still for 3-4 minutes at a time; as a result they may become uncomfortable and tired during the examination. Patients may also feel temporary discomfort during the eye examinations due to the bright light used in the tests. During the intraocular pressure measurement, there is a remote chance of getting a scratch on the surface of the eye (corneal abrasion); the likelihood is remote and when they do occur, such abrasions tend to resolve quickly. In rare cases, the use of numbing eye drops during the study procedures may cause an allergic reaction, difficulty in breathing or low blood pressure. Cannulation and intravenous administration of the study drug may cause bruising, inflammation, infection, or bleeding at the site; the patient may feel a sharp scratch due to the insertion of the needle into the vein. Patients will be encouraged to tell the study doctor should they feel faint during the procedure. Experience has shown that such side effects are usually mild and tend to resolve quickly.
The study drug ANX776 is a combination of two molecules: Annexin and a fluorescent label molecule that allows us to see the sick cells. Annexin is a naturally occurring protein found in the human body, which has been widely used in laboratories to identify distressed dying cells for many years. To date, among all clinical studies on Annexin 5, none of them has shown any adverse events in humans. ANX776 has been previously tested in 129 patients and healthy volunteers, where it has been observed to be well tolerated with all adverse events classified as mild to moderate, transient, and unlikely to be related to the study drug.

Where is the study run from?
Imperial College London (UK)

When is the study starting and how long is it expected to run for?
April 2022 to December 2027

Who is funding the study?
Boehringer Ingelheim (USA)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2021-005248-31

Integrated Research Application System (IRAS)
1004250

Protocol serial number
21WE6670

Study information

Scientific Title
Detection of apoptosing retinal cells in patients with naïve wet age-related macular degeneration as a biomarker for macular atrophy development in patients undergoing anti-VEGF treatment (DAB)

Acronym
DAB

Study objectives
1. To investigate the use of Detection of Apoptosing Retinal Cells (DARC) as a biomarker to predict the onset of macular atrophy (MA) in patients with treatment naïve wet age-related macular degeneration (AMD), who undergo anti-VEGF treatment with absent macular atrophy at baseline. The primary outcome is the development of MA at 12 months and the objective of this study is to establish whether the DARC convolutional neural network (CNN) score at baseline and its change at months 3 and 6 from baseline can predict this outcome. Time frame: at baseline, 3 months, 6 months and 12 months.
2. To assess the correlation between known precursors of MA on fundus autofluorescence (FAF), optical coherence tomography (OCT) and DARC
3. To assess the correlation between response to treatment (anatomical and visual) and change

in DARC signal from baseline at months 3, 6 and 12
4. To assess the safety of intravenous administration of ANX776 performed at baseline, month 3 and month 6

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, London Brent Research Ethics Committee (80 London Road, Skipton House, London, SE1 6LH, UK), ref: 22/LO/0348

Primary study design
Observational

Study design
Observational study

Study type(s)
Diagnostic

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

Interventions
DARC dye (0.4 mg ANX776) is administered as an intravenous contrast agent for retinal imaging.

The Detection of Apoptosing Retinal Cells (DARC) compound or ANX776 consists of Annexin 5a (Anx5a), covalently bound to an infrared fluorescent dye molecule called Dye-776 (DY-776). The Anx5a variant used in this project is commonly known as Anx-128 and differs from the wild type by two single amino acid mutations. The addition of an exposed thiol group at the N-terminus affords increased conjugation efficiency for the molecular tag. DY-776 is a proprietary dye produced by the company Dyomics and is available for conjugation in its maleimide form, providing 1:1 dye: protein ratio. ANX776 is a diagnostic agent and therefore subjects will only receive doses of the medicinal product according to the follow-up investigations schedule.

Note there is no randomisation, and only one arm; this is a natural history study.

On average, patients are expected to attend seven clinic visits including the loading phase over a 12-month period. In order to avoid extra visits to the hospital site, study visits will be coordinated such that they fall on the same day as the regular care visits. The primary objective will be to see if the DARC scores at the start of the study and after 3 and 6 months are predictive of macular atrophy as defined by current gold standard imaging at 12 months.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
ANX776

Primary outcome(s)
1. Macular atrophy development measured using the DARC CNN score at baseline, 3 and 6 months
2. Presence of MA measured using the DARC CNN score at 12 months

Key secondary outcome(s)
1. Development of MA measured using OCT and FAF morphological biomarkers at 12 months
2. Prognostic value of CNN DARC score at baseline in relation to MA development at 12 months
3. Prognostic value of change from baseline of CNN DARC score at month 3 in relation to MA development at 12 months
4. Prognostic value of change from baseline of CNN DARC score at month 6 in relation to MA development at 12 months
5. OCT morphological biomarkers at baseline that correlate with MA development and their correlation to CNN DARC score

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Adults aged ≥50 years
2. Best corrected visual acuity between 6/12 and 6/96 (30-70 letters)
3. Wet AMD established on FAF, optical coherence tomography angiography (OCT-A) and OCT performed at baseline
4. Absence of MA as defined per protocol
5. Undergoing standard of care wet AMD treatment
6. Treatment-naïve (no previous anti-VEGF)
7. Sufficiently clear ocular media in the studied eye
8. Adequate pupillary dilation
9. Fixation to permit quality fundus imaging
10. Ability to give informed consent
11. The ability to understand and comply with the trial consent process and procedures
12. Refractive error not higher than the spherical equivalent of +/-6 D

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
50 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Previous anti-VEGF treatment
2. Geographic atrophy and macular atrophy at baseline as defined per protocol
3. Pregnant or lactating, or not using adequate contraception* for the duration of the trial (and 30 days post-injection of study drug)
4. Receiving active treatment in any studies of investigational drugs for geographic atrophy (GA) /dry AMD in the study eye
5. Co-existing glaucoma, diabetic retinopathy, macular dystrophies, hypertensive retinopathy and other retina conditions, inherited retinal conditions (such as vitelliform macular dystrophy, Stargardt, ADFVM)
6. Presence of epiretinal membrane (ERM)
7. Any evidence of ocular inflammation
8. History of retinal surgery, or other surgical intervention for AMD in the study eye
9. Previous laser photocoagulation for CNV, diabetic macular edema, retinal vein occlusion, and proliferative diabetic retinopathy in the study eye
10. Prior treatment with Visudyne (photodynamic Therapy [PDT]), external-beam radiation therapy, or transpupillary thermotherapy in the study eye
11. History of prophylactic subthreshold laser treatment for AMD in the study eye
12. Previous intravitreal drug delivery in the study eye (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, anti-complement agents, or device implantation)
13. A single intraoperative administration of a corticosteroid during cataract surgery for cystoid
14. Any concurrent ocular or intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could do either of the following:
14.1. Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
14.2. If allowed to progress untreated, could likely contribute to the loss of visual potential in that eye
15. Previous violation of the posterior capsule in the study eye unless it occurred as a result of Yttrium Aluminum Garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation. For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should not have exceeded 6 diopters of myopia.
16. Intraocular surgery (including cataract surgery) in the study eye within 3 months preceding Day 1
17. History of glaucoma-filtering surgery in the study eye
18. History of corneal transplant in the study eye
19. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within 12 months after screening, e.g. hip replacement
20. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s)

Date of first enrolment
03/01/2022

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
-
-
England
-

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

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

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No