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A phase II clinical trial of Detection of Apoptosing Retinal Cells (DARC II)

Submission date	Recruitment status	[_] Prospectively registered
03/04/2017	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
03/04/2017	Completed	[X] Results
Last Edited	**Condition category**	[X] Individual participant data
22/05/2023	Eye Diseases	

Plain English summary of protocol

Background and study aims
The retina is the name given to the layer at the back of the eye which is sensitive to light. When light enters the eye, the cells that make up the retina convert the light rays into electrical impulses, which travel via the optic nerve into the brain so they can be interpreted as images. Apoptosis is a process of programmed cell death or “cellular suicide”. DARC Technology (Detection of Apoptosing Retinal Cells) is a new technique that uses the unique properties of the eye to make it possible to view nerve cells in the eye dying via optosis. The technique uses a substance called ANX776, which has previously been shown to be well tolerated in patients and cause minimal side effects. The aim of this study is to further evaluate the extent to which it is possible to see apoptosis in retinal cells in patients with a range of long-term eye diseases and healthy people of the same age.

Who can participate?
Adults with eye diseases and healthy volunteers of the same age.

What does the study involve?
All participants attend a single study visit at which they receive an injection of ANX776 into a vein. Following this, they undergo an eye exam in order to look at the retina. Participants are followed up with a telephone call after 30 days to find out if they have had any side effects.

What are the possible benefits and risks of participating?
There are unlikely to be any direct benefits involved with participating, although the information gained from this study may help to improve treatment for future patients. The main risks are discomfort during the eye examination, or discomfort caused by bright, flashing lights. One of the tests is an intra-ocular pressure measurement (which measures the pressure inside the eye). There is a very small chance of getting a scratch on the surface of the eye during this test. If this does happen, it should heal on its own. The trial involves eye numbing drops which in rare cases may cause an allergic reaction, difficulty in breathing or low blood pressure. The study drug will be injected using a cannula. Risks and side effects are bruising, swelling, infection, or bleeding.

Where is the study run from?
Western Eye Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2017 to August 2018

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Ms Francesca Cordeiro
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Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number
2016-002531-15

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
31894

Study information

Scientific Title
A phase II, open label, non-randomised, single centre, clinical trial of ANX776 in healthy volunteers and patients with Glaucoma, Age-Related Macular Degeneration, Optic Neuritis and Down’s Syndrome

Acronym
DARC II

Study objectives
Current study hypothesis as of 21/06/2017:
The aim of this study is to evaluate the efficacy of DARC in visualising apoptotic retinal cells in patients with glaucoma, age-related macular degeneration, optic neuritis, Down's syndrome and in healthy volunteers

Previous study hypothesis:
The aim of this study is to evaluate the efficacy of DARC in visualising apoptotic retinal cells in patients with glaucoma, age-related macular degeneration, optic neuritis, and in healthy volunteers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London – Harrow REC, 20/12/2016, ref: 16/LO/1700

Study design
Non-randomised; Interventional; Design type: Diagnosis, Drug, Imaging

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Specialty: Ophthalmology, Primary sub-specialty: Retina (including Diabetes); UKCRC code/ Disease: Eye/ Other disorders of eye and adnexa

Interventions
The intervention involves as a single injection of the study drug (0.4mg of ANX776). The injection will be given through a cannula that will be placed in a vein in the participants arm. The injection will only last a few seconds, and the cannula will be removed immediately after the injection. Images of the participants retina will be taken using a computer imaging system called scanning laser ophthalmoscopy. All participants will be followed up for adverse events for 30 days by receiving a telephone call 30 days after the injection to check if they have experienced any side effects.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
Efficacy of the intervention ascertained by the DARC Count, which is the number of apoptosing retinal cells visualised 4 hours after the ANX776 injection.

Secondary outcome measures
Safety, defined as absence of adverse events of grade 3 or above and measured by the Common Terminology Criteria for Adverse Events (CTCAE) scale in clinic after the injection, and by telephone 30 days after the injection.

Overall study start date
01/07/2016

Completion date
31/08/2018

Eligibility

Key inclusion criteria
Current inclusion criteria as of 21/06/2017:
General Inclusion Criteria are:
1. Age ≥ 18 years
2. Clear optical media in the studied eye
3. Refractive error not higher than spherical equivalent of 10 D
4. Women of childbearing potential identified as not pregnant and have agreed to complete a pregnancy test

Group Specific Inclusion criteria are:
Glaucoma:
1. Subjects will show progression in one or more of the parameters measured and will have at least one eye with a diagnosis of glaucoma (abnormal optic disc and/or visual field defect or both); be diagnosed as a glaucoma suspect or ocular hypertensive (elevated IOP).
2. Subjects proven to be able to perform reliable visual field testing using the HFA 640, central 24-2 program, to yield full thresholds, and have had good fundoscopy with assessment of their optic disc.

Age-related Macular Degeneration:
1. Patients with AMD as defined by:
2. Early AMD mainly characterised by drusen, retinal pigment epithelium (RPE) pigment changes.
3. Late AMD mainly characterised as: geographic atrophy of the RPE (dry AMD).
4. Neovascular AMD (wet AMD).

Optic Neuritis:
1. Clinical diagnosis of optic neuritis affecting one eye within two years
2. Visual acuity in affected eye ≤ 6/12 at worst point

3. Corrected vision in unaffected eye ≥ 6/6
4. No history of optic neuritis or other ocular disease in either eye prior to the episode of optic neuritis
5. Subjects proven to be able to perform reliable visual field testing using the HFA 640, central 24-2 program, to yield full thresholds, and have had good fundoscopy with assessment of their optic disc

Down's Syndrome:
1. Confirmation of Down's syndrome diagnosis as provided by parent of GP
2. Capacity to provide assent
3. Previously participated in an invasive research trial with the Cambridge Intellectual and Developmental Disabilities Research Group (CIDDRG)
4. No clinical diagnosis of dementia or other psychiatric illness
5. No evidence of serious cognitive decline or onset of dementia from historical records

Healthy Volunteers:
1. Confirmation of medical history as confirmed by General Practitioner
2. No evidence of any eye disease

Previous inclusion criteria:
General Participant Inclusion Criteria
1. Age ≥ 18 years
2. Clear optical media in the studied eye
3. Refractive error not higher than spherical equivalent of 10 D and best corrected visual acuity
4. Equal to 6/24 or better at qualification
5. Women of childbearing potential identified as not pregnant and have consented to complete a pregnancy test
6. Subjects who have personally signed and dated the informed consent document indicating that they have been informed of all pertinent aspects of the study

Group Specific Participant Inclusion Criteria

Glaucoma Participant Inclusion Criteria:
1. Glaucoma group subjects will show progression in one or more of the parameters measured and will have at least one eye with a diagnosis of glaucoma (abnormal optic disc and/or visual field defect or both); be diagnosed as a glaucoma suspect or ocular hypertensive (elevated IOP)
2. Subjects proven to be able to perform reliable visual field testing using the HFA 640, central 24-2 program, to yield full thresholds, and have had good fundoscopy with assessment of their optic disc

AMD Participant Inclusion Criteria:
1. Patients with AMD as defined by:
1.1. Early AMD mainly characterised by drusen, retinal pigment epithelium (RPE) pigment changes
1.2. Late AMD mainly characterised as: geographic atrophy of the RPE (dry AMD)
2. Neovascular AMD (wet AMD)

Optic Neuritis Participant Inclusion Criteria:
1. Clinical diagnosis of optic neuritis affecting one eye within two years
2. Visual acuity in affected eye ≤ 6/12 at worst point
3. Corrected vision in unaffected eye ≥ 6/6
4. No history of optic neuritis or other ocular disease in either eye prior to the episode of optic

neuritis
5. Subjects proven to be able to perform reliable visual field testing using the HFA 640, central 24-2 program, to yield full thresholds, and have had good fundoscopy with assessment of their optic disc

Healthy Volunteers Participant Inclusion Criteria:
1. Confirmation of medical history as confirmed by General Practitioner
2. No evidence of any eye disease

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 120; UK Sample Size: 120

Total final enrolment
113

Key exclusion criteria
Current exclusion criteria as of 21/06/2017:
General Exclusion Criteria are:
1. Presence of severe, unstable or uncontrolled systemic disease
2. Known intolerance to IMP
3. Body weight <40kg or >150kg
4. Inability to comply with the study or follow-up procedures
5. Any subjects with a known history of clotting diseases (including DVTs), and subjects taking anticoagulants
6. Ocular surgery within the past 3 months or planned surgery in the study eye, during the course of the trial
7. Pregnant or lactating, or not using adequate contraception for the duration of the trial (and 30 days post injection of study drug)
8. Currently being treated for cancer or any other disease likely to adversely affect participation in this study
9. AIDS / HIV
10. History of alcoholism or drug addiction
11. History or active uveitis
12. History of systemic vasculitis, collagenosis or ongoing treatment of cancer
13. Evidence of previous retinal vascular disease
14. Individuals with terminal illness, or mental illness affecting their compliance with the study
15. Any other disease, condition or laboratory abnormality that in the opinion of the CI may increase the risk for the participation or may interfere with the interpretation of study results and in the judgement of the Investigator would make the subject inappropriate for entry into

the study.
16. Central corneal thickness <450 µm or >650µm
17. Currently, or within the last 3 months, enrolled in a clinical trial of an Investigational Medicinal Product
18. History of retinal laser photocoagulation
19. Media opacities or retinal pathology or amblyopia significantly limiting visual acuity, visual field test or retinal imaging
20. Any other condition or pathological process that in the opinion of the investigator would not make the participant suitable for the trial

Group Specific Exclusion criteria are:
Glaucoma:
1. Uncontrolled I0P >24mmHg
2. Angle closure/narrow glaucoma. Mean deviation at HVF worse than -12dB

Age-related Macular Degeneration:
1. Presence of choroidal neovascularisation (CNVM)
2. Current or past use for more than 30 days of chloroquine, hydroxychloroquine, chlorpromazine, thioridazine, quinine sulfate, clofazimine, cisplatin, carmustine, (BCNU), deferoxamine, amiodarone, isoretinoin, or gold

Optic Neuritis:
1. There are no specific exclusion criteria for optic neuritis participants

Down's Syndrome:
1. Clinical diagnosis of dementia or other psychiatric illness
2. Evidence of serious cognitive decline or onset of dementia from historical records
3. Unable to give assent to the study, or unable to have a legal representative give full informed consent

Healthy Volunteers:
1. Evidence of any historical retinal eye disease

Previous exclusion criteria:
General Participant Exclusion Criteria
1. Presence of severe, unstable or uncontrolled systemic disease
2. Known intolerance to IMP
3. Body weight <40kg or >150kg
4. Inability to comply with the study or follow-up procedures
5. Any subjects with a known history of clotting diseases (including DVTs), and subjects taking anticoagulants
6. Ocular surgery within the past 3 months or planned surgery in the study eye, during the course of the trial
7. Pregnant or lactating, or not using adequate contraception* for the duration of the trial (and 30 days post injection of study drug)
8. Currently being treated for cancer or any other disease likely to adversely affect participation in this study
9. AIDS/HIV
10. History of alcoholism or drug addiction
11. History or active uveitis
12. History of systemic vasculitis, collagenosis or ongoing treatment of cancer
13. Evidence of previous retinal vascular disease

14. Individuals with terminal illness, or mental illness affecting their compliance with the study
15. Any other disease, condition or laboratory abnormality that in the opinion of the CI may increase the risk for the participation or may interfere with the interpretation of study results and in the judgement of the Investigator would make the subject inappropriate for entry into the study
16. Central corneal thickness <450 pm or >650pm
17. Currently, or within the last 3 months, enrolled in a clinical trial of an investigational medicinal product
18. History of retinal laser photocoagulation
19. Media opacities or retinal pathology or amblyopia significantly limiting visual acuity, visual field test or retinal imaging
20. Any other condition or pathological process that in the opinion of the investigator would not make the patient suitable for the trial
21. For the purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilised (i.e. hysterectomy). For women of childbearing potential who may participate in the study, the following reliable form of contraception are acceptable (e.g. oral contraceptive and condom, intra--uterine device (IUD) and condom, diaphragm with spermicide and condom)

Group Specific Participant Exclusion Criteria

Glaucoma Participant Exclusion Criteria
1. Uncontrolled I0P >24mmHg
2. Angle closure/narrow glaucoma. Mean deviation at HVF >12dB

AMD Participant Exclusion Criteria
1. Presence of ocular conditions with increased risk of choroidal neovascularisation (CNVM)
2. Current or past use for more than 30 days of chloroquine, hydroxychloroquine, chlorpromazine, thioridazine, quinine sulfate, clofazimine, cisplatin, carmustine, (BCNU), deferoxamine, amiodarone, isoretinoin, or gold

Optic Neuritis Participant Exclusion Criteria
1. Corticosteroid use in the past 2 months

Healthy Volunteers Participant Exclusion Criteria
1. Evidence of any historical retinal eye disease

Date of first enrolment
08/02/2017

Date of final enrolment
30/06/2017

Locations

Countries of recruitment
United Kingdom

Study participating centre

Western Eye Hospital
171 Marylebone Road
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Sponsor information

Organisation
University College London

Sponsor details
Comprehensive Clinical Trials Unit
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Sponsor type
University/education

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location

United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal

Intention to publish date
31/08/2019

Individual participant data (IPD) sharing plan
The identity of participants and any personal details will be kept confidential. No named information about the participants will be published in any report of this study.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	02/07/2020	22/05/2020	Yes	No
Results article	results	01/01/2021	29/12/2020	Yes	No
Results article	review	01/01/2022	14/11/2022	Yes	No
Dataset	dataset		19/05/2023	No	No
Poster results	Abnormal retinal apoptosis morphometry in glaucoma and optic neuritis	04/05/2023	19/05/2023	No	No
Poster results	Characterising DARC (Detecting Apoptosing Retinal Cells) spots in Optic Neuritis (ON) and healthy eyes	04/05/2022	19/05/2023	No	No
Poster results	Characterising DARC (Detecting Apoptosing Retinal Cells) spots in glaucoma and healthy eyes	04/05/2022	19/05/2023	No	No
Protocol file	version 3.0	10/11/2016	22/05/2023	No	No
HRA research summary			26/07/2023	No	No