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NicotinAMide in Glaucoma (NAMinG): a randomised, placebo-controlled, multi-centre, Phase III trial

Submission date 14/07/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 07/11/2023	**Overall study status** Ongoing	
Last Edited 30/12/2024	**Condition category** Eye Diseases	

Plain English summary of protocol

Background and study aims

Glaucoma is a long-term eye disease which can cause permanent loss of sight and sometimes blindness. It is the world's most common cause of irreversible blindness. Vision loss happens because of damage to the important nerve at the back of the eye called the optic nerve. Most people receiving current glaucoma treatments (eye drops or laser therapy) do not experience noticeable vision loss. However, a significant minority do lose vision. We cannot cure glaucoma, but we can treat it so that the damage is slowed down or stopped, so more vision is kept for longer. There are 2 big risk factors of Glaucoma - being an older person and having high pressure inside the eye. High pressure damages the optic nerve and being older makes this damage more likely. Some people get glaucoma even if they have normal eye pressure so we think that the optic nerve in some people is more easily damaged. At the moment, we cannot tell who these people are. Recent research has looked at parts of cells called 'mitochondria'. These produce energy and might affect how likely it is that vision could be damaged by eye pressure. The nerve cells in the eye need a great deal of energy to function and survive. Vitamin B3, also known as nicotinamide (NAM), may improve the way mitochondria work. This research study wants to know if NAM treatment can protect against people losing sight because of glaucoma getting worse.

Who can participate?

Patients aged 18 years or older, who have been recently diagnosed (within the last 12 months) with early to moderate open-angle glaucoma (OAG) in at least one eye.

What does the study involve?

There will be two groups, but all will receive normal care to lower eye pressure (drops or laser); one group will receive NAM and the other group will receive dummy treatment (placebo). The trial will be randomised. Vision will be monitored through standard of care eye tests, questionnaires will be completed, blood tests will be required and there will be more visits to the hospital (3 extra than normal over 30 months). A successful outcome would lead to greatly reduced sight loss in glaucoma. Treatment with pills may also be easier for patients and would significantly reduce cost to NHS.

There is a total of 8 clinic visits, so 3 extra visits in addition to the participants routine visits. This has been reduced from the original concept so as not to be too onerous based on the feedback received from a patient web focus group. The visits, where possible, have been kept in line with normal routine care. Participants will be reimbursed (up to £30) for the travel costs incurred in attending the additional visits.

What are the possible benefits and risks of participating?
Benefits:
There is no guarantee that the Nicotinamide treatment will benefit patients however, the information we get from the trial will help the trial team find out if Nicotinamide provides better outcomes for people with glaucoma and therefore, will improve treatment for all glaucoma patients in the future.
Risks:
Adverse Events/Side Effects:
Nicotinamide (NAM) is known to be well-tolerated and the great majority of people taking NAM at the doses prescribed in the trial have no side effects. A patient attendee from the web focus group mentioned that the trial is particularly attractive as the treatment is non-invasive with a low risk of side effects. However, in any clinical trial, there is a chance of experiencing side-effects from the trial medications. The possible (including very rare) side effects of NAM are: flushing, gastro-intestinal symptoms, liver function test abnormalities, eye symptoms, fatigue, headaches, and low insulin sensitivity. Participants will be informed of the risks during the informed consent process and they will be asked to record in their dosing dairy any side effects they experience, which will be reviewed regularly at each clinic visit. The research team will also be in constant contact with the participants via telephone calls scheduled in between the clinic visits. Participants will also be informed to notify the research team should they experience any serious side effects/serious adverse events or if they are hospitalised. Participants will be provided with an alert card, which they will carry with them at all times and it will contain contact details of the trial team during in-office/out-of-office hours.

Interactions with other medications:
There are some medications that can cause side-effects when taken with NAM. Participants will be asked to take all their medications, including supplements to their Screening visit so that the research team can review their concomitant medication before entering the trial. Participants will be instructed to inform the research team of all medications (prescribed and non-prescribed) that they take during the course of trial and this will be reviewed at each clinic visit. There are some medications that preclude the participant from entering the trial and the research team will inform the participant of this and this information will be detailed in the Participant Information Sheet (PIS). A Participant Medication Checklist Letter will also be provided to participants, alongside their appointment letter for their Screening visit as a reminder to bring all their medication and those medications that are not permitted in the trial.

Pregnancy:
We do not know if NAM is a risk for a pregnant woman, an unborn baby, or a breastfeeding child, so pregnant and breastfeeding women will not be allowed to take part in the trial. Male and female participants will be asked to take highly effective contraceptive measures during the course of the trial starting from the time of informed consent and for 30 days after their last administration of the trial drug. Urine pregnancy tests for women of child bearing potential (WOCBP) will be performed at each clinic visit.

Blood samples:
The collection of blood samples can be uncomfortable, but rarely results in any serious problems. Reported side effects include feeling light-headed or faint, bruising and/or discomfort around the needle site. Every effort will be made by the research team to minimise this.

Visual field assessment:
Visual field assessments occur during clinic visits as part of standard of care, however there are some trial visits where the visual field assessment is required to be repeated twice. A 30 minute break will be given in between these repeated tests to avoid long durations of assessing the eyes and to ensure the correct visual field tests are performed, a participant visual field reminder card will be supplied to the participant by the research team, which they can bring to each clinic visit and hand to the technician performing the visual field assessment.

Where is the study run from?
UCL Comprehensive Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
July 2023 to November 2026

Who is funding the study?
NIHR

Who is the main contact?
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Contact information

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Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05405868

Clinical Trials Information System (CTIS)
2021-006867-58

Integrated Research Application System (IRAS)
1006433

Central Portfolio Management System (CPMS)
54918

Protocol serial number
CCTU/2020/365

Study information

Scientific Title
A Phase III, double-masked, randomised, placebo-controlled trial investigating the safety and efficacy of nicotinamide (NAM) to slow visual field loss in adults with open-angle glaucoma

Acronym
NAMinG

Study objectives
Primary objective:
To evaluate the effect of high-dose Nicotinamide (NAM) on Visual Field (VF) loss (change from baseline in Mean Deviation (MD)) in recently diagnosed glaucoma patients over 27 months.

Clinical safety and secondary efficacy objectives:
1. Evaluate the effect of high dose NAM on VF sensitivity over the initial 3 months (0-3 months – neuro-recovery).
2. Evaluate NAM safety.
3. Evaluate quality of life outcome (EQ-5D-5L (with vision bolt-on) and GQL-15 differences between treatment arms.

Mechanistic objectives:
1. Quantify association between mitochondrial function and rate of VF loss (placebo group).
2. Assess whether any benefit of NAM on a) rate of VF loss and b) level of mitochondrial function is greater when baseline mitochondrial function is poor or when baseline serum NAM levels are low.
3. Test hypothesis that lower lymphocyte mitochondrial function correlates with lower serum NAM levels and lower lymphocyte NAD+ levels; assess each as a biomarker for VF progression.
4. Evaluate association of NAM, NAD and OCR levels with the EPIC-Norfolk FFQ outcomes

between treatment arms.
5. Assess whether NAM lowers IOP.
6. Quantify association between mitochondrial function and quality of life measures.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/11/2023, East Midlands - Leicester South Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK; +44 (0)207 104 8143; leicestersouth.rec@hra.nhs.uk), ref: 23/EM/0175

Study design
Interventional double-blind randomized placebo-controlled trial

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Open-angle glaucoma

Interventions
All participants will receive initial treatment of Standard of Care IOP lowering therapy (prior to randomisation). Then will be randomly allocated (via an online web-based randomisation service called Sealed Envelope) to one of two treatment arms, a 1:1 ratio to receive either:
Arm A: Nicotinamide 750 mg tablets (to be taken orally with food); two tablets a day (one in the morning and one in the evening; total 1.5 g/day) for the first 6 weeks, thereafter four tablets a day (two in the morning and two in the evening; total 3.0 g/day) for the remainder of the treatment period (total 27 months).
Arm B: Matching placebo tablets (to be taken orally with food); two tablets a day (one in the morning and one in the evening) for the first 6 weeks, thereafter four tablets a day (two in the morning and two in the evening) for the remainder of the treatment period (total 27 months).

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Visual Field (VF) mean deviation (MD) at 27 months.

Key secondary outcome(s))
Clinical safety and efficacy outcomes:
1. The difference in VF MD at 3 months (0-3 months – neuro-recovery) between the NAM group

and the placebo group, measured using the HFA Mark II (or II-i) or HFA3 with the SITA Standard 24-2 programme.
2. Safety profile of high dose NAM measured by liver function tests (LFTs) and glycosylated haemoglobin (HbA1c) at screening, month 3 and month 18.
3. Adverse events during the study period for each participant from baseline to month 27.
4. Quality-of-Life outcome differences between the two treatment groups at baseline, month 3 and month 27, measured by the EQ-5D-5L (with vision bolt-on) and GQL-15.

Mechanistic outcomes:
The following outcomes will be measured from the blood samples and VFs collected over the course of the trial.
At Moorfields Eye Hospital (MEH), King's College Hospital and up to 2 further sites ONLY (Biomarker Sub-Study):
1. Impact of NAM treatment on mitochondrial function (ATP-linked oxygen consumption rate (OCR)) in the NAM and placebo groups between baseline and month 27.
2. The association between a) ATP-linked OCR and b) NAD levels and rate of VF loss in the placebo group between baseline and month 27.
3. The association between lymphocyte mitochondrial function (ATP-linked OCR), and serum NAM levels, lymphocyte NAD+ and oxidised glutathione levels in the placebo and NAM groups at baseline.
4. Association of NAM, NAD, and OCR levels with the EPIC Food Frequency Questionnaire responses in the placebo and NAM groups at baseline.
5. The effect of NAM on a) rate of VF loss (between month 3 and month 27) and b) level of mitochondrial function overall and in participants with low vs high baseline mitochondrial function and low vs high baseline NAM levels.
6. The association between lymphocyte mitochondrial function (ATP-linked OCR) and quality of life measures in the placebo and NAM groups between baseline and month 27.

At all sites:
7. The association between baseline NAM levels and rate of VF loss (between baseline and month 27) in the placebo group at all sites.
8. Association between NAM dosing and IOP (between baseline and month 27) in the active and placebo groups at all sites.

Completion date
30/11/2026

Eligibility

Key inclusion criteria
1. Patients who have been recently diagnosed (within the last 12 months) with early to moderate open-angle glaucoma (OAG) in at least one eye* (including primary OAG, NTG and pseudoexfoliation glaucoma)
2. Open angle on gonioscopy
3. Adults aged 18 years or over
4. Snellen visual acuity 6/12 or better in at least one eye meeting the visual field (VF) criteria
5. Visual Field (VF) mean deviation (MD) no worse than -12dB in either eye
6. A negative pregnancy test result at the screening and baseline visit prior to randomisation for women of childbearing potential

7. Ability to provide informed consent to participate
8. Able and willing to attend trial visits and comply with trial procedures for the duration of the trial

* Data to be collected from both eyes, the eye with the worst visual field loss at baseline will be used in the primary analysis.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Pigment dispersion glaucoma
2. Pregnancy (or planned pregnancy during the trial) and/or breastfeeding
3. Women of childbearing potential and male participants with a partner of childbearing potential not willing to use highly effective contraception for the duration of the trial treatment and for the time period specified following last trial treatment administration.
4. Current treatment with either isoniazid, pyrazinamide, carbamazepine, phenobarbital or primidone
5. Current liver disease or laboratory results with elevated levels of liver transaminases (AST or ALT >3 x ULN) at screening visit.
6. Renal failure (eGFR <30mL/min/1.73m^2) at screening visit
7. Conditions affecting both eyes*** which may affect the VF test result:
a. Diabetic retinopathy or any other retinal disease causing VF loss
b. Clinically relevant cataract (likely to require cataract surgery within the next 2 years)
c. Dementia or other non-glaucomatous neurological disease causing VF loss
d. Adnexal conditions causing VF loss (including, but not limited to blepharochalasis)
8. Diagnosed with cancer in the last 5 years (with exception of non-melanoma skin cancer)
9. Any clinical condition that, in the investigator's opinion would make the participant unsuitable for the trial
10. Concurrently enrolled in any other interventional trial or participation in previous clinical trial of glaucoma
11. Current use of, and unwilling to abstain from, over-the-counter additional vitamin B3/NAM oral supplements (including skin preparations such as ointments/emulsions), Ginkgo Biloba and /or Coenzyme Q10 supplements, throughout the duration of their participation in the trial.

*** If only one eye is affected and the other is eligible, participant can still enter the trial.

Date of first enrolment
18/01/2024

Date of final enrolment
31/05/2025

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Study participating centre
Moorfields Eye Hospital
162 City Road
London
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Study participating centre
Kings College Hospital
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Study participating centre
Manchester Royal Eye Hospital
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Sponsor information

Organisation
UCL Comprehensive Clinical Trials Unit

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Applications for access to the trial dataset at the end of the trial, should be submitted formally in writing to UCL CCTU and will be considered, and approved in writing after formal consideration by the trial oversight committees and the CI. Data sharing can be considered for use in studies that have been ethically approved.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	04/08/2023	01/03/2024	No	Yes
Protocol file	version 2.0	05/09/2023	30/12/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes