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Treatment of severe Diabetic macular oedema with Anti-vascular endothelial growth factor (anti-VEGF) monotherapy versus treatment with anti-VEGF followed by subthreshold Micropulse lasEr when the thickness of the central retina goes below 400 microns: a pragmatic randomised equivalence trial

Submission date 27/09/2024	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 18/11/2024	**Overall study status** Ongoing	
Last Edited 02/05/2025	**Condition category** Eye Diseases	

Plain English Summary

Background and study aims

The macula is the centre of the retina; it gives central sight, colour and fine detail. People with diabetes may develop diabetic macular oedema (DMO). In DMO, fluid leaks from blood vessels and builds up at the macula, causing sight loss. DMO can be mild or severe; this is determined by measuring, in microns (μm), how thick the macula is. One μm is one-thousandth of a millimetre. People presenting with mild DMO (macula less than 400 μm thick; normally it is around 250 μm but varies with sex and ethnicity) are offered macular laser treatment. Laser works well for these patients. Subthreshold micropulse laser (SML), which does not damage the macula, works as well as standard laser, which produces a burn, and is cost-effective.

However, many people present with severe DMO (macula 400 μm or thicker) where the laser does not work well. The standard treatment is eye injections of anti-VEGFs. VEGF stands for vascular endothelial growth factor. VEGF is high in eyes with DMO and causes blood vessel leakage. Anti-VEGFs block VEGF. They are given monthly to begin with, then every 2-3 months for months or years until DMO clears. In many patients DMO comes back after clearing and anti-VEGFs need to be re-started most often monthly initially again.

To improve the care of people with severe DMO this study will compare the current standard care (anti-VEGFs alone) with a strategy in which patients begin with an anti-VEGF but switch to SML once the macula is less than 400 μm thick.

Who can participate?

Patients aged over 18 years with type 1 or type 2 diabetes and severe DMO

What does the study involve?
Participants are randomly allocated to be treated with either anti-VEGFs alone or anti-VEGFs then SML once the macula is less than 400 µm thick.

What are the possible benefits and risks of participating?
It is considered that the risk associated with the anti-VEGF and SML used within the DAME study is no higher than the risk of standard care. There are a number of expected events associated with the administration of anti-VEGF, SML and intravitreal steroids, Patients will be asked at each visit specifically about each of the following: self-reported central/paracentral scotomas, self-reported reduced colour vision, self-reported metamorphopsia, corneal epithelial erosion, corneal ulcer, endophthalmitis, intraocular inflammation (anterior, posterior or panuveitis), intraocular pressure elevation (over 21 mmHg), intraocular haemorrhage (suprachoroidal /vitreous/pre-retinal haemorrhage), retinal tear, retinal detachment, retinal vasculitis, retinal vascular occlusion (retinal vein or retinal artery occlusion), lens touch (which may occur at the time of an intravitreal injection and may be seen only post-administration in the form of a focal cataract), allergic reaction to any treatments given, including eye drops, angina, myocardial infarction, stroke, transient ischaemic attack (TIA), kidney disease. These events will be collected as safety outcomes and any adverse effects will be monitored by the trial team and DMEC.

Where is the study run from?
Queen's University Belfast (UK)

When is the study starting and how long is it expected to run for?
September 2024 to September 2028

Who is funding the study?
National Institute for Health and Care Research (UK)

Who is the main contact?
1. Prof. Noemi Lois, n.lois@qub.ac.uk
2. Mary Guiney, mary.guiney@nictu.hscni.net

Study website
https://nictu.hscni.net/service/dame/

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010626

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
24014NL-UC, CPMS 65230

Study information

Scientific Title
Treatment of severe Diabetic macular oedema with Anti-vascular endothelial growth factor (anti-VEGF) monotherapy versus treatment with anti-VEGF followed by subthreshold Micropulse lasEr when the thickness of the central retina goes below 400 microns: a pragmatic randomised equivalence trial

Acronym
DAME

Study hypothesis
Primary objective:
To determine if the clinical effectiveness of anti-VEGFs and SML is equivalent to anti-VEGF monotherapy

Secondary objectives:
1. To determine the cost-effectiveness of anti-VEGFs and SML compared to anti-VEGF monotherapy via an economic evaluation
2. To evaluate the participant experience and acceptability of anti-VEGFs and SML compared to anti-VEGF monotherapy via a mixed methods evaluation

3. To evaluate the post-trial implementation and scalability of anti-VEGFs and SML via a process evaluation

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/11/2024, South Central - Oxford B Research Ethics Committee (Health Research Authority, 2 Redman Place, Stratford, E20 1JQ, United Kingdom; +44 (0)207 104 8134, +44 (0) 207 104 8019; oxfordb.rec@hra.nhs.uk), ref: 24/SC/0330

Study design
Pragmatic allocation-concealed single-masked (outcome assessors) multicentre randomized (1:1) equivalence trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

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

Condition
Severe diabetic macular oedema (DMO).

Interventions
Comparator Arm: Anti-VEGF Monotherapy (standard care)
Anti-VEGFs including ranibizumab and biosimilars, aflibercept, faricimab, and brolucizumab will be used, as per the standard of care at participating sites. The anti-VEGF should be administered in line with the summary of product characteristics (SmPC).

Intervention Arm: Subthreshold Micropulse Laser (SML)
SML will be applied in line with the DAME Guideline and follow the DAME participant pathway.

Eligible participants who provide consent will be randomised 1:1 to receive SML or to continue with anti-VEGF monotherapy. A minimisation algorithm will be used to ensure balanced allocation of participants across trial arms for potentially important factors including centre, duration of DMO (≤1year, >1year), number of doses of anti-VEGFs received up to the time of randomisation (1-6; 7-12), type of anti-VEGF used (ranibizumab, ranibizumab-biosimilar, Brolucizumab, aflibercept, or faricimab) up to the time of randomisation, which will be continued throughout the trial unless lack of efficacy is observed and rescue treatment is needed, presenting BCVA [BCVA ≥ 69 ETDRS letters (Snellen equivalent ≥ 20/40; logMAR ≥ 0.3), 24–68

ETDRS letters (Snellen equivalent ≤20/50-20/320; logMAR 0.4–1.2) and CI-DMO (Yes, No). Minimising randomisation by these variables will ensure both trial arms will be balanced with regard to these potentially important baseline characteristics.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Aflibercept, brolucizumab, ranibizumab, faricimab

Primary outcome measure
Change in best corrected visual acuity (BCVA) in the study eye from randomisation (baseline) to 104 weeks (24 months) (equivalence margin +/- 5 ETDRS letters)

Secondary outcome measures
All measured at 104 weeks (24 months) from randomisation:
1. Central Retinal Thickness in the study eye. CRT in the central 1 mm of the retina as measured using Spectral-Domain optical Coherence Tomography (SD- OCT)
2. Health-related and vision-related quality of life. National Eye Institute Visual Function Questionnaire (NEI VFQ) 25 and the EuroQoL (EQ 5D 5L) questionnaire
3. Safety based on determined safety outcomes, adverse events, and serious adverse events
4. Number of treatments used (anti-VEGF injections, SML sessions) in the study eye from baseline to week 104
5. Number/proportion of people receiving “rescue” treatment in the study eye from baseline to week 104
6. Number of rescue treatments received in the study eye from baseline to week 104
7. Number/proportion of people discontinuing treatment (with reasons)
8. Number/proportion of people losing (with reasons) ≥5, ≥10 and ≥15 ETDRS letters of best-corrected visual acuity (from baseline to week 104) in the study eye
9. Number/proportion of people gaining ≥5, ≥10 and ≥15 ETDRS letters (from baseline to week 104) in the study eye
10. Number/proportion of people with CRT ≤300µm in the study eye in the central 1 mm if the retina as determined using SD-OCT
11. Number/proportion of people with no DMO, as determined by the ophthalmologists evaluating the patient
12. Health and social care service use and non-healthcare costs as determined using a Health Service Use Questionnaire and Patient Cost Questionnaire
13. Participant experience and acceptability as determined by focus group discussions, the Acceptability Questionnaire (Theoretical Framework of Acceptability (TFA)) distributed at week 104, and also by the use of Visual Analogue Score questionnaires that will be distributed 60 minutes prior to treatment, immediately after treatment and 24 hours after treatment at all instances in which treatment is given

Overall study start date
24/09/2024

Overall study end date
30/09/2028

Eligibility

Participant inclusion criteria
1. Adults (>18 years)
2. Diabetes type 1 or type 2
3. Presented with severe centre-involving (CI)-DMO (CRT ≥400 µm)
4. Within the first year of initiating anti-VEGF therapy but who still have DMO and their CRT is below 400 µm (and it remains, at the time of randomisation) following anti-VEGF therapy in either one eye or both eyes

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
264

Participant exclusion criteria
1. Causes of macular oedema other than DMO
2. DMO with CRT ≥400 µm
3. Receipt of anti-VEGFs before their presentation with severe DMO (previous macular laser treatment for DMO is allowed)
4. Use of unlicensed anti-VEGFs (e.g. bevacizumab)
5. Inability, for any reason, to attend study visits
6. Active proliferative diabetic retinopathy (PDR) (treated and inactive PDR is allowed)
7. Use of pioglitazone which cannot be stopped for the duration of the trial
8. Cataract surgery or laser pan-retinal photocoagulation (PRP) within the previous 6 weeks
9. Currently enrolled in a CTIMP (Clinical Trial of an Investigational Medical Product)
10. Declined consent for participation

Recruitment start date
01/06/2025

Recruitment end date
30/04/2026

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
The Hillingdon Hospital
Pield Heath Road
Uxbridge
United Kingdom
UB8 3NN

Study participating centre
Frimley Park Hospital
Portsmouth Road
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United Kingdom
GU16 7UJ

Study participating centre
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Study participating centre
The Sussex Eye Hospital
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Study participating centre
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Study participating centre
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Sponsor information

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Sponsor type
University/education

Website
http://www.belfasttrust.hscni.net/

ROR
https://ror.org/02tdmfk69

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

Publication and dissemination plan

The results of DAME will be disseminated widely through presentations at national and international ophthalmic/diabetes meetings and at invited speaker's lectures. The results will be presented at participant group meetings. Diabetes UK Northern Ireland has agreed to contribute to the dissemination efforts to ensure the results are available to participants, their families, and the public. The research team includes lead clinicians and researchers with contacts across the globe.

They will use these international contacts to ensure trial results are disseminated widely and incorporated into future guidelines on diabetic retinopathy. DAME will be reported in accordance with the CONSORT guideline. If necessary, the CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances (CONSERVE) statement will also be applied in the event that extenuating circumstances require major modifications to the trial during its course. The trial protocol, statistical analysis plan and health economic analysis plan will be made publicly available to ensure transparency in our methodology.

In accordance with the open-access policies proposed by the NIHR we plan to publish the clinical findings of the trial as well as a separate paper describing the health economic findings of the trial in high-quality, high-impact, peer-reviewed open-access journals. Other manuscripts are planned (e.g. a manuscript presenting data on patient experience and acceptability of the treatments; a manuscript with the results of the SWAT; others).

We will actively promote the findings of the study to journal editors and opinion leaders in ophthalmology and diabetes to ensure findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. The most significant results will be communicated to the wider public through media releases. An ongoing update of the study will also be provided on the NICTU website.

Intention to publish date

31/03/2029

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	09/09/2024	01/10/2024	No	No