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	Recruitment status Recruiting	[X] Prospectively registered			
27/09/2024		[X] Protocol			
Registration date	Overall study status	Statistical analysis plan			
18/11/2024	Ongoing	Results			
Last Edited	Condition category	☐ Individual participant data			
05/08/2025	Eye Diseases	[X] Record updated in last year			

Plain English summary of protocol

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, dame@nictu.hscni.net

Contact information

Type(s)

Scientific, Principal investigator

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Type(s)

Public

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

Integrated Research Application System (IRAS)

1010626

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number

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 objectives

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

Study type(s)

Safety, Efficacy

Health condition(s) or problem(s) studied

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 (\leq 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 \geq 69 ETDRS letters (Snellen equivalent \leq 20/40; logMAR \geq 0.3), 24–68 ETDRS letters (Snellen equivalent \leq 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

Phase

Phase III

Drug/device/biological/vaccine name(s)

Aflibercept, brolucizumab, ranibizumab, faricimab

Primary outcome(s)

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

Key secondary outcome(s))

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

Completion date

30/09/2028

Eligibility

Key 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 μ m (and it remains, at the time of randomisation) following anti-VEGF therapy in either one eye or both eyes

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

All

Key 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

Date of first enrolment

19/05/2025

Date of final enrolment

30/04/2026

Locations

Countries of recruitment

United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre The Hillingdon Hospital

Pield Heath Road Uxbridge United Kingdom UB8 3NN

Study participating centre Frimley Park Hospital

Portsmouth Road Frimley Camberley United Kingdom GU16 7UJ

Study participating centre Kings College Hospital

Mapother House De Crespigny Park Denmark Hill London United Kingdom SE5 8AB

Study participating centre James Cook University Hospital

Marton Road Middlesbrough United Kingdom TS4 3BW

Study participating centre Chelsea and Westminster Hospital

Chelsea & Westminster Hospital 369 Fulham Road London United Kingdom SW10 9NH

Study participating centre Central Middlesex Hospital

Acton Lane London United Kingdom NW10 7NS

Study participating centre Moorfields Eye Hospital

162 City Road London United Kingdom EC1V 2PD

Study participating centre Sunderland Eye Hospital

Queen Alexandra Rd Sunderland United Kingdom SR2 9HP

Study participating centre Royal Gwent Hospital

Cardiff Road Newport United Kingdom NP20 2UB

Study participating centre Bristol Eye Hospital

Lower Maudlin Street Bristol United Kingdom BS1 2LX

Study participating centre University Hospital Southampton

Southampton University Hospital Tremona Road Southampton United Kingdom SO16 6YD

Study participating centre Gloucestershire Royal Hospital

Great Western Road

Gloucester United Kingdom GL1 3NN

Study participating centre
Royal Liverpool University Hospital
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre Hull Royal Infirmary

Anlaby Road Hull United Kingdom HU3 2JZ

Study participating centre Queens Medical Centre

Nottingham University Hospital Derby Road Nottingham United Kingdom NG7 2UH

Study participating centre Royal Victoria Hospital 274 Grosvenor Road

Belfast United Kingdom BT12 6BA

Study participating centre The Sussex Eye Hospital

Eastern Road Brighton United Kingdom BN2 5BF

Study participating centre Torbay Hospital

Torbay Hospital Newton Road Torquay United Kingdom TQ2 7AA

Study participating centre East Surrey Hospital

Canada Avenue Redhill United Kingdom RH1 5RH

Study participating centre Birmingham Midland Eye Centre (bmec)

City Hospital N H S Trust Dudley Road Birmingham United Kingdom B18 7QH

Study participating centre Sandwell and West Birmingham Hospitals NHS Trust

Midland Metropolitan University Hos Grove Lane Smethwick United Kingdom B66 2QT

Study participating centre Singleton Hospital

Sketty Lane Sketty Swansea United Kingdom SA2 8QA

Study participating centre Swansea Bay University Local Health Board

Tonna Hospital Tonna Uchaf Tonna Neath United Kingdom SA11 3LX

Sponsor information

Organisation

Belfast Health and Social Care Trust

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

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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 2.0	09/09/2024	01/10/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes