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Synopsis

Fenofibrate and progression of retinopathy in adults with diabetes: the randomised placebo-controlled LENS trial

David Preiss[1*] Jennifer Logue[2] Emily Sammons[1] Mohammed Zayed[1] Graham Scotland[3] Mekazin Tsehaye[3] Jonathan Emberson[1] Rachel Wade[1] Karl Wallendszus[1] Will Stevens[1] Rosanna Cretney[1] Simon Harding[4] Graham Leese[5] Gemma Currie[6] Caroline Styles[7] and Jane Armitage[1] on behalf of the LENS Collaborative Group

[1]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[2]Faculty of Health and Medicine, Lancaster University, Lancaster, UK
[3]Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
[4]Department of Eye and Vision Science, University of Liverpool and St Paul's Eye Unit, Liverpool University Hospitals NHS Foundation Trust, Liverpool, Merseyside, UK
[5]Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK
[6]School of Cardiovascular & Metabolic Health, University of Glasgow, Glasgow, UK
[7]Department of Ophthalmology, NHS Fife, Queen Margaret Hospital, Dunfermline, UK

[*]**Corresponding author** lens@ndph.ox.ac.uk

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Abstract

Background: Diabetic retinopathy is a leading cause of visual loss. Hypothesis-generating data from cardiovascular outcome trials suggest that fenofibrate therapy may reduce the progression of diabetic retinopathy.
Objective: To determine whether treatment with fenofibrate reduces the progression of diabetic retinopathy.
Design and methods: We conducted a parallel-group, double-masked, placebo-controlled clinical trial of fenofibrate. A web-based algorithm allocated participants to treatment arms by minimisation.
Setting and participants: The trial was positioned within NHS Scotland's Diabetic Eye Screening Programme. Adults with diabetes and non-referable retinopathy or maculopathy (based on Diabetic Eye Screening retinal image grading) were eligible.
Interventions: Study treatment was mailed to participants' homes. Participants who were eligible at the screening assessment entered an active pre-randomisation run-in during which they took 145 mg fenofibrate. After randomisation, participants received 145 mg fenofibrate tablets or placebo. Study treatment was taken daily in those with normal renal function, or on alternate days in those with impaired renal function.
Main outcome measures: The primary outcome was a composite of developing referable diabetic retinopathy or maculopathy, or requiring treatment for diabetic retinopathy or maculopathy. Incremental cost-effectiveness was assessed in terms of the primary outcome and per modelled quality-adjusted life-year gained.
Data sources: Data were obtained from 6-monthly interviews by research nurses and linkage to national healthcare data sets. Selected adverse events were adjudicated by study clinicians masked to treatment allocation.
Results: One thousand four hundred and eighty-four participants entered the pre-randomisation run-in, of whom 1151 were randomised. The primary outcome occurred in 131 (22.7%) of 576 participants assigned fenofibrate and 168 (29.2%) of 575 participants assigned placebo (hazard ratio 0.73; 95% confidence interval 0.58 to 0.91; $p = 0.006$) over a median of 4.0 years. Any progression of retinopathy or maculopathy, and development of macular

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oedema were also reduced. There was no effect on visual function, quality of life, or visual acuity. Fenofibrate use resulted in a non-significant reduction in 6-monthly health service costs (mean difference −£101, 95% confidence interval −£243 to £42), leading to dominance over standard care and a high probability of cost-effectiveness. Based on modelling (assuming no difference in background healthcare costs by treatment allocation), fenofibrate led to a small increase (£6) in cost for a small gain (0.02) in quality-adjusted life-years; incremental cost-effectiveness ratio £406 per quality-adjusted life-year gained. The probability of cost-effectiveness was 79–86% at thresholds of £20,000–30,000 per quality-adjusted life-year gained.

Limitations: Early Treatment Diabetic Retinopathy Study retinopathy grading is considered the gold standard, but it is not used in large-scale retinal screening programmes; Diabetic Eye Screening grading is based on Early Treatment Diabetic Retinopathy Study but is less granular.

Conclusions: Fenofibrate was clinically effective and cost-effective for reducing the progression of diabetic retinopathy compared with placebo among participants with early retinal changes.

Future work: LENS participants will be followed for 10 years to assess the long-term effects of fenofibrate therapy.

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Introduction

Diabetic retinopathy is a common progressive microvascular complication of diabetes mellitus. It is a leading cause of visual loss worldwide, and the only major cause to increase in many regions of the world over the last 30 years.[1] Vision may be threatened by disease of the retina (diabetic retinopathy) or the macula (diabetic maculopathy). Progression of retinopathy to proliferative retinopathy – the development of disorganised and friable blood vessels – may lead to vitreous haemorrhage, retinal detachment and neovascular glaucoma, with a potential threat to vision. Diabetic maculopathy is characterised by exudates, haemorrhages and/or microaneurysms in the area of the macula. This may progress to macular oedema and may also impact on vision. In this report, the term *diabetic retinopathy* will generally refer to both retinopathy and maculopathy.

Key risk factors for the progression of diabetic retinopathy include longer duration of diabetes, worse glucose control and hypertension.[2] There are few therapeutic options that can slow the progression of retinopathy. There is evidence from major randomised trials that reducing blood pressure modestly reduces the development and progression of retinopathy.[3] Landmark trials of different strategies to control glucose have also shown that moderately good glycaemic control substantially reduces complications of diabetic retinopathy compared with poor glycaemic control.[4,5] However, trials comparing intensive with less intensive glucose-control conducted in the last two decades have demonstrated only modest ocular benefit of intensive control.[6] Furthermore, good glucose control is challenging to achieve for many people, whether due to lack of access to therapies or difficulty in maintaining control over a prolonged period of time. Treatments for advanced diabetic retinopathy – retinal laser and intravitreal injections – require expertise and specialist equipment to deliver, are expensive to healthcare systems, are associated with iatrogenic risks such as eye infection, and may be ineffective.[7]

There is therefore a lack of clinically efficacious and cost-effective therapies that can be used earlier in the course of disease in people with diabetic retinopathy. However, few trials are conducted in people with earlier stages of retinopathy because it progresses slowly. Therefore, more people would need to participate to provide adequate statistical power to identify a significant treatment effect. Population-based diabetic retinal screening is recommended to identify people with diabetes at risk of vision-threatening disease so that treatment, such as retinal laser or intravitreal injections, can be started before vision is impacted.[8] Large-scale retinal screening programmes may also facilitate the conduct of randomised trials, and potentially offer the opportunity to intervene if effective therapies can be identified, in those with earlier retinal disease. However, such programmes have not been harnessed in this way to date.

Fenofibrate is an orally administered peroxisome proliferator-activated receptor alpha agonist. Its effects on circulating lipids are to reduce triglycerides and apolipoprotein B-containing lipids [non-high-density lipoprotein (HDL) and low-density lipoprotein (LDL)] levels.[9] Two major randomised placebo-controlled cardiovascular outcome trials of fenofibrate therapy, both conducted in participants with type 2 diabetes, reported data for diabetic retinopathy outcomes between 2005 and 2009. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, adjudicated reports of laser therapy for diabetic retinopathy were proportionally reduced by 31% [164 first events in 4895 (3.4%) participants on fenofibrate vs. 238 first events in

4900 (4.9%) participants on placebo] in a tertiary outcome analysis.[10,11] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study was conducted in 5518 participants on background simvastatin. In the ACCORD Eye substudy, 1998 ACCORD Lipid participants underwent standardised eye examinations and fundal photography at baseline, and 1593 had these investigations repeated after 4 years. The ACCORD Eye composite outcome of laser treatment, vitrectomy or three-step progression on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale was proportionally reduced by 40% [52 first events in 806 (6.5%) participants on fenofibrate vs. 80 first events in 787 (10.2%) participants on placebo].[12]

During the conduct of the Lowering Events in Non-proliferative retinopathy in Scotland (LENS) trial described in this manuscript, we pooled summary data regarding use of laser therapy for the treatment of diabetic retinopathy or diabetic macular oedema from major randomised trials of fenofibrate.[13] Qualifying trials needed to include at least 1000 participants with diabetes, have a planned follow-up of at least 2 years, and be placebo-controlled. We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials to identify relevant trials. Data were obtained for three trials – published data were available from the FIELD trial,[11] summary data were provided by the Lipids in Diabetes Study investigators,[14] and the National Heart, Lung, and Blood Institute provided individual participant data to allow analysis of this outcome in the full ACCORD Lipid trial population.[15] All three trials were cardiovascular outcome trials. All participants in the three trials were included, regardless of the presence or absence of diabetic retinopathy at baseline. Together, these trials included 19,504 participants and weighted mean follow-up was 4.0 years. Fenofibrate reduced mean triglycerides by 0.33–0.57 mmol/l (20–30%), mean total cholesterol by 0.16–0.57 mmol/l (3–12%) and mean LDL cholesterol by 0–0.36 mmol/l (0–12%) compared with placebo at 1 year across the trials. During follow-up, 391 (4.0%) participants allocated fenofibrate, and 501 (5.1%) participants allocated placebo received laser treatment for diabetic eye disease, a 23% proportional reduction [odds ratio (OR) 0.77, 95% confidence interval (CI) 0.67 to 0.88; $p = 0.0001$].[13]

Given that these results emerged from subsidiary outcomes in randomised trials with non-significant results for their primary cardiovascular outcomes, they may represent chance findings and should be considered hypothesis-generating. With the exception of Australia's Therapeutic Goods Administration, major drug regulators do not currently license fenofibrate to treat patients with diabetic retinopathy. Major national and international diabetes guidelines also do not generally recommend fenofibrate for this indication. There is therefore a need to conduct trials specifically designed to investigate the effect of fenofibrate on the progression of diabetic eye disease. The LENS trial – a parallel-group, double-masked, randomised, placebo-controlled clinical trial, positioned within Scotland's national Diabetic Eye Screening (DES) Programme – was designed to assess the effect of fenofibrate on the progression of diabetic retinopathy in people with early diabetic eye disease.

Methods

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Trial design and oversight

The LENS trial was initiated by investigators at the Central Coordinating Office (CCO) at the Nuffield Department of Population Health (NDPH), University of Oxford. The trial was sponsored by the University of Oxford and is registered at ClinicalTrials.gov (NCT03439345) and International Standard Randomised Controlled Trial Number (ISRCTN15073006). It was conducted at 16 hospital sites across all 11 NHS Health Boards in mainland Scotland. The trial was designed to be streamlined and it was embedded within routine clinical care. Characteristics of the participants and trial methods, and the main trial results, have already been reported.[16,17] The study protocol and any updates to it (available at www.isrctn.com/ISRCTN15073006) were approved by the West of Scotland Research Ethics Committee. It was made publicly available on the ISRCTN website from May 2020. The trial had oversight from a Steering Committee that includes patient representatives. An independent Data Monitoring Committee regularly reviewed unmasked data. Fenofibrate and identical matching placebo tablets were provided by the pharmaceutical company, Mylan (now part of Viatris). The trial was primarily funded by the National Institute for Health and Care Research's (NIHR) Health Technology Assessment (HTA) Programme. NDPH funded the packaging, storage and selection for mailing of study treatment. This report was written by the Writing Group on behalf of the LENS Collaborative Group (membership is provided in the Additional information).

Participants

Adults (aged ≥ 18 years) with diabetes mellitus and non-referable diabetic retinopathy or maculopathy were potentially eligible to join the trial. Non-referable disease was defined according to NHS Scotland's

DES Programme grading scheme (*Table 1*) as: (1) mild background retinopathy (R1 grade) in both eyes or observable background retinopathy (R2 grade) in one/both eyes at the latest retinal screening assessment; or (2) observable maculopathy (M1 grade) in one/both eyes at a retinal screening assessment in the last 3 years (though participants were invited based on non-referable disease at their latest retinal screening). Estimated glomerular filtration rate (eGFR) had to be ≥ 40 ml/minute/1.73 m^2 at the screening assessment. Full details regarding the eligibility criteria are provided in *Table 2*. All participants provided written informed consent.

Trial procedures

Retinal screening is one of numerous national health screening programmes offered by the NHS in Scotland.[18] It is routinely offered to people with diabetes aged ≥ 12 years by the national DES Programme. Single 45° macula-centred retinal digital photographs are taken with non-mydriatic cameras using a staged imaging protocol.[19] Photographs are first taken without the use of mydriatic eye drops. Mydriatic drops are used if undilated images are inadequate. If adequate images are still not obtained, slit lamp biomicroscopy examination is arranged. The images are graded according to the NHS Scotland DES Programme grading scheme (see *Table 1*) in 10 grading centres, an approach validated for detecting referable retinopathy requiring regular ophthalmological review.[20,21] Images undergo three levels of grading – Level 1 (typically conducted using image analysis software) to identify images with any retinal disease, Level 2 (by junior graders) to identify images with potentially sight-threatening disease and Level 3 (by senior graders) to make the final decision regarding which patients require specialist referral or further investigation. Trained NHS retinal image graders participate in regular quality assurance exercises.[17] Best corrected visual acuity (BCVA) is also recorded at these visits. Scottish Care Information – Diabetes (SCI Diabetes) is NHS Scotland's national integrated electronic diabetes patient record.[22] It is used in general practice and NHS Scotland hospitals to support the management of diabetes. Available data from SCI Diabetes and DES include biochemistry [e.g. eGFR, creatinine, lipids, glycated haemoglobin (HbA1c), urine albumin creatinine ratio (UACR)] and retinal screening results. These and other national data sets supported streamlined recruitment and follow-up of LENS trial participants.

Adults across Scotland with non-referable retinopathy or maculopathy were invited to join the LENS trial.[17] Site staff pre-screened interested respondents to reduce the chance of ineligible people attending a trial screening visit in person. Eligibility, including eGFR, was checked at an in-person trial screening visit. Site investigators reviewed information collected at the trial screening visit and they were responsible for determining whether or not a participant should enter the pre-randomisation run-in phase. Eligible participants entering the run-in were mailed a 10-week supply of open-label nanoparticle fenofibrate 145 mg tablets. Those with screening eGFR ≥ 60 ml/minute/1.73 m^2 took one tablet daily and those with eGFR 40–59 ml/minute/1.73 m^2 took one tablet on alternate days. The main purposes of the run-in were to identify and exclude participants who were likely to be non-adherent and to provide an opportunity to measure on-treatment renal function and liver function tests prior to randomisation. Approximately 8 weeks later, participants attended an in-person randomisation assessment. At this assessment, participants needed to report taking run-in treatment at least 70% of the time, and the eGFR had to be ≥ 30 ml/minute/1.73 m^2 (to allow for the expected rise in serum creatinine due to fenofibrate treatment) to proceed.[23,24] During the coronavirus disease discovered in 2019 (COVID-19) pandemic, a small number of randomisation assessments were conducted by telephone, and eGFR was checked as soon as possible thereafter (but prior to randomisation), based on temporary restrictions at sites.

The dose frequency of study treatment after randomisation depended on renal function. Participants with a randomisation assessment eGFR ≥ 60 ml/minute/1.73 m^2 commenced one tablet of study treatment daily and those with eGFR 30–59 ml/minute/1.73 m^2 commenced one tablet on alternate days. Randomised participants continued retinal screening as directed by the DES Programme and continued their usual diabetes care. They were contacted by a LENS research nurse by telephone approximately once every 6 months. There was also an option for follow-up via review of medical records or by contact with their usual doctor if a participant was not contactable by telephone or had declined further telephone contact. Participants received regular supplies of randomised study treatment by post. eGFR results from routine NHS care were monitored centrally via SCI Diabetes after randomisation. If post-randomisation eGFR fell to 30–59 ml/minute/1.73 m^2 in a participant on daily treatment, study treatment was dropped to one tablet on alternate days (and could not be increased to daily therapy again). If eGFR fell below 30 ml/minute/1.73 m^2, study treatment was discontinued (but could be resumed if renal function subsequently improved). Linkages to DES and other national healthcare data sets were performed regularly to identify various prespecified outcomes.

TABLE 1 NHS Scotland's DES Programme grading scheme

Grade	Description	Findings	Outcome
Retinopathy (excluding the macula)			
R0	No diabetic retinopathy anywhere	–	Rescreen in 12–24 months
R1	Mild background diabetic retinopathy	The presence of at least one of any of the following features anywhere: • Dot haemorrhages/microaneurysms • Hard exudates • Cotton wool spots • Blot haemorrhages[a] • Superficial/flame-shaped haemorrhages	Rescreen in 12 months
R2	Observable background diabetic retinopathy	Four or more blot haemorrhages[a] in one hemi-field only (inferior and superior hemi-fields delineated by a line passing through the centre of the fovea and optic disc)	Rescreen in 6 months
R3	Referable background diabetic retinopathy	Any of the following features: • Four or more blot haemorrhages[a] in both inferior and superior hemi-fields • Venous beading • Intraretinal microvascular abnormalities (IRMAs)	Specialist referral (routine)
R4	Proliferative diabetic retinopathy	Any of the following features: • Active new vessels • Vitreous haemorrhage	Specialist referral (urgent)
R4i[b]	Treated proliferative diabetic retinopathy	Any of the following features: • Inactive new vessels with evidence of laser treatment	Rescreen in 12 months
R6	Not adequately visualised	Retina not sufficiently visible for assessment	Technical failure
Maculopathy			
M0	No maculopathy	No features ≤ 2 disc diameters from the centre of the fovea sufficient to qualify for M1 or M2	Rescreen in 12–24 months
M1	Observable maculopathy	Lesions as specified below within a radius of > 1 but ≤ 2 disc diameters from the centre of the fovea: • Any hard exudates	Rescreen in 12 months
M2[c,d]	Referable maculopathy	Lesions as specified below within a radius of ≤ 1 disc diameter of the centre of the fovea: • Any blot haemorrhages[a] • Any hard exudates	OCT surveillance scan or rescreen in 12 months

a Blot haemorrhage has the same or greater diameter as a retinal vein crossing the optic disc.
b R4i is not counted towards the primary outcome as it represents inactive disease.
c At the start of LENS and until end-2021, patients in Scotland with M2 retinal screening results required referral to a specialist. During 2022, the DES programme started to introduce a phased change to the management pathway of patients with M2 disease. In the new pathway, M2 with poor visual acuity (e.g. 6/9.5 or worse) leads to optical coherence tomography (OCT) imaging followed by referral to an ophthalmologist if there is macular oedema.
d From 2021, the definition of referable maculopathy (M2) was limited to exudates (i.e. blot haemorrhage was excluded).

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TABLE 2 Eligibility criteria for the LENS trial

Inclusion criteria
All these criteria must be fulfilled:
• Capable of giving informed consent
• Diabetes mellitus (any type except gestational diabetes)
• Age ≥ 18 years
• Non-referable diabetic retinopathy [defined according to NHS Scotland's DES grading scheme as mild background retinopathy (R1) in both eyes or observable background retinopathy (R2) in one/both eyes at the most recent NHS retinal screening assessment; or observable maculopathy (M1) in one/both eyes at any NHS retinal screening assessment in the last 3 years]
• Willing to either complete electronic questionnaires or conduct telephone interviews for collection of questionnaire data
Exclusion criteria
None of these criteria must be fulfilled:
• Referable diabetic retinopathy [defined by NHS Scotland's DES grading scheme as referable background retinopathy (R3) or proliferative retinopathy (R4) or referable maculopathy (M2) in either eye]
• History of gallbladder disease (cholecystitis, symptomatic gallstones, cholecystectomy)
• History of acute or chronic pancreatitis
• ALT or AST > 2X ULN at screening visit; ALT or AST > 2.5X ULN at randomisation visit
• CK > 3X ULN at screening visit; CK > 3X ULN at randomisation visit
• eGFR < 40 ml/minute/1.73 m^2 at screening visit; eGFR < 30 ml/minute/1.73 m^2 at randomisation visit
• Cirrhosis of any aetiology or any other serious hepatic disease
• Female who is pregnant, breastfeeding, currently trying to become pregnant or of child-bearing potential and not practising birth control
• Ongoing vitamin K antagonist (warfarin, phenindione, acenocoumarol), cyclosporine, colchicine, ketoprofen, daptomycin, fibrate therapy or treatment with rosuvastatin 40 mg daily
• Previous myositis, myopathy or rhabdomyolysis of any cause or diagnosed hereditary muscle disorder
• Renal replacement therapy
• Organ transplant
• Intolerance to any fibrate
• Medical history that might limit the individual's ability to take study treatment for the duration of the study
• Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the trial or may influence the result of the trial, or the participant's ability to participate in the trial
• Participation in any other study or trial that excludes coenrolment or if the intervention being investigated in another trial has the potential to interact with fenofibrate therapy
• Not adherent to active run-in treatment

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal.

A study treatment mailing error, temporarily affecting 28 participants, occurred in late 2022 and was reported to the Medicines and Healthcare products Regulatory Agency (MHRA). More details are provided in *Appendix 1*.

Randomisation and masking

Participants were randomised by a web-based algorithm in a 1 : 1 ratio to receive fenofibrate or matching placebo. Randomisation was performed with the use of minimisation and included a 10% stochastic element. Categories of sex, age, type of diabetes, eGFR at randomisation, HbA1c, use of statin, most recent maculopathy grade and most recent retinopathy grade were used in the minimisation algorithm. Participants, site staff, trial staff, and NHS Scotland DES retinal imagers and graders were masked to the allocated treatment arm for the duration of the trial.

We did not assess whether or not participants were able to discern which arm they had been randomised to.

Linkage to NHS data sets

The Community Health Index number is a unique 10-character numeric identifier allocated to each NHS Scotland patient. This allowed linkage to national healthcare data sets including:

- *Diabetic Eye Screening*: retinal images and results from retinal screening
- *SCI Diabetes*: integrated electronic patient record used in general practice and hospitals to support treatment of diabetes, including biochemistry and retinal screening data
- *National Records of Scotland death registrations*
- *Prescribing Information System (PIS)*: data regarding medicines prescribed in the community
- *General Acute Inpatient and Day Case – Scottish Morbidity Record (SMR01)*: data regarding hospitalisations (for health economic analyses only)
- *Outpatient Appointments and Attendances – Scottish Morbidity Record (SMR00)*: data for outpatient hospital appointments (for health economic analyses only).

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Outcomes

The primary outcome of the LENS trial was time to the first occurrence of the composite of either developing referable diabetic retinopathy or maculopathy, or requiring treatment for diabetic retinopathy or maculopathy (namely intravitreal injection of medication, retinal laser therapy or vitrectomy) in either eye. Referable eye disease was defined according to NHS Scotland's DES Programme grading scheme (see *Table 1*) as any of: referable background (i.e. moderately severe or severe non-proliferative) diabetic retinopathy (R3 grade), or proliferative diabetic retinopathy (R4 grade), or referable maculopathy (i.e. blot haemorrhage or exudate within one disc diameter distance of the foveal centre) (M2 grade). Secondary outcomes included time to any progression of diabetic retinopathy or maculopathy; the development of referable maculopathy; the development of macular oedema [including both centre-involving and non-centre-involving macular oedema identified during slit lamp examination or optical coherence tomography (OCT)]; change in visual function [based on Visual Function Questionnaire-25 (VFQ-25) data], quality of life [based on EuroQol-5 Dimensions, five-level version (EQ-5D-5L) questionnaire data] and BCVA [based on the better seeing eye (BSE)]; components of the primary outcome (namely development of referable retinopathy or maculopathy; and treatment thereof), and the primary outcome in six pre-specified subgroups. An additional post hoc subgroup analysis based on statin use at baseline is also included in this report. Adverse event reports of eye procedures, vitreous haemorrhages and macular oedema were adjudicated by CCO doctors, masked to treatment allocation. Referable retinopathy or maculopathy was generally identified during DES screening but could also be identified via other routes, for example during reporting and adjudication of adverse events.

In versions 1.0–6.3 of the protocol (noting that the trial commenced recruitment with version 6.0 in place) and in earlier entries of the LENS trial in clinical trial registries (NCT03439345, ISRCTN15073006), the terms 'referable' and 'clinically significant' were used interchangeably to describe the development of a grading of diabetic retinopathy or maculopathy that would be counted as a primary outcome. During the trial, the Steering Committee recognised that this could prove confusing given that 'clinically significant' is a specific description used to categorise advanced macular oedema. Therefore, the wording in both the final protocol (version 7.0) and in the clinical trial registries was updated to use consistent terminology by only referring to progression of diabetic retinopathy or maculopathy to a grade consistent with a primary outcome as 'referable' disease (i.e. to avoid the term 'clinically significant'). There was no change to the components of the primary outcome before or during the conduct of the trial, that is, the update referred to above was only a clarification regarding the description of the primary outcome. The primary outcome therefore remained unchanged throughout the conduct of the trial.

Details of the pre-specified efficacy assessments are provided in *Appendix 2*. Further information regarding adjudication and the definitions of outcomes is provided in *Report Supplementary Material 1*.

Statistical analysis

NHS Scotland DES Programme data showed that progression from non-referable to referable eye disease in the potentially eligible population would occur in approximately 29% of individuals over 4 years. We calculated that a sample size of 1060 participants would provide 85% power to detect a 33% proportional reduction in the primary outcome (at two-sided $p < 0.05$), based on 222 participants experiencing a primary outcome event over 4 years, allowing for 15% dropout (e.g. no longer

attending retinal screening). The trial was designed to continue until two rules were met: (1) at least 222 primary outcome events had occurred; and (2) at least 4 years had elapsed after randomising the median participant.

For time-to-event analyses, Cox proportional hazards regression analyses, adjusted for baseline covariates used for minimised randomisation, were used to estimate the hazard ratios (HRs), 95% CIs and corresponding *p*-values, comparing participants allocated fenofibrate with those allocated placebo. The unit of analysis was the participant (i.e. data from either eye could contribute). The primary estimand was the rate of first occurrence of the primary outcome in the target population allocated fenofibrate relative to the rate of first occurrence of the primary outcome in the target population allocated placebo, conditional on the baseline covariates used in minimised randomisation, ignoring any non-fatal intercurrent events, and in the hypothetical absence of death from any cause. For continuous measures with baseline and repeated follow-up values, linear mixed-model for repeated-measures (MMRM) analyses were conducted to estimate the mean values by treatment allocation at each follow-up time point, as well as the trial-averaged difference in mean follow-up levels between the randomised treatment groups. The MMRM models adjusted for the baseline value of the relevant measure, as well as the baseline minimisation criteria, and they assumed an unstructured covariance matrix. Analyses compared outcomes from randomisation to the end of the scheduled treatment period among all participants allocated at randomisation to receive fenofibrate versus placebo (i.e. 'intention-to-treat' analyses). *p*-values are reported for the primary and secondary outcomes; however, multiple testing was not formally accounted for in these analyses. NDPH at the University of Oxford holds the full database. NDPH staff performed analyses (excluding health economic analyses) using SAS software, version 9.4 (SAS Institute, Cary, NC, USA) and the figures were constructed using R software, versions 4.3.2 and 4.3.3 (The R Foundation for Statistical Computing, Vienna, Austria). Versions of the statistical analysis plan (see *Report Supplementary Material 2*) were made available publicly from February 2023 via the ISRCTN registry and were published prior to unmasking of the trial results.[17]

Representativeness of LENS trial participants

To assess the representativeness of randomised LENS participants compared to potentially eligible people in Scotland, summary data were obtained from SCI Diabetes in August 2023.[17] This was achieved by SCI Diabetes repeating the same recruitment search as was originally used to invite potentially eligible people living in participating health boards (based on age ≥ 18 years, non-referable retinopathy and eGFR ≥ 40). Representativeness was evaluated by visual inspection of data and not by formal statistical comparison (given the overlap between LENS trial participants and those categorised as potentially eligible based on the SCI Diabetes search performed in August 2023).

Clinical results

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Trial participants

Seventeen thousand one hundred and twenty-nine individuals were invited to participate across mainland Scotland. Of them, 3981 (23.2%) responded positively and were pre-screened with 2348 excluded before screening. Of 1633 participants who were screened, 1484 entered the active pre-randomisation run-in and commenced open label fenofibrate (*Figure 1*).

The latter part of recruitment was impacted upon by the COVID-19 pandemic when sites closed temporarily to face-to-face screening and randomisation assessments. Information regarding serious adverse events during the active run-in is provided in *Appendix 3*, *Table 17*. One participant on concomitant simvastatin therapy developed rhabdomyolysis during the active run-in and was not randomised. From September 2018 to July 2021, 1151 participants were randomised. *Figure 2* shows the cumulative numbers entering the run-in and being randomised over time.

Recruitment by health board is provided in *Appendix 3*, *Table 18*. Important prognostic characteristics were well balanced between the two arms (*Table 3*).

The mean age of participants was 61 years, 73% were men, 26% had type 1 diabetes, mean duration of diabetes was 18 years and mean HbA1c was 66 mmol/mol. The substantial majority (96%) had bilateral mild background retinopathy, and 10% had observable maculopathy in at least one eye.[17] Due to the effect of fenofibrate, the proportion with eGFR < 60 ml/minute/1.73 m^2 increased from 9% at the screening assessment to 23% at the randomisation assessment, as expected.

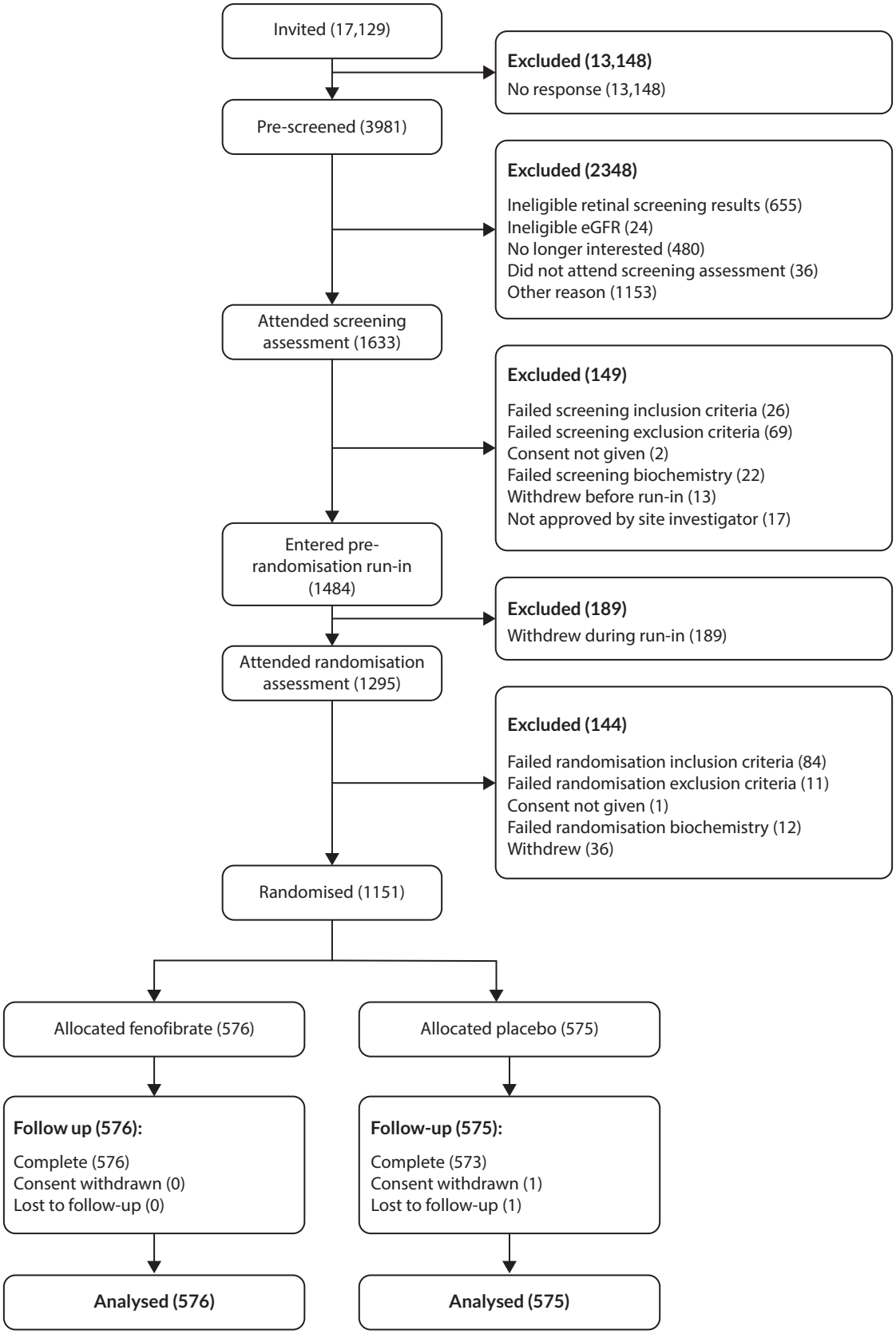

FIGURE 1 LENS trial Consolidated Standards of Reporting Trials diagram. This figure has been reproduced with permission from Preiss *et al.*[16] Copyright © 2024 Massachusetts Medical Society.

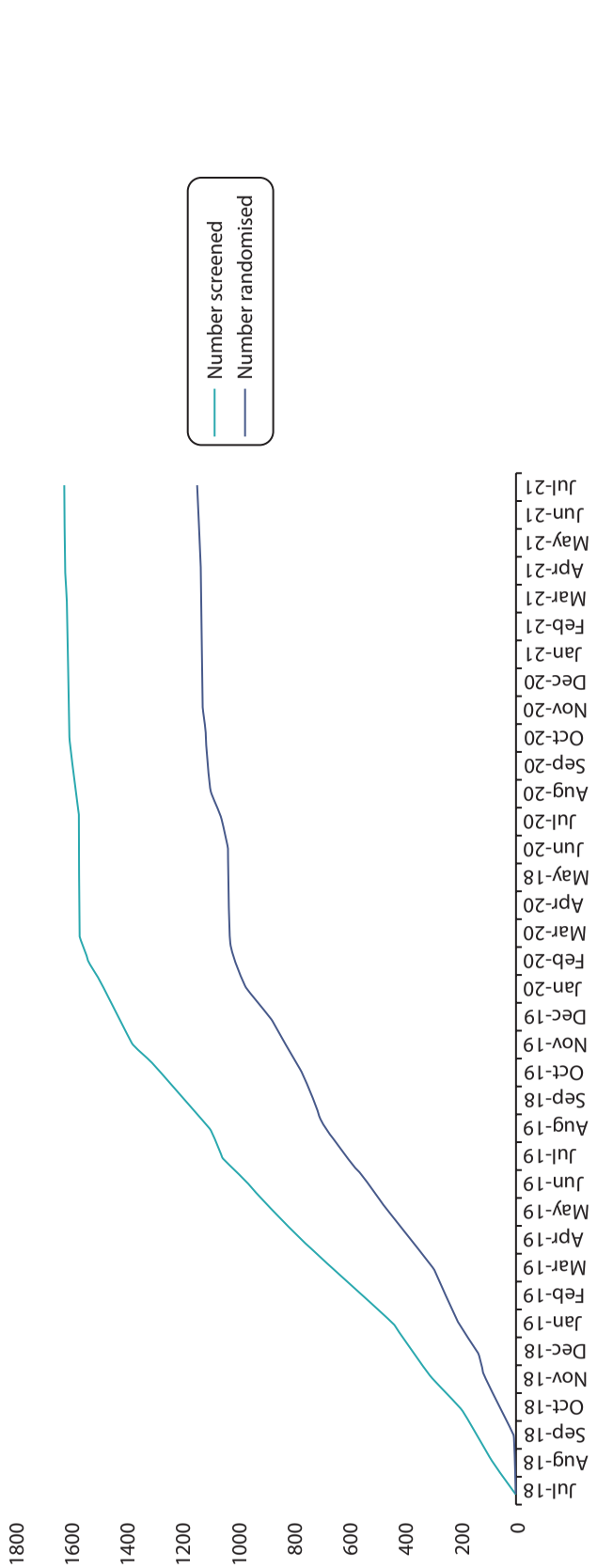

FIGURE 2 Cumulative recruitment by month.

TABLE 3 Characteristics of LENS participants

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)
Demographics		
Age at randomisation (years)	60.8 (12.4)	60.6 (12.3)
Sex		
Male	420 (73%)	419 (73%)
Female	156 (27%)	156 (27%)
Ethnicity[a]		
White	567 (98%)	558 (97%)
Other	9 (2%)	17 (3%)
Prior disease		
Type of diabetes mellitus		
Type 1	154 (27%)	151 (26%)
Type 2	421 (73%)	423 (74%)
Other	1 (0%)	1 (0%)
Duration of diabetes (years)	18.3 (10.5)	17.7 (10.0)
Retinopathy grading (worse eye)[b]		
No retinopathy (R0)	5 (1%)	4 (1%)
Mild background retinopathy (R1)	562 (98%)	564 (98%)
Observable background retinopathy (R2)	9 (2%)	7 (1%)
Maculopathy grading (worse eye)[b]		
No maculopathy (M0)	517 (90%)	515 (90%)
Observable diabetic maculopathy (M1)	59 (10%)	60 (10%)
Retinopathy[b]		
R0 R0	5 (1%)	4 (1%)
R1 R0	12 (2%)	8 (1%)
R1 R1	550 (95%)	556 (97%)
R2 R0	0 (0%)	1 (0%)
R2 R1	5 (1%)	5 (1%)
R2 R2	4 (1%)	1 (0%)
Maculopathy[b]		
M0 M0	517 (90%)	515 (90%)
M1 M0	49 (9%)	51 (9%)
M1 M1	10 (2%)	9 (2%)
Retinal laser treatment or intravitreal injections	52 (9%)	57 (10%)
Vitrectomy	6 (1%)	8 (1%)

continued

TABLE 3 Characteristics of LENS participants (*continued*)

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)
Retinal laser treatment or intravitreal injections or vitrectomy	53 (9%)	59 (10%)
Myocardial infarction	46 (8%)	46 (8%)
Coronary artery bypass surgery or coronary stent	53 (9%)	46 (8%)
Stroke or TIA	47 (8%)	43 (7%)
Non-coronary arterial revascularisation	7 (1%)	12 (2%)
Cardiovascular disease[c]	103 (18%)	96 (17%)
Lower limb skin ulceration	20 (3%)	20 (3%)
Non-traumatic lower limb amputation	4 (1%)	8 (1%)
Clinical measurements		
Body mass index (kg/m^2)[d,e]	30.9 (6.4)	30.7 (6.0)
Blood pressure (mmHg)[d,e]		
Systolic	136.7 (17.2)	136.4 (17.9)
Diastolic	75.4 (9.4)	75.5 (9.3)
Laboratory measurements		
HbA1c (mmol/mol)[e,f]	66 (16)	66 (16)
HbA1c (%)[e,f]	8.2 (1.5)	8.2 (1.5)
Creatinine (µmol/l)		
Screening[f]	78.0 (18.7)	77.8 (18.2)
Randomisation[d]	89.7 (22.8)	88.6 (21.9)
eGFR at screening (ml/minute/1.73 m^2)[f]		
< 60	58 (10%)	40 (7%)
≥ 60	518 (90%)	535 (93%)
eGFR at randomisation (ml/minute/1.73 m^2)[d]		
< 60	130 (23%)	131 (23%)
≥ 60	446 (77%)	444 (77%)
Total cholesterol (mmol/l)[e,f]	4.0 (0.9)	4.1 (1.0)
HDL cholesterol (mmol/l)[e,f]	1.3 (0.4)	1.3 (0.4)
Triglycerides (mmol/l)[e,f]	1.5 (1.0–2.3)	1.6 (1.1–2.2)
Use of concomitant medications		
Non-insulin glucose-lowering therapy	396 (69%)	389 (68%)
Insulin	256 (44%)	249 (43%)
Statin	425 (74%)	429 (75%)
RAAS blockade	345 (60%)	341 (59%)

TABLE 3 Characteristics of LENS participants (*continued*)

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)
Other history		
Smoking		
Never smoked	291 (51%)	289 (50%)
Previous smoker	224 (39%)	218 (38%)
Current smoker	61 (11%)	68 (12%)

RAAS, renin–angiotensin–aldosterone system; TIA, transient ischaemic attack.
a Ethnicity was reported by participants.
b Retinopathy and maculopathy gradings were recorded from the SCI Diabetes system up to randomisation; worse eye retinopathy was defined as R2 > R1 > R0; worse eye maculopathy defined as M1 > M0.
c Cardiovascular disease is defined as previous myocardial infarction, coronary revascularisation, non-coronary revascularisation, stroke or transient ischaemic attack.
d Based on measurements at the randomisation assessment.
e Missing data: blood pressure 70 participants, body mass index 35 participants, HbA1c 74 participants, total cholesterol 12 participants, HDL cholesterol 23 participants, triglycerides 17 participants.
f Based on blood tests at the screening assessment.

Note
Plus–minus values are means ± standard deviation; triglycerides are shown as median (interquartile range). Percentages may not total 100 because of rounding.

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Final follow-up assessments were conducted from July to September 2023 when the criteria for ending the trial were met. At the end of the scheduled treatment period, complete data were available for 1149 randomised participants (99.8%) (*Table 4*).

Median follow-up until the end of the scheduled treatment period was 4.0 (interquartile range 3.6–4.3) years. Additional information regarding mean duration of follow-up is provided in *Appendix 3*, *Table 19*. The frequency of retinal screening was similar in both groups after randomisation (*Table 5*).

Further details about retinal screening during the trial, including information about retinal image quality and the use of mydriasis, are provided in *Appendix 3*, *Table 20*. Ninety-five per cent of retinal images met the highest available level of image quality.

Adherence to study treatment

Average self-reported adherence to the assigned study treatment regimen was very similar between the arms (88% for fenofibrate and 89% for placebo) (*Table 6*).

As expected, more participants assigned daily treatment with fenofibrate transitioned to alternate day treatment than placebo due to the effect of fenofibrate on eGFR (driven by the requirement in the protocol to reduce dose frequency). There were no significant differences in the number of participants who discontinued fenofibrate compared with placebo overall or for any specific reason (see *Appendix 3*, *Table 21*).

Effects on the primary outcome and secondary outcomes

The primary outcome occurred in significantly fewer participants in the fenofibrate group than in the placebo group [131 (22.7%) vs. 168 (29.2%); HR 0.73, 95% CI 0.58 to 0.91; $p = 0.006$] (*Figure 3*, *Table 7*) during the scheduled treatment period, representing an absolute reduction of 6.5% (95% CI 1.4% to 11.5%) over a median of 4.0 years of follow-up.

There was no evidence of differential proportional effects within pre-specified subgroup categories, including type 1 versus type 2 and other types of diabetes, normal versus

TABLE 4 Completeness of follow-up

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)	Total (*N* = 1151)
Complete follow-up information	576 (100.0%)	573 (99.7%)	1149 (99.8%)
Final follow-up assessment with participant	504 (87.5%)	502 (87.3%)	1006 (87.4%)
Final follow-up assessment by medical records/general practice	37 (6.4%)	33 (5.7%)	70 (6.1%)
Death before end of final follow-up period	35 (6.1%)	38 (6.6%)	73 (6.3%)
Registry data confirming vital status during final follow-up period	0 (0.0%)	0 (0.0%)	0 (0.0%)
Incomplete follow-up information	0 (0.0%)	2 (0.3%)	2 (0.2%)
Full withdrawal of consent	0 (0.0%)	1 (0.2%)	1 (0.1%)
No final follow-up assessment (loss to follow-up)	0 (0.0%)	1 (0.2%)	1 (0.1%)

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TABLE 5 Retinal screening episodes after randomisation

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)
Retinal screening episodes		
Count	1485	1469
Average per participant (SE)	2.58 (0.04)	2.55 (0.04)

SE, standard error.

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impaired renal function, and statin use or non-use (*Figure 4*, see *Appendix 3*, *Table 22*).

Results for the two components of the primary outcome were consistent with the overall result (*Figure 5*, see *Table 7*), with referable retinopathy or maculopathy developing in 130 (22.6%) participants allocated fenofibrate and 168 (29.2%) participants allocated placebo (HR 0.72, 95% CI 0.57 to 0.91; $p = 0.005$), and with treatment for retinopathy or maculopathy occurring in 17 (3.0%) participants allocated fenofibrate and 28 (4.9%) participants allocated placebo (HR 0.58, 95% CI 0.31 to 1.06; $p = 0.08$). A more detailed breakdown of the primary outcome, including numbers of participants receiving treatment with laser, intravitreal injection and vitrectomy, respectively, is provided in *Appendix 3*, *Table 23*.

Any retinopathy or maculopathy progression was lower in the fenofibrate group [185 participants (32.1%)] than the placebo group [231 participants (40.2%)] (HR 0.74, 95% CI 0.61 to 0.90; $p = 0.003$). A similar proportional reduction was observed for referable maculopathy, affecting 107 (18.6%) participants allocated fenofibrate and 149 (25.9%) participants allocated placebo (HR 0.66, 95% CI 0.52 to 0.85; $p = 0.001$) (see *Figure 5*, *Table 7*). Macular oedema was also reduced, occurring in 22 (3.8%) participants in the fenofibrate group and 43 (7.5%) in the placebo group (HR 0.50, 95% CI 0.30 to 0.84; $p = 0.008$) (see *Figure 5*, *Table 7*).

TABLE 6 Adherence to randomised study treatment

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)	Total (*N* = 1151)
Full study			
All regimens			
Randomisation	576/576 (100%)	575/575 (100%)	1151/1151 (100%)
Trial mid-point	495/560 (88%)	500/561 (89%)	995/1121 (89%)
End of study	421/541 (78%)	427/535 (80%)	848/1076 (79%)
Trial average	88%	89%	89%
Daily			
Randomisation	447/447 (100%)	448/448 (100%)	895/895 (100%)
Trial mid-point	344/379 (91%)	374/421 (89%)	718/800 (90%)
End of study	268/329 (81%)	322/392 (82%)	590/721 (82%)
Trial average	90%	89%	90%
Alternate days			
Randomisation	129/129 (100%)	127/127 (100%)	256/256 (100%)
Trial mid-point	151/181 (83%)	126/140 (90%)	277/321 (86%)
End of study	153/212 (72%)	105/143 (73%)	258/355 (73%)
Trial average	83%	88%	85%
Censored at primary outcome			
All regimens			
Randomisation	576/576 (100%)	575/575 (100%)	1151/1151 (100%)
Trial mid-point	443/498 (89%)	428/475 (90%)	871/973 (90%)
End of study	325/412 (79%)	303/372 (81%)	628/784 (80%)
Trial-average	89%	90%	90%
Daily			
Randomisation	447/447 (100%)	448/448 (100%)	895/895 (100%)
Trial mid-point	302/331 (91%)	316/350 (90%)	618/681 (91%)
End of study	198/237 (84%)	227/270 (84%)	425/507 (84%)
Trial-average	91%	91%	91%
Alternate days			
Randomisation	129/129 (100%)	127/127 (100%)	256/256 (100%)
Trial mid-point	141/167 (84%)	112/125 (90%)	253/292 (87%)
End of study	127/175 (73%)	76/102 (75%)	203/277 (73%)
Trial-average	84%	89%	86%

Note
Trial-averaged adherence was calculated by defining each day from randomisation to censoring for each participant as compliant or not compliant, then by dividing the sum of all compliant days by all days of follow-up.

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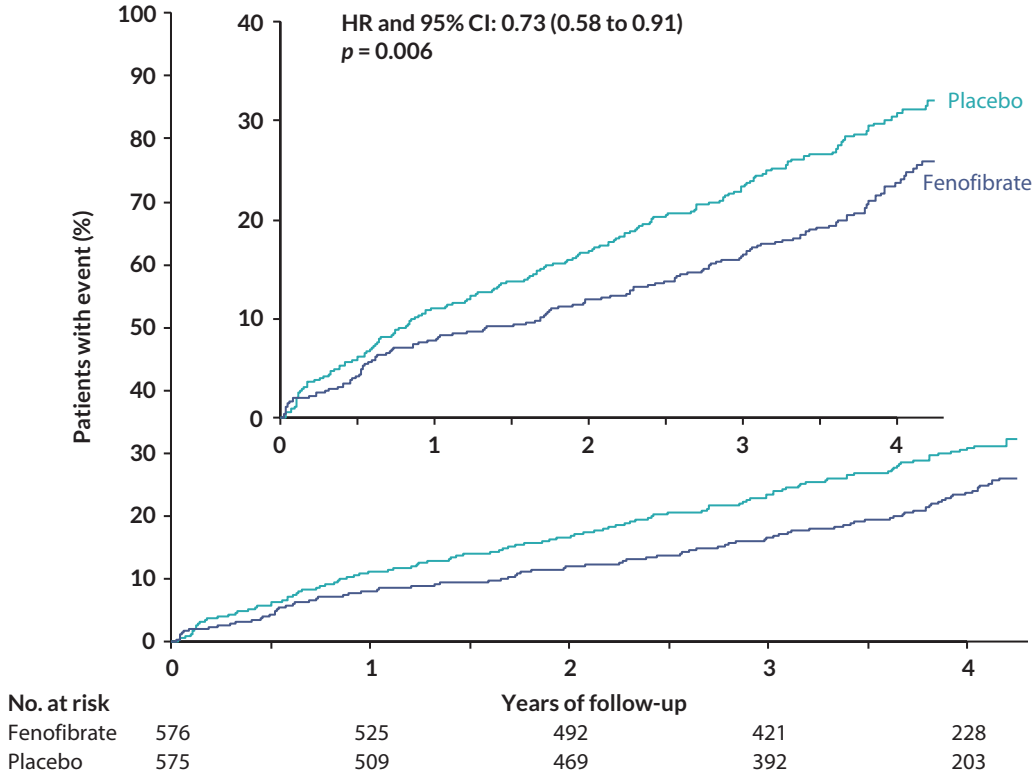

FIGURE 3 Effect of fenofibrate compared to placebo on referable diabetic retinopathy or treatment of diabetic retinopathy. The figure shows results of the primary composite outcome of referable diabetic retinopathy or maculopathy, or treatment thereof, with intravitreal injection of medication, retinal laser therapy or vitrectomy. This figure has been reproduced with permission from Preiss *et al.*[16] Copyright © 2024 Massachusetts Medical Society.

TABLE 7 Effect of fenofibrate compared to placebo on primary outcome and secondary retinopathy outcomes

	Fenofibrate (*N* = 576)		Placebo (*N* = 575)			
	N (%)	Events per 100 person-years	*N* (%)	Events per 100 person-years	HR (95% CI)	*p*
Primary composite outcome and its components						
Referable retinopathy or maculopathy	130 (22.6%)	6.6	168 (29.2%)	9.1	0.72 (0.57 to 0.91)	0.005
Treatment for diabetic retinopathy: intravitreal injection, laser photocoagulation or vitrectomy	17 (3.0%)	0.8	28 (4.9%)	1.3	0.58 (0.31 to 1.06)	0.08
Primary composite outcome: referable diabetic retinopathy or treatment for diabetic retinopathy	131 (22.7%)	6.7	168 (29.2%)	9.1	0.73 (0.58 to 0.91)	0.006
Secondary outcomes						
Progression of diabetic retinopathy	185 (32.1%)	10.2	231 (40.2%)	13.4	0.74 (0.61 to 0.90)	0.003
Referable maculopathy	107 (18.6%)	5.3	149 (25.9%)	7.9	0.66 (0.52 to 0.85)	0.001
Macular oedema	22 (3.8%)	1.0	43 (7.5%)	2.0	0.50 (0.30 to 0.84)	0.008

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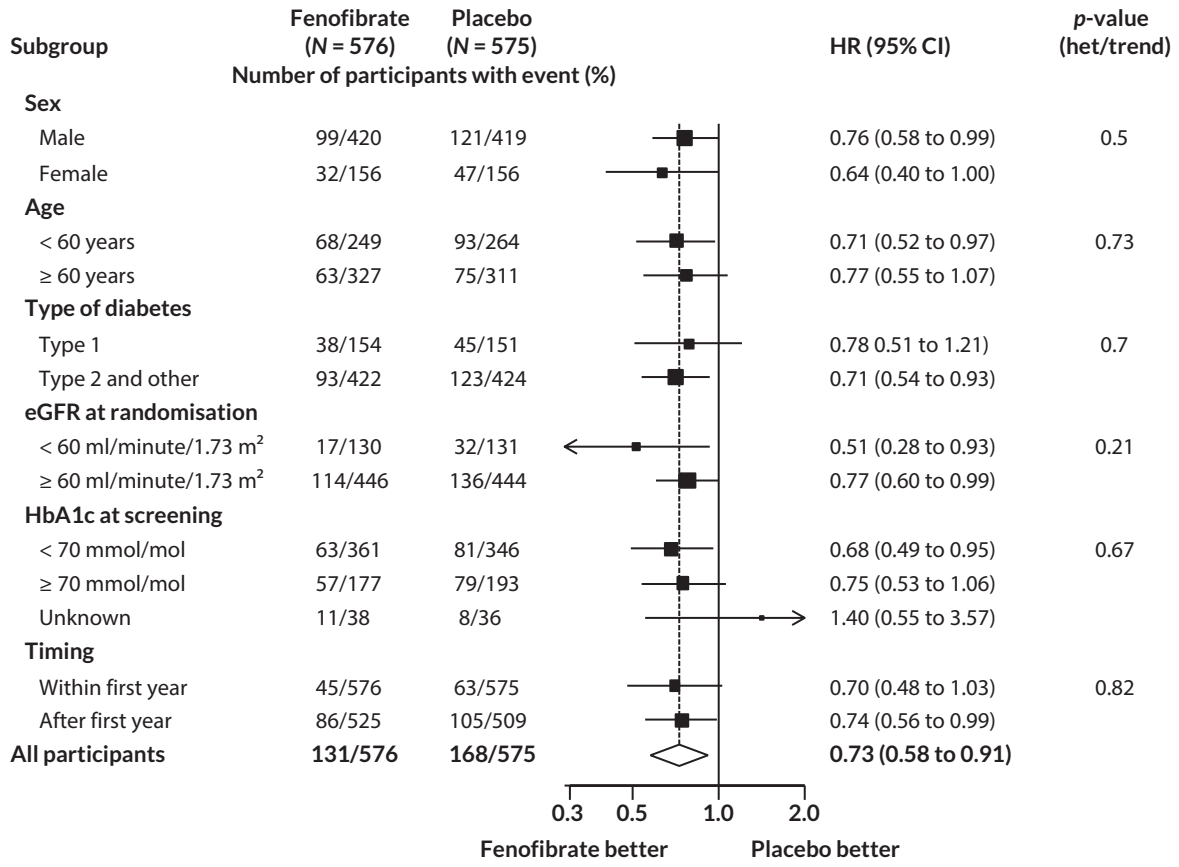

FIGURE 4 Effect of fenofibrate compared to placebo on the primary outcome by pre-specified subgroups. The figure shows the HRs for the primary outcome in pre-specified subgroups defined according to baseline characteristics. The area of each box is proportional to the inverse of the variance of the log HRs. The diamond represents the result of the primary analysis (the width of the diamond indicates the 95% CIs). The dashed line indicates the HR in the overall population. het, heterogeneity. This figure has been reproduced with permission from Preiss *et al.*[16] Copyright © 2024 Massachusetts Medical Society.

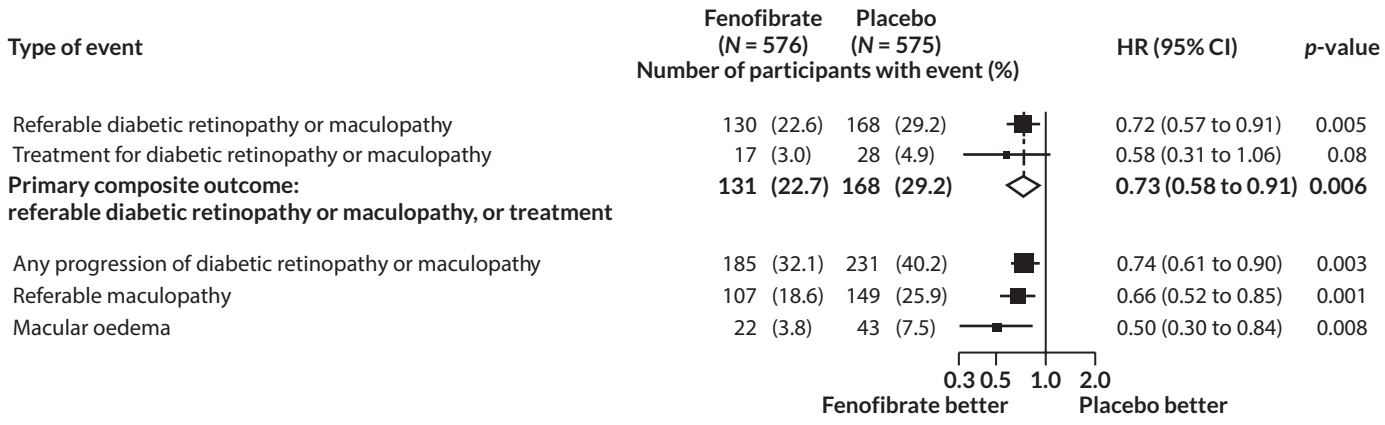

FIGURE 5 Effect of fenofibrate compared to placebo on primary and secondary retinopathy outcomes. A single participant may have had multiple events and may contribute information to more than one row. The area of each box is proportional to the inverse of the variance of the log HRs. The diamond represents the result of the primary analysis (the width of the diamond indicates the 95% CIs). The dashed vertical line indicates the HR for the primary outcome. Parts of this figure have been reproduced with permission from Preiss *et al.*[16] Copyright © 2024 Massachusetts Medical Society.

There was no significant effect of allocation to fenofibrate compared to placebo on visual function, quality of life or BCVA (*Table 8*).

The sensitivity analysis for BCVA, based on the worse seeing eye (WSE), also demonstrated no effect (see *Appendix 3*, *Table 24*).

Effects on other efficacy, biochemical and safety outcomes

There was no significant difference in the occurrence of major cardiovascular events or non-traumatic lower limb amputation in the fenofibrate group compared to the placebo group (*Table 9*), and no significant effect on UACR (*Table 10*).

TABLE 8 Effect of fenofibrate compared to placebo on secondary outcomes of visual acuity, visual function and quality of life

	Number		Baseline-adjusted mean (SE)			
	Fenofibrate	Placebo	Fenofibrate	Placebo	Difference between groups (95% CI)	*p*
Visual acuity						
Baseline	548	552	0.04 (0.01)	0.03 (0.01)		
Year 1	394	367	0.04 (0.00)	0.04 (0.00)		
Year 2	233	256	0.06 (0.01)	0.05 (0.01)		
Year 3	365	354	0.05 (0.00)	0.05 (0.01)		
Year 4	376	362	0.07 (0.01)	0.06 (0.01)		
Year 5	169	159	0.07 (0.01)	0.08 (0.01)		
Average of post-randomisation results	555	557	0.06 (0.00)	0.05 (0.00)	0.00 (−0.01 to 0.01)	0.36
VFQ-25 composite score						
Baseline	576	575	91 (0)	92 (0)		
Year 2	455	465	90 (0)	90 (0)		
End of trial	432	434	89 (0)	89 (0)		
Average of post-randomisation results	491	498	90 (0)	89 (0)	0 (−1 to 1)	0.58
EQ-5D-5L index score						
Baseline	573	569	0.81 (0.01)	0.81 (0.01)		
Year 2	450	458	0.76 (0.01)	0.76 (0.01)		
End of trial	429	425	0.74 (0.01)	0.74 (0.01)		
Average of post-randomisation results	490	495	0.75 (0.01)	0.75 (0.01)	0.00 (−0.02 to 0.02)	0.93
EQ-5D-5L visual analogue scale						
Baseline	576	574	81 (1)	81 (1)		
Year 2	453	462	76 (1)	76 (1)		
End of trial	431	431	74 (1)	76 (1)		
Average of post-randomisation results	491	495	75 (1)	76 (1)	−1 (−2 to 1)	0.43

SE, standard error.

Note
Analyses of visual acuity are based on BCVA.

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TABLE 9 Effect of fenofibrate compared to placebo on tertiary outcomes

	Fenofibrate (*N* = 576)		Placebo (*N* = 575)			
	N (%)	Events per 100 person-years	*N* (%)	Events per 100 person-years	HR (95% CI)	*p*
Major cardiovascular events[a]	45 (7.8%)	2.1	43 (7.5%)	2.0	1.05 (0.69 to 1.60)	0.81
Non-traumatic lower limb amputation[b]	4 (0.7%)	0.2	11 (1.9%)	0.5	0.35 (0.11 to 1.12)	0.08

a Composite of any major cardiovascular event (myocardial infarction, stroke, coronary or peripheral revascularisation).
b Composite of any non-traumatic lower limb amputation [minor amputation (distal to the ankle) or major amputation (through or proximal to the ankle)].

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TABLE 10 Effect of fenofibrate compared to placebo on renal function, lipids and UACR

	Number		Baseline-adjusted mean (SE)		Difference between groups (95% CI)	*p*
	Fenofibrate	Placebo	Fenofibrate	Placebo		
eGFR – mL/minute/1.73 m²						
Baseline	576	575	86.9 (0.8)	87.2 (0.8)		
Year 1	460	463	75.3 (0.4)	83.8 (0.4)		
Year 2	460	458	74.1 (0.4)	82.9 (0.4)		
Year 3	475	473	73.6 (0.5)	81.2 (0.5)		
Year 4	421	416	73.5 (0.5)	81.2 (0.5)		
Year 5	151	155	73.1 (0.8)	80.1 (0.8)		
Average of post-randomisation results	569	572	73.9 (0.4)	81.9 (0.4)	−7.9 (−9.1 to −6.8)	< 0.001
Total cholesterol – mmol/l						
Baseline	572	567	4.04 (0.04)	4.05 (0.04)		
Year 1	397	398	3.90 (0.03)	4.06 (0.03)		
Year 2	386	383	3.91 (0.03)	4.09 (0.03)		
Year 3	400	407	3.93 (0.03)	4.08 (0.03)		
Year 4	344	348	4.00 (0.04)	4.02 (0.04)		
Year 5	97	96	3.95 (0.06)	3.99 (0.06)		
Average of post-randomisation results	565	561	3.94 (0.03)	4.05 (0.03)	−0.11 (−0.18 to −0.04)	0.003
Non-HDL cholesterol – mmol/l						
Baseline	568	560	2.74 (0.04)	2.75 (0.04)		
Year 1	365	362	2.62 (0.03)	2.78 (0.03)		
Year 2	362	353	2.65 (0.03)	2.80 (0.03)		

continued

TABLE 10 Effect of fenofibrate compared to placebo on renal function, lipids and UACR (*continued*)

	Number		Baseline-adjusted mean (SE)		Difference between groups (95% CI)	*p*
	Fenofibrate	Placebo	Fenofibrate	Placebo		
Year 3	370	374	2.67 (0.03)	2.80 (0.03)		
Year 4	319	314	2.73 (0.04)	2.71 (0.04)		
Year 5	91	90	2.68 (0.06)	2.66 (0.06)		
Average of post-randomisation results	539	532	2.67 (0.03)	2.75 (0.03)	−0.08 (−0.15 to −0.00)	0.04
HDL cholesterol – mmol/l						
Baseline	568	560	1.31 (0.02)	1.30 (0.02)		
Year 1	366	362	1.27 (0.01)	1.28 (0.01)		
Year 2	362	353	1.26 (0.01)	1.28 (0.01)		
Year 3	370	375	1.25 (0.01)	1.27 (0.01)		
Year 4	319	314	1.26 (0.01)	1.29 (0.01)		
Year 5	91	90	1.25 (0.02)	1.32 (0.02)		
Average of post-randomisation results	539	532	1.26 (0.01)	1.29 (0.01)	−0.03 (−0.05 to −0.01)	0.004
Triglycerides – mmol/l						
Baseline	571	563	1.58 (0.04)	1.54 (0.04)		
Year 1	290	276	1.28 (0.03)	1.53 (0.03)		
Year 2	282	263	1.30 (0.03)	1.50 (0.03)		
Year 3	283	288	1.33 (0.03)	1.56 (0.03)		
Year 4	236	225	1.32 (0.03)	1.53 (0.04)		
Year 5	58	57	1.43 (0.08)	1.61 (0.09)		
Average of post-randomisation results	449	430	1.33 (0.02)	1.54 (0.03)	−13.7% (−18.1% to −9.1%)	< 0.001
***HbA1c* – mmol/mol**						
Baseline	538	539	66.4 (0.7)	66.3 (0.7)		
Year 1	467	480	66.0 (0.5)	66.9 (0.5)		
Year 2	451	450	66.9 (0.6)	67.6 (0.6)		
Year 3	465	468	66.3 (0.6)	66.7 (0.6)		
Year 4	412	413	67.0 (0.7)	66.9 (0.7)		
Year 5	142	148	67.1 (1.1)	66.1 (1.1)		
Average of post-randomisation results	568	569	66.7 (0.5)	66.8 (0.5)	−0.2 (−1.5 to 1.2)	0.82
***HbA1c* – %**						
Baseline	538	539	8.22 (0.06)	8.22 (0.06)		
Year 1	467	480	8.19 (0.04)	8.27 (0.04)		
Year 2	451	450	8.27 (0.05)	8.33 (0.05)		
Year 3	465	468	8.22 (0.06)	8.26 (0.05)		

TABLE 10 Effect of fenofibrate compared to placebo on renal function, lipids and UACR (*continued*)

	Number		Baseline-adjusted mean (SE)		Difference between groups (95% CI)	*p*
	Fenofibrate	Placebo	Fenofibrate	Placebo		
Year 4	412	413	8.29 (0.06)	8.27 (0.06)		
Year 5	142	148	8.29 (0.11)	8.20 (0.10)		
Average of post-randomisation results	568	569	8.25 (0.04)	8.27 (0.04)	−0.01 (−0.13 to 0.11)	0.82
UACR – mg/g						
Baseline	312	310	14.4 (1.2)	16.6 (1.4)		
Year 1	289	267	11.7 (0.7)	12.8 (0.8)		
Year 2	261	236	12.0 (0.9)	15.2 (1.2)		
Year 3	270	282	13.7 (1.0)	16.9 (1.3)		
Year 4	243	237	14.4 (1.2)	17.7 (1.5)		
Year 5	66	74	16.9 (2.2)	15.5 (2.2)		
Average of post-randomisation results	462	474	13.6 (0.8)	15.5 (0.9)	−12.4% (−25.8% to 3.5%)	0.12

SE, standard error.

Notes
Values are arithmetic means (SE) for eGFR, total cholesterol, non-HDL cholesterol, HDL cholesterol and HbA1c; geometric means (approximate SE) for triglycerides and urine albumin to creatinine ratio. For triglycerides and the urine albumin to creatinine ratio, the difference reflects a percentage difference.
Post-randomisation results were calculated from NHS primary care and outpatient clinic data.

Source
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Estimated glomerular filtration rate was 7.9 ml/minute/1.73 m^2 lower in the fenofibrate group than the placebo group on average, with similar results during each year of follow-up (*Figure 6*, see *Table 10*).

Total cholesterol, non-HDL cholesterol and triglycerides were lower in participants allocated fenofibrate compared to placebo, but differences were small in absolute terms (see *Table 10*). The effect of fenofibrate was also explored according to baseline renal function (see *Appendix 3*, *Tables 25* and *26*). The trial-averaged change in eGFR on fenofibrate versus placebo was similar in participants with baseline eGFR ≥ 60 ml/minute/1.73 m^2 (−8.5 ml/minute/1.73 m^2) and < 60 ml/minute/1.73 m^2 (−6.5 ml/minute/1.73 m^2). Reductions in total cholesterol, non-HDL cholesterol and triglycerides were observed in participants with baseline eGFR ≥ 60 ml/minute/1.73 m^2 but not in participants with eGFR < 60 ml/minute/1.73 m^2.

Overall, 35 (6.1%) participants allocated fenofibrate and 38 (6.6%) participants allocated placebo died (see *Appendix 3*, *Table 27*). Rates of fatal and non-fatal serious adverse events (combined), grouped according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class, were similar between treatment groups (*Table 11*) and there were no cases of myopathy or rhabdomyolysis in randomised participants.

There were small numbers of cases of macular oedema and intravitreal injection not related to diabetic eye disease (see *Appendix 3*, *Table 28*).

Insulin use in participants with type 1 diabetes

We observed that, of the 305 participants reported to have type 1 diabetes, 27 were not recorded as using insulin at baseline based on data entered into case report forms by study staff. For 25 of the 27, NHS

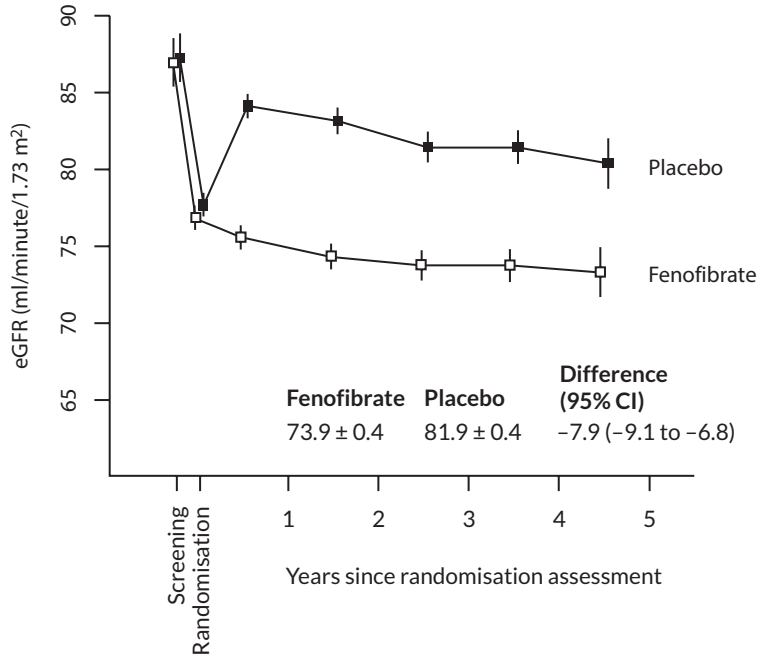

FIGURE 6 Effect of fenofibrate compared to placebo on renal function. The figure shows mean eGFR at the screening assessment, the randomisation assessment and in 1-year windows after randomisation by treatment allocation (using results from primary care and NHS outpatient clinics). Linear MMRM analyses were used to estimate the mean eGFR by treatment group at each follow-up time point, as well as a trial-averaged difference in mean follow-up levels, between fenofibrate and placebo. The models adjusted for baseline (screening) eGFR and the randomisation minimisation criteria, and assumed an unstructured covariance matrix. Vertical lines indicate the 95% CIs for the estimated means. The co-ordinates of the boxes are shifted slightly on the *x*-axis to avoid overlap. This figure has been reproduced with permission from Preiss *et al.*[16] Copyright © 2024 Massachusetts Medical Society.

TABLE 11 Serious adverse events grouped by MedDRA system organ class

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)		
	N (%)	*N* (%)	Relative risk (95% CI)	Absolute excess (SE)
Blood and lymphatic system disorders	5 (0.9%)	2 (0.3%)	2.64 (0.51 to 13.66)	0.52% (0.46%)
Cardiac disorders	37 (6.4%)	36 (6.3%)	1.04 (0.66 to 1.64)	0.16% (1.44%)
Congenital, familial and genetic disorders	0 (0.0%)	0 (0.0%)		
Ear and labyrinth disorders	0 (0.0%)	0 (0.0%)		
Endocrine disorders	1 (0.2%)	1 (0.2%)	1.79 (0.07 to 46.79)	0.00% (0.25%)
Eye disorders	6 (1.0%)			
Gastrointestinal disorders	21 (3.6%)	27 (4.7%)	0.78 (0.44 to 1.38)	−1.05% (1.18%)
General disorders and administration site conditions	12 (2.1%)	16 (2.8%)	0.75 (0.36 to 1.59)	−0.70% (0.91%)
Hepatobiliary disorders	6 (1.0%)	7 (1.2%)	0.86 (0.29 to 2.56)	−0.18% (0.62%)
Immune system disorders	0 (0.0%)	0 (0.0%)		
Infections and infestations	49 (8.5%)	50 (8.7%)	0.99 (0.67 to 1.47)	−0.19% (1.65%)
Injury, poisoning and procedural complications	23 (4.0%)	28 (4.9%)	0.84 (0.48 to 1.46)	−0.88% (1.21%)
Investigations	4 (0.7%)	3 (0.5%)	1.43 (0.32 to 6.47)	0.17% (0.46%)
Metabolism and nutrition disorders	16 (2.8%)	21 (3.7%)	0.75 (0.39 to 1.45)	−0.87% (1.04%)

TABLE 11 Serious adverse events grouped by MedDRA system organ class (*continued*)

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)		
	N (%)	*N* (%)	Relative risk (95% CI)	Absolute excess (SE)
Musculoskeletal and connective tissue disorders	11 (1.9%)	7 (1.2%)	1.59 (0.62 to 4.12)	0.69% (0.73%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	29 (5.0%)	23 (4.0%)	1.26 (0.73 to 2.18)	1.03% (1.22%)
Nervous system disorders	33 (5.7%)	27 (4.7%)	1.27 (0.76 to 2.12)	1.03% (1.31%)
Pregnancy, puerperium and perinatal conditions	0 (0.0%)	0 (0.0%)		
Psychiatric disorders	6 (1.0%)	5 (0.9%)	1.24 (0.37 to 4.18)	0.17% (0.57%)
Renal and urinary disorders	14 (2.4%)	10 (1.7%)	1.46 (0.64 to 3.31)	0.69% (0.84%)
Reproductive system and breast disorders	2 (0.3%)	1 (0.2%)	2.76 (0.22 to 34.07)	0.17% (0.30%)
Respiratory, thoracic and mediastinal disorders	19 (3.3%)	14 (2.4%)	1.34 (0.67 to 2.67)	0.86% (0.98%)
Skin and subcutaneous tissue disorders	3 (0.5%)	4 (0.7%)	0.74 (0.16 to 3.35)	−0.17% (0.46%)
Social circumstances	0 (0.0%)	0 (0.0%)		
Surgical and medical procedures	50 (8.7%)	52 (9.0%)	0.95 (0.64 to 1.40)	−0.36% (1.68%)
Vascular disorders	3 (0.5%)	4 (0.7%)	0.83 (0.18 to 3.71)	−0.17% (0.46%)
Product issues	0 (0.0%)	0 (0.0%)		
Subtotal: Any serious adverse event	**208 (36.1%)**	**204 (35.5%)**	**1.02 (0.84 to 1.24)**	**0.63% (2.83%)**

SE, standard error.

Note
Figures are number of participants (%).

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prescription records confirmed that they were routinely prescribed insulin around the time of randomisation. The remaining two participants (where prescription data were unavailable) were contacted by telephone and they also confirmed regular use of insulin at baseline. Therefore, all 305 participants recorded as having type 1 diabetes were taking insulin at baseline.

Representativeness of LENS trial participants

LENS participants were representative of patients across mainland Scotland who were potentially eligible to join the trial with respect to key risk factors for the progression of diabetic retinopathy (including age, type of diabetes, HbA1c, most recent retinal screening results and renal function) (*Table 12*). However, LENS participants included proportionally fewer women and fewer people of non-White ethnicity than observed in national data.

Cost-effectiveness analysis

Introduction

This chapter reports on the methods and results of the economic evaluation of fenofibrate versus standard care (placebo). This includes a within-trial cost-effectiveness analysis assessing the incremental cost per case of referable diabetic eye disease averted and a decision modelling exercise to extrapolate the longer-term incremental cost per quality-adjusted life-year (QALY) gained.

Methods

The evaluation adopted a Scottish health service perspective on costs (2022–3 prices) and a patient perspective on health benefits. Cost and benefits occurring beyond year 1 were discounted at a rate of 3.5%. Patient-level healthcare resource use data were

TABLE 12 Representativeness of LENS trial participants compared to potentially eligible people in Scotland

	Potentially eligible people[a]	LENS participants
N	31,118	1151
Age at randomisation (years)	60.5 (15.3)	60.7 (12.3)
Sex		
Male	18,958 (61%)	839 (73%)
Female	12,160 (39%)	312 (27%)
Ethnicity[b]		
White	24,001 (91%)	1125 (98%)
Other	2475 (9%)	26 (2%)
Type of diabetes mellitus[c]		
Type 1	8232 (27%)	305 (26%)
Type 2 or other	22,886 (74%)	846 (74%)
Retinopathy grading (worse eye)[d]		
No retinopathy (R0)	35 (0%)	9 (1%)
Mild background retinopathy (R1)	29,964 (96%)	1126 (98%)
Observable background retinopathy (R2)	1119 (4%)	16 (1%)
Maculopathy grading (worse eye)[d]		
No maculopathy (M0)	26,779 (86%)	1032 (90%)
Observable diabetic maculopathy (M1)	4339 (14%)	119 (10%)
HbA1c (mmol/mol)	68.0 (18.2)	66.4 (16.0)
eGFR (ml/minute/1.73 m^2)		
< 60	4019 (13%)	98 (9%)
≥ 60	27,099 (87%)	1053 (91%)
Scottish Index of Multiple Deprivation[e]	2.8 (1.4)	3.0 (1.4)

a Based on SCI Diabetes search for summary data regarding patients with (1) non-referable retinopathy at most recent retinal screening, and (2) eGFR ≥ 40 ml/minute/1.73 m^2 at most recent blood test.
b Ethnicity for potentially eligible individuals based on 26,476 (85% of total) with available information.
c Excludes gestational diabetes.
d Worse eye retinopathy defined as R2 > R1 > R0; worse eye maculopathy defined as M1 > M0.
e Based on quintiles of SIMD (calculated based on seven domains: income, employment, education, health, access to services, crime and housing) where a lower score represents greater social deprivation.

Note
Results are shown as *N* (%) or mean (standard deviation).

combined with published unit costs (see *Appendix 3*, *Table 29*) to determine total health service costs incurred over follow-up. Responses to the EQ-5D-5L at baseline, 2 years and the end of follow-up were used to estimate participant-level health state utility weights. The within-trial analysis focused on estimating differences in costs and clinical outcomes, with cost-effectiveness expressed in terms of the incremental cost per case of referable disease averted with fenofibrate versus placebo at 2 years post randomisation. The incremental cost per QALY gained was calculated using a decision analytic model. Model inputs were based on LENS trial data, supplemented with published literature.

The analysis followed the intention-to-treat principles and outcome definitions as described in the statistical analysis plan for the LENS trial (see *Report Supplementary Material 2*). A detailed health economics analysis plan was

agreed prior to unmasking of treatment allocation (see *Report Supplementary Material 1*).

Assessment of costs and outcomes

Data for the economic evaluation were collected via several sources: trial case report forms; routinely collected health records; trial-specific patient questionnaires; and the validated EQ-5D-5L.

Cost of trial intervention (fenofibrate)

Fenofibrate treatment, as recorded in the LENS trial database, was dispensed and costed on a 6-monthly basis. Since the formulation of fenofibrate used in the LENS trial (145 mg nanoparticle formulation) is not currently available in the UK NHS, the drug tariff price for the most frequently prescribed bioequivalent formulation (200 mg micronised capsules) was used.[25,26] Those with reduced renal function (eGFR 30–59 ml/minute/1.73 m^2) were assumed to require one 200 mg capsule every second day. The impact of applying the cost of a daily 67 mg dose for those with chronic kidney disease was assessed in sensitivity analysis.

Cost of treatment monitoring

Drug safety was monitored by review of routinely collected blood tests (linked from SCI-Diabetes) requested at the discretion of participants' general practitioners (GPs) or hospital doctors. Requested monitoring tests for creatinine, HbA1c, lipids and UACR were costed based on published unit costs of laboratory services in Scotland.[27] Five minutes of nurse time and 5 minutes of physician time, required to obtain samples and review results, were factored in for groups of tests by date of request.[28]

Cost of retinal screening and diabetic retinopathy-related interventions

Retinal screening episodes (including digital retinal photography, slit-lamp examination and OCT surveillance) were linked from NHS Scotland's DES Programme, and costed using previously published cost estimates, inflated to 2022–3 prices using the NHS Cost Inflation Index.[28–30]

Diabetic retinopathy-related referrals and interventions were captured using linked data on ophthalmology outpatient visits (from SMR00) and admissions (SMR01), combined with data on diabetic retinopathy-related interventions recorded in the study database. Ophthalmology hospital activity was costed using relevant Scottish Health Service costs by specialty and setting of care (outpatient, inpatient, day case).[27] English-specific NHS reference costs were tested in sensitivity analysis.[31] For anti-vascular endothelial growth factor (VEGF) injections, normally delivered as a course of treatment, it was necessary to assume that these would be administered at the frequency observed over 2 years in an observational NHS cohort study (6.3 treatments in year 1, and 2.9 treatments in year 2).[32] List prices for aflibercept treatment were applied in the base case.[25] Since this treatment is available to the NHS at an undisclosed discounted price, sensitivity analysis explored the impact of reduced prices.

Cost of other relevant secondary healthcare utilisation

Scottish health service costs were applied to all inpatient (SMR01) and outpatient hospital activity (SMR00) occurring post randomisation up to the final follow-up date for each participant (see *Appendix 4*).[27] Hospital activity was subdivided into a priori specified clinically relevant specialties (where activity could feasibly be affected by the study drug) and other specialties. Clinically relevant specialties included: General Medicine; Acute Medicine; Cardiology; Endocrinology and Diabetes; Diabetes; Renal Medicine; Vascular Surgery; Cardiac Surgery; and Ophthalmology. For the base case, we report the cost of all care episodes in clinically relevant specialties.

Cost of prescribed medication

Medicines prescribed in the community setting, related to the management of diabetes, lipids and blood pressure, were captured through participant record linkage to the PIS for Scotland. Prescribed medicines were costed using Drug Tariff prices or NHS indicative prices for proprietary medicines.[25] Further details are provided in *Appendix 4*.

Mortality

Deaths were recorded in the study database from reports to the CCO.

Health-related quality of life (quality-adjusted life-years)

The EQ-5D-5L was collected at baseline, approximately 24 months post randomisation, and study exit. In accordance with National Institute for Health and Care Excellence guidance,[33] health state utility values were derived by mapping individual EQ-5D-5L response data to the preferred EuroQol-5 Dimensions, three-level version (EQ-5D-3L) value set.[34] The mapping function developed by Hernández Alava *et al.* was used.[35] MMRM was used to estimate health state utility values for the decision analytic model, which was in turn used to estimate the incremental cost per QALY gained for fenofibrate versus standard care.

Within-trial analysis of costs and outcomes

Categories of resource use and cost were summarised by treatment allocation group, using means and standard deviations (SDs) as the most relevant summary statistic for informing expected costs at the population level. Total

costs were computed at the individual patient level and compared between treatment allocation groups following intention-to-treat principles.

The mean difference in cost by treatment group was estimated at 2 years post randomisation using a generalised linear model (GLM), adjusted for minimisation covariates. A user-written do file, which simultaneously runs four diagnostic tests, was used to select a preferred family (inverse Gaussian) and link function (Power −0.1) for the GLM (https://drhenryglick.com/identifying-better-links-and-families/).

Cost-effectiveness was expressed as the incremental cost per disease progression event averted at 2 years post randomisation. For this purpose, parametric survival analysis was used to estimate the probability of being progression free over 2 years of follow-up (assuming a Weibull distribution). Non-parametric bootstrapping was used to characterise the uncertainty surrounding the joint mean difference in cost and effect, with findings presented graphically on the cost-effectiveness plane and summarised using cost-effectiveness acceptability curves.

Missing data assumptions

With the reliance on population-based routine data sets for collecting resource use data, it was assumed that, where no data were recorded under a given category of resource use, zero costs had been incurred. An exception was made for the small number of cases where retinal treatment was recorded in the study database without accompanying outpatient or inpatient data being recorded in the routine data sets (it should be noted that retinal treatment given in the outpatient setting is not always captured in these routine data sets). In these cases, the expected cost of outpatient appointments or inpatient admissions was applied in line with assumptions about treatment course.

Accounting for censoring of cost data

We conducted a further cost comparison that made use of all the available data using interval methods to account for censoring.[36] The follow-up period was divided into 6-monthly intervals, and the costs incurred within each interval were calculated based on the data of all participants contributing to it (i.e. reaching that follow-up time). These data were treated as repeated measures of 6-monthly cost and analysed using generalised estimating equations (GEEs) to estimate the difference by treatment group and interval number. Within the GEE framework, a gamma family distribution with log link was chosen based on diagnostics carried out for a standard GLM model (equivalent to a GEE model with independent correlation structure). All statistical analyses were performed using STATA statistical software, version 16.1 (StataCorp, TX, USA).

Modelling of longer-term cost-effectiveness

A Markov microsimulation model was developed using TreeAge pro software (2024, version R2.1, TreeAge Software LLC) to assess the longer-term cost-effectiveness of fenofibrate. The model simulated the progression of observable diabetic retinopathy (bilateral R1 or unilateral/bilateral R2 or unilateral/bilateral M1) to referable retinopathy (R3, active R4 or M2 in at least one eye) or diabetic retinopathy-related intervention (retinal laser therapy, vitrectomy or intravitreal injection of medication due to diabetic retinopathy). Following progression to referable or treated diabetic retinopathy, monitoring and treatment costs and expected changes in visual acuity (VA) and health-related quality of life were modelled. The model takes a health service perspective on costs, and a patient perspective on health outcomes. Cost-effectiveness was assessed over a medium (5–10 year) to long-term (20–30 year) time horizon.

Population

Characteristics of the simulated individuals were randomly drawn from the baseline demographics and clinical characteristics of the LENS trial participants in terms of age group (< 30; ≥ 30 to < 50; ≥ 50 to < 70; ≥ 70 years), sex, type of diabetes (type 1, type 2, other), HbA1c category (< 64; ≥ 64 mmol/mol; unknown), eGFR category (< 60; ≥ 60 ml/minute/1.73 m^2), statin use, baseline maculopathy grade (none, observable) and baseline retinopathy grade (none, mild, observable).

Intervention and comparator

The modelled intervention was 200 mg (micronised) fenofibrate once daily for those with eGFR ≥ 60 ml/minute/1.73 m^2, and 200 mg (micronised) fenofibrate every second day for those with eGFR 30–59 ml/minute/1.73 m^2.[25,26] The proportion of prescriptions at once daily frequency was derived from the LENS trial data (= 6392/8875 = 0.72). Discontinuation from study drug for any reason was modelled as observed in the LENS trial and was assumed constant across health states (= 23.4% over a median follow-up of 4 years). Beyond 4 years, no further discontinuation was assumed, unless patients progressed to post-treatment for macular oedema and proliferative retinopathy, after which no further fenofibrate treatment benefits were modelled. The comparator for the model was standard care without fenofibrate. It was assumed that costs and outcomes observed in the placebo arm of the LENS trial are generalisable to standard care.

Model structure

The model used a Markov structure with 10 discrete health states reflecting the progression of diabetic retinopathy and its treatment: observable diabetic retinopathy (bilateral R1, R2 or M1); referable retinopathy (R3 or R4); treated diabetic retinopathy; referable maculopathy (M2); treated diabetic macular oedema; referable retinopathy with referable maculopathy; treated diabetic retinopathy with referable maculopathy; referable retinopathy with treated macular oedema; treated diabetic retinopathy and treated macular oedema; and death (*Figure 7*).

The model operates on a 6-monthly cycle, consistent with the shortest screening interval that people with a R2 grade received in the DES service in Scotland. Treatment for referable disease was modelled as observed in the trial in the 'treated diabetic retinopathy' and 'treated macular oedema' states. Following completion of expected treatment courses, patients remain in the treated states of the model incurring expected follow-up costs and changes in VA as informed by external literature. A microsimulation approach was used to enable tracking of treatment history and individual patient characteristics, which in turn inform expected costs and utility payoffs within health states.

Clinical efficacy inputs

Progression through the health states was modelled using a set of transition probabilities derived, where possible, from parametric survival analysis of the LENS trial time to event data.

Observable diabetic retinopathy to referable retinopathy or referable maculopathy

Transition probabilities from observable to referable retinopathy (R3/R4) and referable maculopathy/macular oedema were informed by parametric survival analysis of the observed time-to-event data. Proportionality of hazards between treatment allocation groups was assessed and accepted based on examination of log–log plots and Schoenfeld residual tests. Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to assess the fit of different proportional hazard models.[37]

Parametric curves were fitted to the cause-specific hazards of the component transitions, referable retinopathy (R3/R4 with or without referable maculopathy/macular oedema) and referable maculopathy/macular oedema alone, censoring for the competing risk.[38] Patients yet to experience an event by the end of study follow-up were

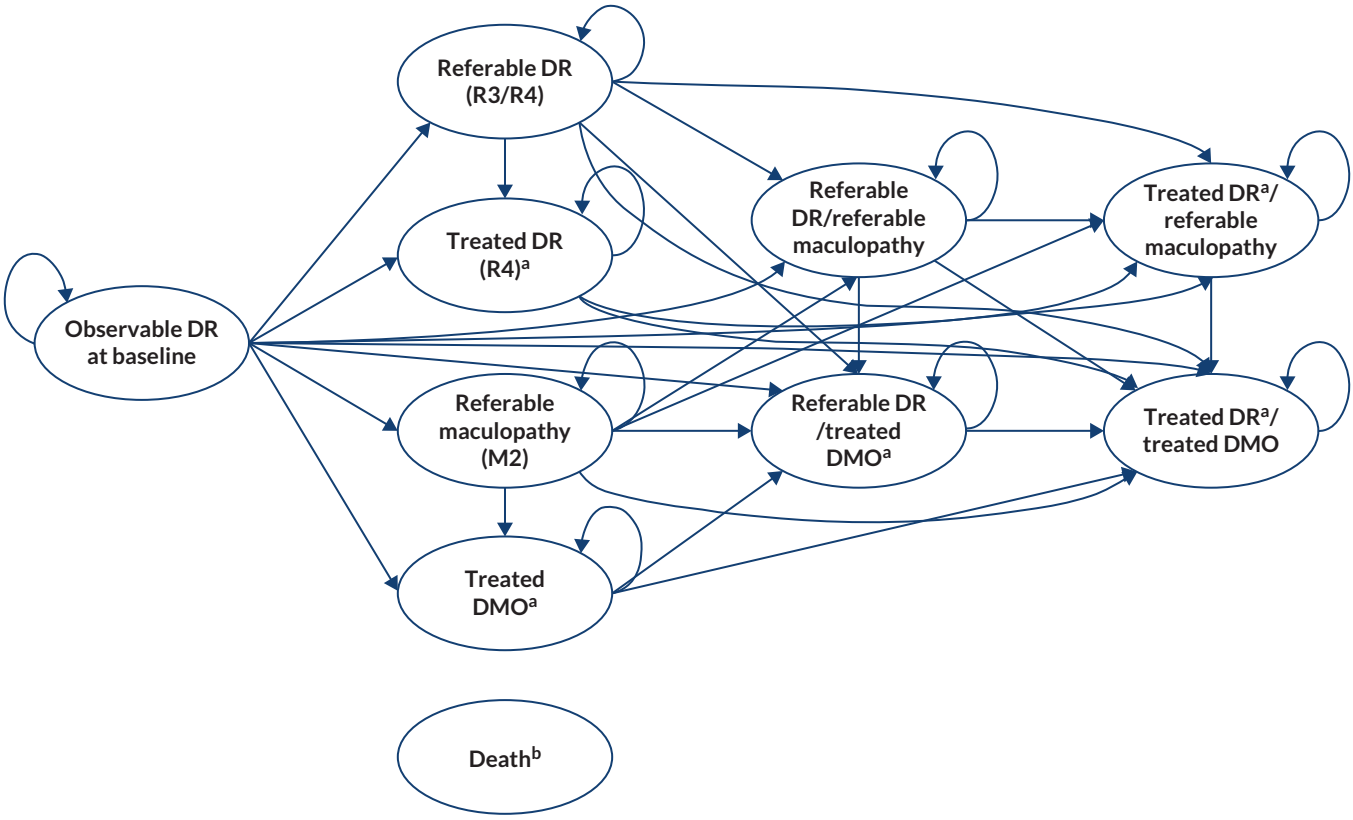

FIGURE 7 Schematic of the Markov microsimulation model. a, Treatment costs and post-treatment changes in VA and associated quality of life captured within these states. b, Death can be entered from any state in each model cycle. DMO, diabetic macular oedema; DR, diabetic retinopathy.

censored according to the pre-specified study censoring rules (see *Report Supplementary Material 2*,). Based on consideration of statistical fit, visual fit to the observed data, and the plausibility of extrapolations, an exponential function was used to model the cause-specific hazard for progression to referable retinopathy (R3/R4) (see *Appendix 3*, *Table 30* and *Appendix 5*, *Figures 15–17*), and a Weibull function was used to model progression to referable maculopathy/macular oedema (see *Appendix 3*, *Table 31* and *Appendix 5*, *Figures 18–20*). The preferred parametric survival models were used to calculate transition probabilities for each referral outcome with adjustment for the competing risk. The final models were adjusted for baseline characteristics, allowing transition probabilities for these events to vary by age group (< 30; ≥ 30 < 50; ≥ 50 < 70; ≥ 70 years), sex, type of diabetes (type 1, type 2, other), HbA1c (< 64; ≥ 64 mmol/mol; unknown), eGFR (< 60; ≥ 60 ml/minute/1.73 m^2), statin use, baseline maculopathy grade (none, observable) and baseline retinopathy grade (none, mild, observable).

Two alternative options were considered for the effects of fenofibrate treatment: (1) application of the overall treatment effect on the primary outcome to the cause-specific hazards; (2) application of separate treatment effects estimated for each cause-specific hazard. Option one was applied in the base case, since existing evidence supports a consistent treatment effect across the retinopathy and maculopathy components of the primary outcome,[11] and the LENS trial was not powered to detect differences in treatment effects for these components. The proportional hazards assumption was maintained over the model time horizon in the base-case analysis. The impact of removing any treatment effect beyond the end of the trial follow-up period was assessed in sensitivity analysis.

Referable retinopathy to diabetic retinopathy intervention

Following progression to referable disease, data from the LENS trial were used to inform transition probabilities from:

- referable maculopathy (M2) to referable retinopathy (R3/R4)
- referable retinopathy (R3/R4) to referable maculopathy (M2)
- referable maculopathy to treatment for diabetic macular oedema
- referable retinopathy (R3/R4) to treatment for proliferative retinopathy (R4).

These transitions were informed by observed time-to-event data by treatment allocation group, using the time of progression to referable retinopathy or referable maculopathy as time zero in the calculation of time at risk. Given the relatively small number of observations on these subsequent transitions, event rates were assumed to follow exponential distributions, with treatment effects applied as HRs, and hazards converted to constant 6-monthly transition probabilities using the following equation:[39]

$$p(t) = 1 - e^{-rt}$$

where p is the transition probability, t is the model cycle length and r is the estimated rate.

Patients not observed to have experienced the event of interest were censored according to the pre-specified censoring rules of the LENS study. The relevant survival curves are presented in *Appendix 5*, *Figures 21–24*. In the base case, the estimated HR for each type of event was applied. Sensitivity analysis was used to explore the impact of applying the HR for the primary composite outcome to the baseline rates underpinning all transitions.

An exception was made for the transition from referable retinopathy (R3/R4 not treated immediately) to treated proliferative diabetic retinopathy, where the proportional hazards assumption did not appear to hold and there was suggestion of a plateau emerging in the available Kaplan–Meier data. Therefore, independent log-normal distributions were selected to model this transition, providing a compromise between statistical and visual fit, and the plausibility of longer-term extrapolations. The application of an exponential function was tested in sensitivity analysis.

Post-treatment progression

To inform expected long-term health outcomes following treatment for referable retinopathy and macular oedema, we used LENS trial data to determine BCVA in the BSE and WSE at the latest available assessment prior to treatment with anti-VEGF or panretinal laser photocoagulation (PRP). For simplicity, ant-VEGF injections were assumed to maintain VA at the pre-treatment level to 2 years post treatment. This is broadly consistent with findings of a recent cohort study evaluating the effectiveness of aflibercept injections in a real-world NHS setting.[32] Beyond 2 years, it was assumed that VA in treated eyes deteriorates slowly at the level observed during the long-term follow-up of patients enrolled in the Protocol T extension study (a mean reduction of 4.7 ETDRS letters between 2 years and 5 years of follow-up under routine management).[40]

For eyes with proliferative diabetic retinopathy treated with PRP, VA changes were modelled to align with those

reported in a retrospective NHS cohort study. Fu *et al.* studied 2336 eyes with stable proliferative diabetic retinopathy following PRP and reported a 50% probability of losing ≥ 5 ETDRS letters or more by 3.32 years. A mean (SD) reduction of 14.2 (13) ETDRS letters was observed at this event.[41] A 6-monthly probability of losing ≥ 5 letters following PRP was estimated from these data and applied in the model, with the number of letters lost drawn from a gamma distribution with mean (SD) matching that reported by Fu *et al.*

Given uncertainty regarding the linkage of treatment to the individual eyes, it was conservatively assumed that post-treatment VA changes apply to the WSE at treatment initiation. Sensitivity analysis assessed the impact of applying VA changes to the BSE.

Mortality

Mortality was modelled by age and sex using UK life tables, adjusted for type 1 and type 2 diabetes using standardised mortality ratios applicable to the Scottish population.[42,43]

Health state utility values

Health state utility values were estimated using a MMRM, with a random effect for individual participant. Alternative models were assessed with fixed effects for various measures of health status, treatment allocation, time from baseline, baseline EuroQol 5 Dimension (EQ-5D) score and selected baseline covariates. Different specifications were assessed and compared in terms of AIC and BIC. The preferred model used pooled data and included: baseline EQ-5D, referable diabetic eye disease of any type, time from baseline and baseline age. The estimated utility decrement associated with developing any referable disease was applied to patients transitioning to any of the post-referral states of the model.

With relatively few patients in the LENS trial reaching more advanced stages of referable disease requiring treatment, the estimated utility decrement associated with referable disease was assumed to capture the effect on quality of life of early referable disease. Longer-term utility impacts following initiation of retinal treatment were therefore modelled through expected impacts on VA. Focused searches of the literature were used to identify studies reporting on the relationship between VA and health state utility values in people with diabetes. The selected source reported EQ-5D utility values based on application of the UK general population valuation tariff to EQ-5D-3L response data collected from 1320 patients enrolled in four trials of intraretinal aflibercept injections for macular oedema.[44] Brazier *et al.* reported predicted EQ-5D values based on regression models accounting for BCVA in the BSE and WSE eye over time. The values from the authors preferred ordinary least squares model were chosen for incorporation in the economic model.

Resource use and costs

Fenofibrate treatment was costed based on the Drug Tariff price for bioequivalent 200 mg micronised capsules as previously described.

Six-monthly health state costs were estimated by analysis of 6-monthly interval costs, inclusive of biochemistry monitoring, hospital resource use in specialties of interest (other than ophthalmology), and relevant community prescribed medicines. GEEs were used to estimate differences in these costs by health state and/or treatment allocation, with only significant effects incorporated in the model. A similar analysis was performed to estimate screening costs by model health state, with the regression including health state indicators for referable maculopathy, treated maculopathy, referable retinopathy and treated retinopathy. Screening costs were assumed to stop for those developing referable retinopathy (R3/R4) or macular oedema requiring treatment, since care and follow-up would move to hospital eye services for these patients.

For those progressing to referable retinopathy (R3) not yet requiring treatment, 6-monthly outpatient monitoring in the hospital eye service was assumed.[29] For those developing referable maculopathy alone, the increased costs of OCT surveillance, as implemented in Scotland for those with M2 and VA ≤ 75 ETDRS letters, were captured as an increase in screening costs.

For those progressing to PRP for proliferative diabetic retinopathy, 2.77 hospital outpatient appointments were assumed for administration of PRP,[45] with an additional ophthalmology outpatient appointment for follow-up during the model cycle of treatment initiation. Based on clinical expert feedback, it was assumed that, following treatment of proliferative diabetic retinopathy, patients would be followed up for 3 years at 6-monthly intervals in the hospital eye service before being discharged back to DES.

For those modelled to receive treatment for macular oedema, the cost of aflibercept injections was applied, with expected numbers of injections informed by the DRAKO cohort study: 6.3 injections in year 1, and 2.9 injections in year 2.[32] An additional ophthalmology outpatient appointment, over and above those required for administration of injections, was added in years 1 and 2 to reflect follow-up without injections. In years 3–5, it was assumed that patients would incur a further

2.45 further injections. This was based on the ratio of the median number of aflibercept injections in years 3–5 and years 1–2 in the Protocol T trial (= 4/15),[7,40] multiplied by the mean number of injections in years 1–2 of the DRAKO cohort study.[32] It was assumed that hospital outpatient monitoring would continue at 6-month intervals in year 3 and then annually thereafter.

It was conservatively assumed that all treatment was for unilateral disease in the base case. Multipliers of 1.9 and 1.4, based on clinical expert opinion, were applied to treatment specific costs for proliferative diabetic retinopathy and macular oedema respectively in sensitivity analysis to account for expected proportions requiring bilateral treatment for these indications. Scottish unit costs were applied to all diabetic retinopathy treatment-related activity and ophthalmology monitoring visits. The application of English-specific unit costs was tested in sensitivity analysis.

Model-based analysis

Monte Carlo simulation was employed to model the progression of individual simulated patients sequentially. These simulated patients were created using bootstrap resampling of the baseline characteristics from LENS trial participants, preserving correlations between them: age group (< 30; ≥ 30 < 50; ≥ 50 < 70; ≥ 70 years), sex, type of diabetes (type 1, type 2, other), HbA1c category (< 64; ≥ 64 mmol/mol; unknown), eGFR category (< 60; ≥ 60 ml/minute/1.73 m^2), statin use, baseline maculopathy grade (none, observable) and baseline retinopathy grade (none, mild, observable). The resulting patient profiles were then integrated with parameter estimates from the fitted survival regression models to simulate individual transition probabilities for the components of the first documented disease progression event [referable maculopathy or treatment for diabetic macular oedema; referable retinopathy (R3/R4) or treatment thereof]. Following initial progression, transitions followed average estimates by treatment allocation group, due to their being too few events to inform transitions by individual characteristics. For deterministic analysis of the model, 500,000 simulations were found to produce stable results.

To characterise second-order uncertainty, model inputs were assigned theoretical probability distributions reflecting uncertainty due to sampling variation. Standard practices were followed when choosing appropriate distributional forms for each parameter, with multivariate normal distributions used to correlate parameter estimates obtained from regression analysis of the trial data.[46] Probabilistic analysis proceeded by running 50,000 first-order simulations for each of 1000 random draws taken from the assigned second-order probability distributions. Results are presented as the incremental cost per QALY gained, with uncertainty presented graphically using the cost-effectiveness plane and cost-effectiveness acceptability curves.[39] A 10-year time horizon was applied in the base case, providing sufficient time for major difference in costs and outcomes to unfold, without the increasing uncertainty that arises from long-term extrapolation. Deterministic scenario analysis explored the impact of varying structural (e.g. choice of parametric survival functions) and methodological assumptions, including the time horizon.

Results

Within-trial analysis of costs and outcomes

A summary of healthcare resource use by treatment allocation over the full follow-up period of the LENS trial is provided in *Appendix 3*, *Table 32*. Corresponding undiscounted costs are provided in *Table 13*.

Healthcare resource use was broadly similar between groups, with no major differences in any single category. Participants in the fenofibrate group had slightly more digital retinal screening episodes, but slightly fewer OCT examinations. The number of biochemistry tests was slightly higher in the fenofibrate group. Participants in the placebo group had slightly more outpatient appointments and more hospital admissions (with greater lengths of stay) in specialties of interest, reflected in higher costs for these categories of care (see *Table 13*).

Results of the within-trial incremental cost-effectiveness analysis are provided in *Table 14*. Given the uncertainty surrounding the relevance of certain costs in the incremental analysis, four options were explored. Costs in the base case included outpatient attendances and inpatient episodes in specialties of interest, and all other categories of resource use. Further scenarios explored: (1) total costs inclusive of all outpatient and inpatient resource use (scenario 1); (2) total costs, inclusive of outpatient attendances in specialties of interest but excluding all inpatient costs (scenario 2); and (3) total costs inclusive of outpatient attendances in specialties of interest and the full cost of any continuous inpatient stay involving at least one episode in a specialty of interest (scenario 3).

In the base case, fenofibrate use was associated with a non-significant reduction in total cost, and a statistically significant increase in the proportion free from referable retinopathy at 2 years, resulting in fenofibrate being dominant (less costly on average and more effective). The same pattern was observed for scenarios 1 and 3. In

TABLE 13 Summary of health service costs per participant by treatment group full follow-up period

Resource use category	Fenofibrate (*N* = 576) (£)	Placebo (*N* = 575) (£)	All participants (*N* = 1151) (£)
Intervention acquisition cost	221 (86)	0	N/A
Screening episodes, mean (SD)	117 (49)	118 (49)	117 (49)
Digital retinal screening	110 (47)	107 (48)	109 (48)
OCT	3 (17)	5 (23)	4 (21)
Slit lamp	4 (17)	5 (18)	4 (18)
Biochemistry tests, mean (SD)	216 (158)	210 (143)	213 (150)
Albumin/creatinine	2 (2)	2 (2)	2 (2)
HDL cholesterol	3 (2)	3 (2)	3 (2)
HbA1c	5 (3)	5 (3)	5 (3)
Triglycerides	2 (2)	2 (2)	2 (2)
Creatinine	7 (6)	7 (6)	7 (6)
Total cholesterol	3 (2)	3 (2)	3 (2)
GP and nurse time	194 (147)	188 (133)	191 (140)
Prescribing episodes (episodes), mean (SD)	3132 (2199)	3116 (2220)	3124 (2209)
Blood pressure	102 (248)	111 (287)	107 (268)
Diabetes	2835 (2126)	2810 (2117)	2823 (2121)
Other	155 (490)	151 (454)	153 (472)
Oedema	2 (10)	3 (12)	3 (11)
Statins	37 (23)	40 (65)	39 (49)
Outpatient visits, mean (SD)	2179 (4171)	2226 (3001)	2202 (3633)
Specialties of interest	1051 (1484)	1167 (1553)	1109 (1520)
Ophthalmology	226 (646)	235 (644)	230 (645)
Others	1127 (3341)	1059 (2222)	1093 (2837)
Anti-VEGF cost	107 (855)	127 (904)	117 (879)
Inpatient/day case (episodes), mean (SD)	5207 (13,170)	6135 (20,803)	5671 (17,405)
Specialties of interest	2475 (8128)	3198 (17,819)	2836 (13,844)
Others	2731 (9144)	2937 (8407)	2834 (8780)
Inpatients/day case (continuous inpatient stays), mean (SD)	5207 (13,170)	6135 (20,803)	5671 (17,405)
Specialties of interest	3073 (10,034)	3987 (18,952)	3529 (15,160)
Others	2134 (7965)	2149 (7033)	2141 (7511)

scenario 2, which excluded all inpatient costs, fenofibrate use was associated with a small non-significant increase in cost, generating a positive incremental cost-effectiveness ratio (ICER) of £2658 per case of referable disease averted.

Figure 8 (for the base case) and *Appendix 5*, *Figures 25–27* summarise the uncertainty surrounding the estimated joint difference in costs and effects based on 1000 bootstrapped replicates of the analysis.

Apart from scenario 2, most of these bootstrapped replicates fall within the southeast quadrant of the cost-effectiveness plane, where fenofibrate is considered a dominant treatment. This results in high probabilities of

TABLE 14 Incremental cost per case of referable disease averted at 2 years

	Cost (£), mean (95% CI)		Free from referable DR, proportion (95% CI)		
	Total	Incremental	Total	Incremental	ICER
Base case (cost inclusive on inpatient episodes and outpatient visits in specialties of interest)					
Fenofibrate	3566 (3088 to 4364)	−254 (−1062 to 624)	0.867 (0.84 to 0.89)	0.044 (0.013 to 0.08)	Dominant
Placebo	3820 (3052 to 4749)		0.823 (0.80 to 0.85)		
Scenario 1 (costs inclusive of inpatient episodes and outpatient visits to all specialties)					
Fenofibrate	5112 (4370 to 6022)	−741 (−1949 to 425)	0.867 (0.84 to 0.89)	0.044 (0.013 to 0.08)	Dominant
Placebo	5853 (4886 to 7014)		0.823 (0.80 to 0.85)		
Scenario 2 (excluding all inpatient costs)					
Fenofibrate	2354 (2216 to 2533)	117 (−118 to 354)	0.867 (0.84 to 0.89)	0.044 (0.013 to 0.08)	2658
Placebo	2238 (2101 to 2398)		0.823 (0.80 to 0.85)		
Scenario 3 (inclusive of the full cost of continuous inpatient spells involving any episodes in a specialty of interest)					
Fenofibrate	3780 (3181 to 4593)	−353 (−1409 to 683)	0.867 (0.84 to 0.89)	0.044 (0.013 to 0.08)	Dominant
Placebo	4134 (3309 to 5150)		0.823 (0.80 to 0.85)		

DR, diabetic retinopathy.

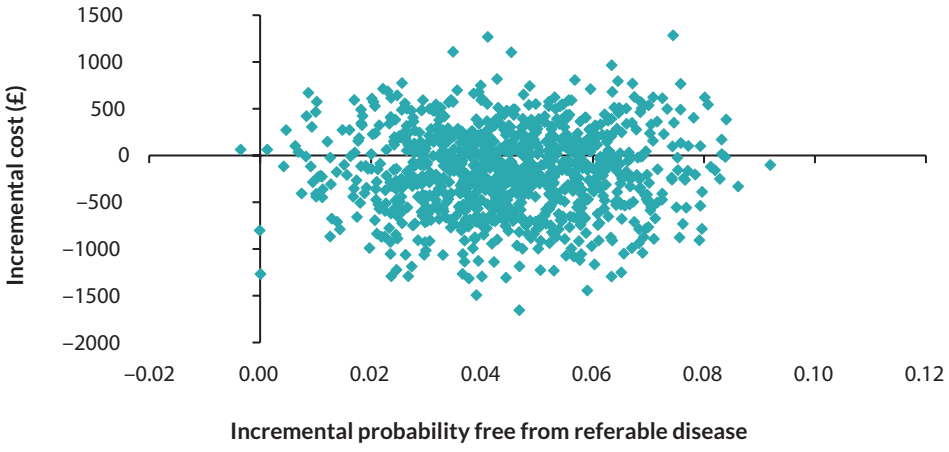

FIGURE 8 Trial-based cost-effectiveness scatterplots for fenofibrate vs. placebo. Cost inclusive of inpatient episodes and outpatient visits in specialties of interest.

cost-effectiveness regardless of willingness to pay (WTP) per case averted, as presented in the corresponding cost-effectiveness acceptability curves (*Figure 9* and *Appendix 5*, *Figures 28*–*30*).

Table 15 presents the results of the 6-month interval-based cost analysis. There was no obvious pattern in the estimated difference in 6-monthly cost by treatment allocation group or by time. Only between 6 months and 1 year was a significant effect estimated, favouring fenofibrate. Averaged over the trial follow-up period, 6-monthly health service costs were slightly lower in the fenofibrate arm, but the difference was not statistically significant. Combined with the significant reduction in the hazard of referable disease, this corroborates the results of the 2-year incremental analysis.

Modelling of longer-term cost-effectiveness

In the model-based analysis, it is conservatively assumed that background health state costs do not vary by health state or treatment allocation. Differences in cost in the model are driven only by fenofibrate treatment

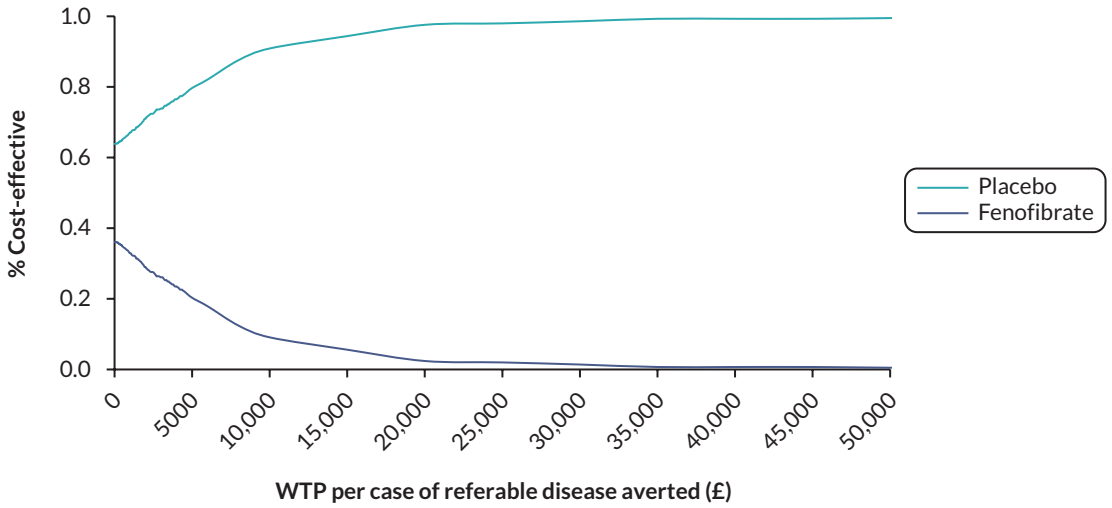

FIGURE 9 Trial-based cost-effectiveness acceptability curves for fenofibrate vs. placebo. Cost inclusive of inpatient episodes and outpatient visits in specialties of interest.

TABLE 15 Comparison of 6-month interval-based costs by treatment group

	Fenofibrate			Placebo			
6 monthly intervals	*N*	Mean cost (£)[a]	SE	*N*	Mean cost (£)[a]	SE	Difference between groups (£) (95% CI)
1	576	690	101	575	808	118	−118 (−421 to 186)
2	573	837	122	573	1317	193	−481 (−927 to −34)
3	570	672	99	571	734	108	−62 (−348 to 223)
4	566	973	143	568	896	132	77 (−304 to 457)
5	560	730	108	564	961	142	−230 (−579 to 118)
6	549	981	147	549	875	131	106 (−278 to 491)
7	509	930	144	513	1080	167	−151 (−582 to 281)
8	467	961	160	459	746	125	214 (−173 to 602)
9	298	761	166	296	1125	246	−364 (−907 to 178)
10	103	2003	748	105	1445	538	558 (−1104 to 2221)
Average over trial follow-up	576	844	49	575	945	55	−101 (−243 to 42)

N, number contributing; SE, standard error.
a Adjusted for minimisation covariates.

acquisition costs, screening costs, ophthalmology referral, monitoring and retinal treatment (laser and anti-VEGF injection) costs. With no effect on mortality, QALY differences are realised through delayed eye disease progression, which was estimated to attract a utility decrement of −0.02 (95% CI −0.042 to 0.003) based on MMRM analysis, and further decrements associated with modelled post-treatment VA losses. All the derived model input parameters are provided in *Appendix 3*, *Table 33*.

Model validation against clinical trial outcomes

The model output was internally validated against the clinical outcomes of the trial (*Figures 10* and *11*). For comparison against the Kaplan–Meier estimates from the trial, the mortality rate was set to zero in the model before being added back in as a competing risk for the analysis.

Incremental cost per quality-adjusted life-year gained

Fenofibrate was associated with a slight increase in cost for a small increase in QALYs over the 10-year time

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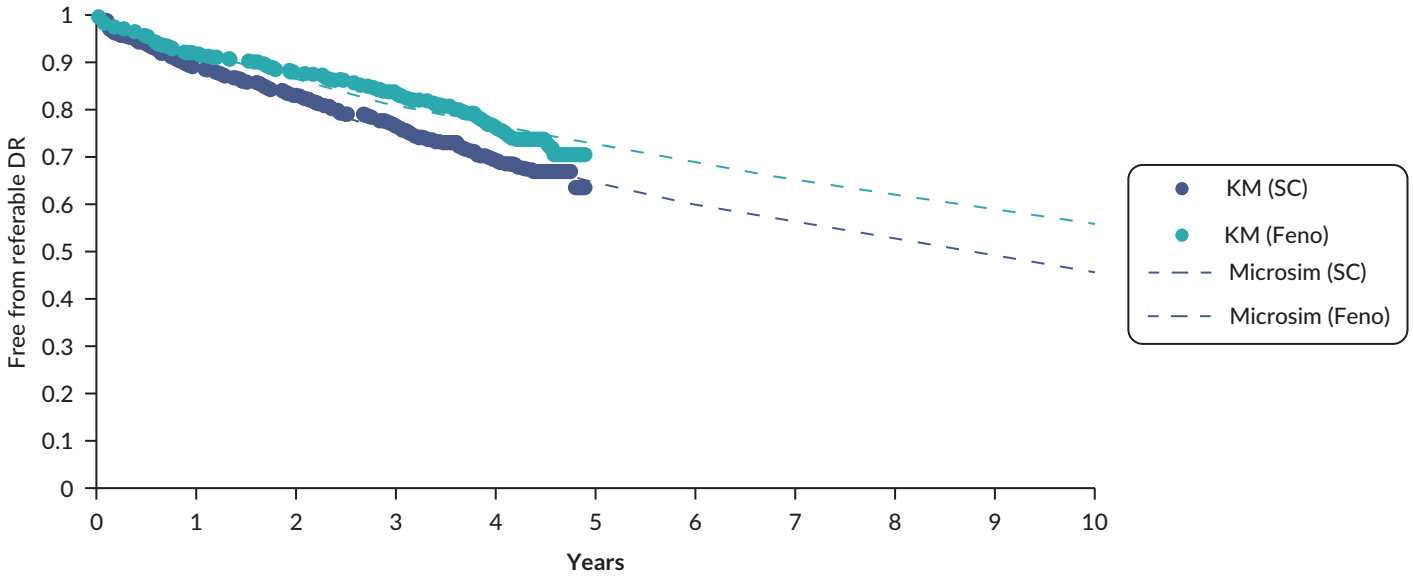

FIGURE 10 Comparison on model output against observed Kaplan–Meier-based estimates of time to any referable diabetic retinopathy. DR, diabetic retinopathy; Feno, fenofibrate; KM, Kaplan–Meier; Microsim, microsimulation model; SC, standard care.

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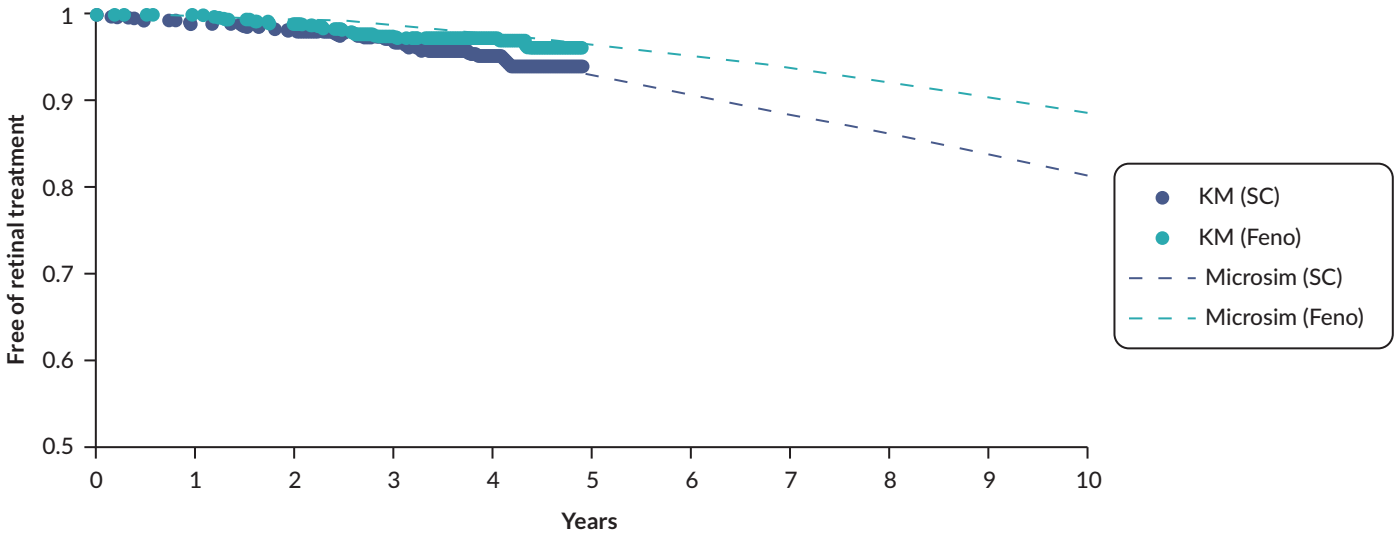

FIGURE 11 Comparison on model output against observed Kaplan–Meier-based estimates of time to any treatment for diabetic retinopathy. Feno, fenofibrate; KM, Kaplan–Meier; Microsim, microsimulation model; SC, standard care.

TABLE 16 Model-based incremental cost per QALY gained (10-year time horizon)

	Cost (£), mean		QALYs, mean		
	Total	Incremental	Total	Incremental	ICER
Base case (deterministic)					
Standard care	14,229		5.423		
Fenofibrate	14,234	6	5.437	0.015	406
Base case (probabilistic)					
Standard care	14,275		5.419		
Fenofibrate	14,283	9	5.434	0.014	613

horizon (*Table 16*). Based on the probabilistic analysis, this translated into a high probability (79–86%) of cost-effectiveness at accepted cost-effectiveness thresholds (£20,000–30,000 per QALY) (*Figures 12* and *13*).

Results of scenario analyses (see *Appendix 3*, *Table 34*) suggest that results are robust to changes in key inputs and assumptions. Over longer-time horizons, approximating the lifetime of older participants, the incremental cost reduced and the QALY gain for fenofibrate increased, resulting in fenofibrate becoming dominant. Reducing the cost of anti-VEGF treatment, increasing the cost of fenofibrate, and removing the relative treatment effects from 5 years all increased the ICER, but it remained below cost-effectiveness thresholds applied in the UK NHS. Inflating PRP and anti-VEGF treatment costs, to account for bilateral treatment in a proportion of patients, resulted in fenofibrate becoming dominant.

Discussion

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Over a 4-year follow-up period in this population of people with diabetes and early retinopathy, fenofibrate led to a 27% lower rate of the progression of, or treatment

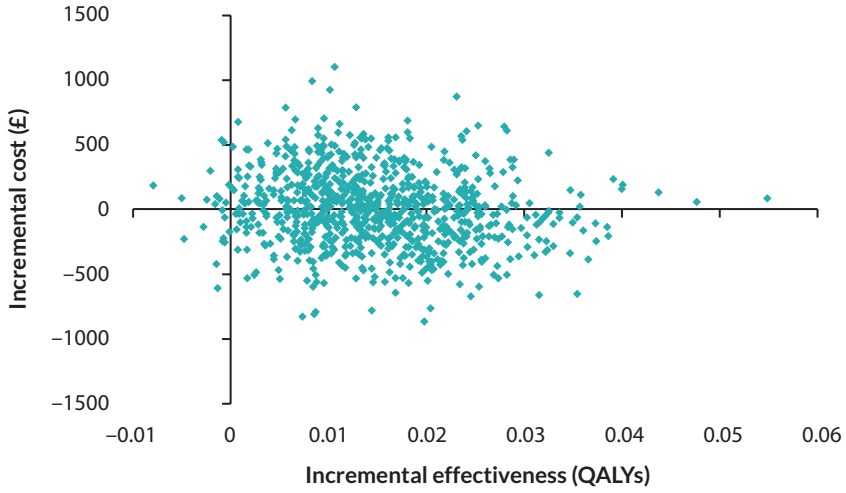

FIGURE 12 Base-case cost-effectiveness scatter plot for fenofibrate vs. standard care. Incr, incremental.

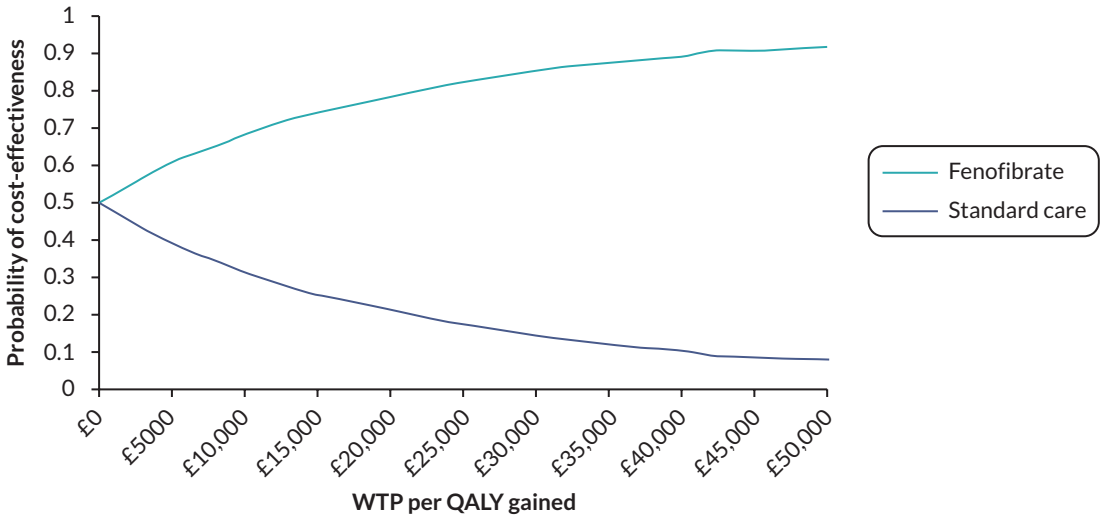

FIGURE 13 Base-case cost-effectiveness acceptability curves for fenofibrate vs. standard care.

for, diabetic retinopathy or maculopathy compared with placebo.[16] We also observed reductions in macular oedema and in any progression of diabetic retinopathy or maculopathy. The trial provides the first randomised evidence for the use of fenofibrate for the treatment of retinopathy in individuals with type 1 diabetes, and the intervention appeared similarly effective in this group compared to participants with type 2 diabetes. Results were also consistent between participants with normal and impaired kidney function.

The proportional effect of fenofibrate on the progression of retinopathy or maculopathy observed in LENS is quantitatively similar to that seen in subsidiary analyses from major cardiovascular trials (*Figure 14*). In the FIELD study, the tertiary outcome of retinal laser therapy was proportionally reduced by 31% [164 (3.4%) events in 4895 participants allocated fenofibrate vs. 238 (4.9%) events in 4900 participants allocated placebo] over 5 years.[10,11] Furthermore, pooled data in 19,000 participants from 3 trials showed a 23% reduction in retinal laser compared to placebo.[13] A FIELD imaging substudy showed a reduction in a post hoc composite outcome of two-step ETDRS Severity Scale retinopathy progression, new macular oedema or retinal laser of a third [53 (11.1%) events in 512 participants vs. 75 (16.1%) events in 500 participants on placebo].[11] In addition, the ACCORD Eye substudy demonstrated a reduction in the composite outcome of three-step ETDRS retinopathy progression, retinal laser or vitrectomy [52 (6.5%) events in 806 participants vs. 80 (10.2%) events in 787 participants on placebo] over 4 years.[12,15]

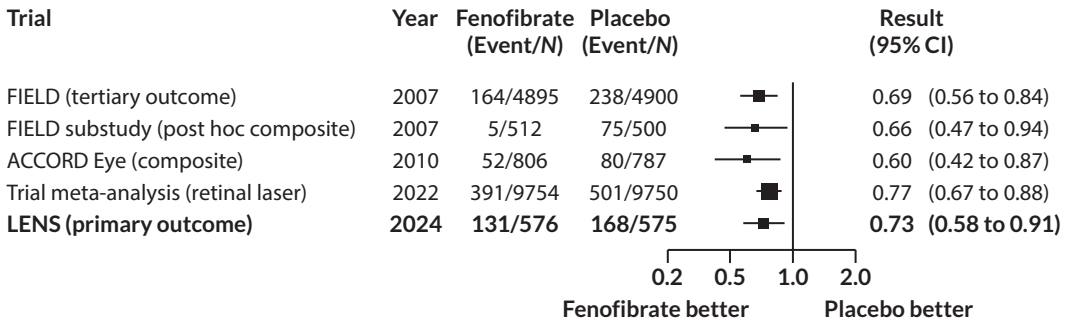

FIGURE 14 LENS results in the context of hypothesis-generating data from cardiovascular outcome trials. This figure shows results with 95% CIs for: the FIELD trial's tertiary outcome (retinal laser treatment for proliferative retinopathy or macular oedema; HR); a post hoc analysis of the FIELD trial's retinopathy substudy (≥ 2-step ETDRS progression, macular oedema, or laser treatment; HR); the pre-specified main outcome for the ACCORD Eye substudy (≥ 3-step ETDRS progression or diabetic retinopathy necessitating laser or vitrectomy; adjusted OR), tabular meta-analysis of three cardiovascular trials (laser treatment for diabetic eye disease; OR); and the LENS trial (primary outcome; HR).

Accumulating evidence suggests that fenofibrate chiefly mediates its effect directly within the eye and not through a reduction in circulating atherogenic lipids. In LENS, reductions in atherogenic lipids were small, yet benefit for retinopathy outcomes was still observed. In the subgroup with impaired renal function at baseline who only took study treatment on alternate days, fenofibrate did not alter lipid levels compared to placebo, yet ocular benefit still emerged. Studies conducted in animal models of diabetic retinopathy have shown that oral administration and intravitreal injection of fenofibrate both reduce retinal vascular leakage and retinal inflammation, while a study of human retinal pigment epithelial cells suggests that fenofibric acid plays a protective role on the blood–retina barrier.[48,49]

Fenofibrate therapy is known to increase blood creatinine levels (and therefore reduce eGFR), an effect that is reversible.[23,24] In LENS, a trial-averaged reduction in eGFR of 8 ml/minute/1.73 m^2 was observed in participants treated with fenofibrate compared to placebo. The fall in eGFR is relevant to clinical care given that the recommended dose of fenofibrate depends on eGFR and because it may complicate interpretation of eGFR results in people with diabetes, a group already at elevated risk of developing chronic kidney disease. However, fenofibrate therapy is also known to reduce UACR levels and a small wash-out post-trial study in 600 FIELD trial participants suggests that fenofibrate may offer protection against renal impairment.[23] Post-trial follow-up of LENS trial participants will enable us to investigate the impact of fenofibrate treatment for 4 years on longer-term renal function.

Over the LENS trial follow-up period, fenofibrate led to a non-significant reduction in healthcare costs and, based on modelling, resulted in an incremental cost per QALY gained that is well below thresholds applied in the NHS. This translates into a high probability that it offers a cost-effective treatment for the population studied. We are aware of only one previous economic evaluation of fenofibrate for the treatment of diabetic retinopathy, available as a published conference abstract, which reported an ICER of AUD 10,221 (2012) per QALY gained versus placebo based on the FIELD trial.[50] While insufficient information is available to make a detailed comparison with this study, it is likely that our lower ICER can be explained by changes in the price of fenofibrate over time, and the higher risk of progression to referable disease in the LENS trial population compared to that of the FIELD trial,[11] the higher baseline risk resulting in a smaller number needed to treat, and greater future savings in ophthalmology referral and treatment costs for a similar relative reduction in the risk of progression.

We consider our findings to be of potential importance to public health given the number of people already living with diabetes globally and projections of how many people are likely to have diabetes in the future. Diabetic retinopathy continues to be among the five leading causes of visual loss worldwide, and the only major cause to increase in recent decades.[1] It is the second most important cause of visual loss in adults of working age in England and Wales.[51] Effective control of blood glucose is an important goal to limit the risk of progressive retinopathy.[4,5] However, many people with diabetes do not manage to achieve a reasonable level of control, whether due to the lack of therapeutic options or monitoring or other reasons and, as a result, many continue to develop progressive retinopathy, even in developed countries. Therapies that reduce the progression of retinopathy, such as fenofibrate, may therefore provide a valuable adjunct to treat people with early diabetic retinopathy. For example, treating

1000 people with a diabetic retinopathy grading similar to LENS participants with fenofibrate for 4 years would result in 65 fewer developing referable disease or requiring treatment.

The LENS trial investigated the use of fenofibrate for people with diabetic retinopathy at risk of progression. This is a group of people for whom there are limited therapeutic options. Other key strengths of the trial include its positioning within routine health care. This allowed us to recruit a high proportion of potentially eligible individuals across Scotland to a placebo-controlled trial and to follow them in a streamlined fashion.[17] Trial participants were similar to the potentially eligible population with regard to key risk factors for diabetic retinopathy progression. Linkage to the national DES Programme has provided a biobank of 9000 retinal images to facilitate further research into the effects of fenofibrate on the retina. Adherence to study treatment was excellent at 88% and completeness of follow-up was over 99%. The design of the trial also allowed it to continue largely unaffected by the COVID-19 pandemic, apart from temporary cessation of the national DES Programme in 2020. There are important limitations to consider, however. Participants with impaired kidney function took study treatment on alternate days, though we noted no difference in the proportional effect on the primary outcome in this group compared to those with normal renal function. Retinal screening in Scotland is similar to other established programmes using a grading scheme aligned to the ETDRS classification used in research studies[52] with a stepwise severity scale where higher grades are increasingly predictive of the development of referable disease.[53] LENS eligibility criteria mapped closely to ETDRS levels 20/35. However, the NHS Scotland scheme does not distinguish higher grades of retinopathy with the same granularity as ETDRS. Single central 45° field images cover a more restricted retinal area, excluding some of the peripheral retina (though importantly it includes the part of the retina most likely to develop vision-threatening disease). Mydriasis was not used in > 70% of retinal screening episodes, but 95% of images had the highest available quality rating. The primary outcome included progression to referable maculopathy, a grade that is consistent with disease progression and which prompts further investigation for macular oedema and subsequent surveillance, but which often does not require treatment in the short term. However, we also observed a reduction in macular oedema, and the reduction in referable maculopathy is quantitatively similar to results from the FIELD trial for laser treatment of macular oedema, supporting its inclusion in the primary outcome.[11] We did not seek information regarding any OCT imaging during outpatient ophthalmology visits that were not arranged by the DES Programme or did not include treatment for retinopathy or maculopathy, so it is possible that we missed some cases of macular oedema. However, development of macular oedema without subsequent detection of referable disease by routine retinal screening or by the need for treatment at a later stage would have been very infrequent. A limitation for the economic analysis is that we did not routinely capture data on the number of anti-VEGF injections or laser sessions received by those initiating treatment. To overcome this, we based assumptions about treatment courses on published observational NHS cohort studies and validated these with expert clinical opinion. The modelled treatment courses should therefore be generalisable across the NHS. People were invited without knowledge of their ethnicity, but the trial included few non-White participants and, while the LENS results are likely to be generalisable to other ethnicities, further trials should be considered.

Equality, diversity and inclusion

Disease burden

According to data published in 2021 by the Global Burden of Disease 2019 Blindness and Vision Impairment Collaborators, diabetic retinopathy is among the leading five causes of visual loss. It ranks as the fourth or fifth leading cause of both blindness and of moderate to severe visual impairment in all regions of the world. Over the last 30 years, the age-standardised prevalence of blindness has increased in many regions (Australasia, Central Asia, East Asia, high-income regions of North America, Oceania, South Asia, Southeast Asia, Southern sub-Saharan Africa and Western sub-Saharan Africa). Major risk factors for progression of retinopathy are duration of diabetes and glycaemic control, and there is no obvious difference in risk between men and women. Very few countries offer national retinal screening programmes.

LENS trial participants

Adults living in mainland Scotland who were identified as meeting key inclusion criteria (based on their most recent retinal screening results and most recent eGFR result) were invited regardless of their address, age, sex, gender or ethnicity. Please refer to sections in the main document, which describe and discuss the representativeness of randomised LENS trial participants compared to the potentially eligible population [see Representativeness of LENS trial participants (*Methods*

section), Representativeness of LENS trial participants (*Results* section), and *Table 12*].

Generalisability and transferability of evidence

Randomised evidence of the effect of fenofibrate on diabetic retinopathy has limited representation from ethnicities other than White people. There is no obvious scientific reason to suppose that the beneficial effect observed in the LENS trial and in other hypothesis-generating trials should not also be present in other groups of people.

Steering committee

The LENS Steering Committee has equal membership of women (seven) and men (seven).

Patient and public involvement

Study design

On 18 March 2015, 2 LENS investigators met with 15 members of the Glasgow South Diabetes UK Group to present and discuss the concept and the design of the LENS trial. The group members provided feedback on patient perceptions of the research question and practicalities of delivering the trial. They indicated that they understood the need for a control (i.e. placebo) group. The letter of support from the Group Secretary following the meeting is included (see *Report Supplementary Material 5*).

Study oversight and conduct

Two patients with diabetes joined the LENS Steering Committee as patient representatives. They participated in all Steering Committee meetings and were involved in reviewing all patient-facing materials (e.g. information leaflets, newsletters) and providing patient perspectives on the trial's conduct and reporting of results. The Royal National Institute for the Blind (RNIB), Scotland, also provided a member to the LENS Steering Committee. The RNIB committee member attended Steering Committee meetings and also reviewed trial materials. RNIB arranged an interview with the Chief Investigator on RNIB Radio to discuss the main results of the trial.

Writing

Two patient representatives assisted with writing the plain language summary.

Dissemination of results

On 28 June 2024, the chief investigator was interviewed on Royal National Institute of Blind People Connect Radio to discuss the LENS trial and its results.

Impact and learning

The results from the LENS trial demonstrate that treatment of people with early diabetic retinopathy with fenofibrate is cost saving and reduces the risk of progression to more advanced disease. The key steps to secure widespread adoption of fenofibrate in routine care are discussed in the next section (see Implications for decision-makers).

LENS also provides an exemplar of how routinely collected healthcare data can be harnessed to recruit participants, follow them up, and obtain information regarding outcomes of interest in the context of a placebo-controlled trial. It will also allow follow-up of trial participants for the next 10 years, providing novel randomised data on the longer-term effects of treatment with fenofibrate on eye health, kidney health and other outcomes.

The trial was in the latter stages of recruitment when the COVID-19 pandemic arrived in the UK. This resulted in many NHS-based research staff being diverted to work in clinical care and/or to focus on COVID-19 research studies. In addition, NHS Scotland's DES Programme was temporarily closed and, when it reopened, it initially ran at a reduced capacity given the need for social distancing and cleaning of equipment. However, the design of the trial meant that it was largely protected from any major impact from the pandemic. The DES Programme caught up with retinal screening (such that it is unlikely that episodes of retinopathy progression were missed due to lack of retinal screening), follow-up assessments were already conducted by telephone based on the trial design and so no change to the method of follow-up was needed, and mailing of study treatment to participants continued uninterrupted.

Participants provided consent for the LENS investigators in NDPH, University of Oxford, to obtain copies of their retinal images. The LENS investigators will be able to use artificial intelligence approaches and image analysis software to gain further insights into the impact of fenofibrate on the retina.

Implications for decision-makers

The LENS trial demonstrates that fenofibrate is a clinically efficacious and cost-effective treatment option in people with early diabetic retinopathy.

At present, use of fenofibrate to treat people with retinopathy in most countries remains off licence. Broad use of this generically available and low-cost medicine

for this indication will depend on the inclusion of new recommendations in relevant clinical guidelines, and on pharmaceutical companies that manufacture fenofibrate successfully applying to regulators to include diabetic retinopathy as an indication. The LENS investigators will work with both groups to facilitate the adoption of new guidance and new indications wherever possible, in the UK and internationally.

Research recommendations

Suggested studies include:

- An individual participant data meta-analysis of placebo-controlled trials regarding the effect of fenofibrate on diabetic retinopathy progression: this would maximise statistical power to investigate the effect of fenofibrate on various important eye outcomes and would also allow detailed exploration in important groups of participants (e.g. with type 1 diabetes).
- A randomised trial of fenofibrate in people with age-related macular degeneration (AMD): there is preliminary evidence from basic science studies suggesting that fenofibrate therapy may be beneficial in the treatment of people with AMD; accumulating evidence suggests that fenofibrate is acting directly within the eye rather than through effects on circulating lipids; there are also some mechanistic features that are shared between AMD and diabetic retinopathy (though there are also important differences); given the low cost of fenofibrate and the fact that AMD is a leading cause of visual loss with no available therapies (except for those who develop vision-threatening wet AMD), a large and streamlined randomised trial should be considered to address this clinical question.

Conclusion

In a randomised trial conducted in participants with early diabetic retinopathy, fenofibrate was both clinically effective and cost-effective for reducing the progression of diabetic retinopathy compared with placebo.

Additional information

CRediT contribution statement

David Preiss (https://orcid.org/0000-0003-3139-1836): Conceptualisation, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft.

Jennifer Logue (https://orcid.org/0000-0001-9549-2738): Conceptualisation, Funding acquisition, Investigation, Methodology.

Emily Sammons (https://orcid.org/0000-0002-8647-0366): Investigation, Writing – reviewing and editing.

Mohammed Zayed (https://orcid.org/0000-0001-9816-983X): Investigation, Software, Investigation, Writing – reviewing and editing.

Graham Scotland (https://orcid.org/0000-0001-5539-8819): Formal analysis, Funding acquisition, Visualisation, Writing – original draft.

Mekazin Tsehaye (https://orcid.org/0009-0007-1832-781X): Formal analysis, Investigation, Writing – reviewing and editing.

Jonathan Emberson (https://orcid.org/0000-0001-7792-9422): Formal analysis, Investigation, Writing – reviewing and editing.

Rachel Wade (https://orcid.org/0000-0001-9826-6322): Formal analysis, Visualisation, Investigation, Writing – reviewing and editing.

Karl Wallendszus (https://orcid.org/0000-0003-0971-3026): Data curation, Formal analysis, Software, Visualisation, Investigation, Writing – reviewing and editing.

Will Stevens (https://orcid.org/0000-0001-8474-4645): Data curation, Formal analysis, Software, Investigation, Writing – reviewing and editing.

Rosanna Cretney (https://orcid.org/0000-0001-7321-5211): Data curation, Software, Investigation, Writing – reviewing and editing.

Simon Harding (https://orcid.org/0000-0003-4676-1158): Methodology, Investigation, Writing – reviewing and editing.

Graham Leese (https://orcid.org/0000-0003-0570-5678): Conceptualisation, Funding acquisition, Investigation, Methodology, Investigation Writing – reviewing and editing.

Gemma Currie (https://orcid.org/0000-0002-0797-0224): Investigation, Writing – reviewing and editing.

Caroline Styles (https://orcid.org/0009-0001-8823-341X): Investigation, Methodology, Writing – reviewing and editing.

Jane Armitage (https://orcid.org/0000-0001-8691-9226): Conceptualisation, Funding acquisition, Investigation, Supervision, Investigation, Writing – reviewing and editing.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used (#datasaveslives). You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to pseudonymised or anonymised data may be granted following review.

Ethics statement

The LENS trial was approved by the West of Scotland Research Ethics Committee 1 on 27 September 2016 (IRAS project ID 209579).

Information governance statement

The University of Oxford is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Oxford is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights, and the contact details for our Data Protection Officer here (https://compliance.admin.ox.ac.uk/data-protection-policy).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/AAPH5610.

Primary conflicts of interest: NDPH at the University of Oxford has a staff policy of not accepting personal honoraria or consultancy fees (see www.ndph.ox.ac.uk/about/independence-of-research). Jennifer Logue was an employee of AstraZeneca from 2022 to 2025 and of Roche from 2025 (neither of which had any role in the funding, design, delivery or results of this study) with an honorary academic appointment at Lancaster University, has received funding for conference attendance and advisory board membership from Novo Nordisk, and was previously a member of the HTA Clinical Evaluation and Trials Committee.

Other authors declare no conflicts of interest. Mylan (now part of Viatris) provided bulk study treatment free of charge but played no role in the design or conduct of the trial. NDPH at the University of Oxford, covered the costs of storing, packaging, and preparation for mailing of study treatment.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

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Award publications

This synopsis provided an overview of the research award *A randomised placebo-controlled clinical trial of fenofibrate to prevent progression of non-proliferative retinopathy in diabetes (LENS: Lowering Events in Non-proliferative retinopathy in Scotland)*.

Other articles published as part of this thread are:

The LENS Collaborative Group. Design, recruitment and baseline characteristics of the LENS trial. *Diabet Med* 2024;**41**:e15310. https://doi.org/10.1111/dme.15310

Preiss D, Logue J, Sammons E, Zayed M, Emberson J, Wade R, *et al*. Effect of Fenofibrate on Progression of Diabetic

Retinopathy. *NEJM Evid* 2024;**3**(8). https://doi.org/10.1056/EVIDoa2400179

For more information about this research please view the award page (https://www.fundingawards.nihr.ac.uk/award/14/49/84).

Additional outputs

American Diabetes Association Scientific Sessions. The Effect of Fenofibrate on Progression of Diabetic Retinopathy – Results from the LENS Trial (main results presentation), Orlando FL, 21 June 2024.

American Diabetes Association Scientific Sessions. Leveraging Diabetic Retinopathy Screening Programs in Clinical Trials (presentation regarding trial methodology), Orlando, FL, 22 June 2024.

Scotland G, Tsahye M, Styles C, Logue J, Sammons E, Zayed M, *et al*. Cost-effectiveness of fenofibrate versus standard care for reducing the progression of diabetic retinopathy: an economic evaluation based on data from the LENS trial. *Diabet Med* 2025;**42**:e70098. https://doi.org/10.1111/dme.70098

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Members of the LENS Collaborative Group

David Preiss, Jennifer Logue, Emily Sammons, Mohammed Zayed, Graham Scotland, Mekazin Tsehaye, Jonathan Emberson, Rachel Wade, Karl Wallendszus, Will Stevens, Rosanna Cretney, Simon Harding, Graham Leese, Gemma Currie, Caroline Styles, Jane Armitage, Paula Williamson, Jonathan Bodansky, Allan Cairns, Sue Dickie, Gillian Hallard, Gozie Joe Adigwe, Laura Jones, Timothy Lyons, Isla Mackenzie, Dermot Neely, Sarah Wild, Ian Young, Praveen Patel, Alan Watkins, Natalie Staplin, Sarah Howard, Kate Sawyer, Karen Taylor, Patricia Achiri, Andy Burke, Susan Hurley, Gareth McChlery, Kevin Murphy, Sandra Pickworth, Alison Timadjer, Kate Gardiner, Monique Willett, Liz Wincott, Matthew Beesley, Charles Cutting, Monika Raj, Ian Roure, Michelle Goonasekera, Graham Bagley, Anne Whitehouse, Isobel Young, Gavin Brown, Kate Bird, Heather Halls, Guanguo Cui, Charles Daniels, Angela Field, Bob Goodenough, Youcef Mostefai, Samee Syed, Angela Chamberlain, Carol Knott, Anna Liew, Juliette Meek, Meera Mistry, Andrea Wilson, Patrick Zettegren, Rach AitSadi, Ian Barton, Alex Baxter, Clive Berry, Rijo Kurien, Michael Lay, Aleksandra Murawska, James Thompson, Allen Young, Enti Spata, Rachel Raff, Crispian Howard, Diann Taggart, Paul Connelly, Mohan Varikkara, Scott Blackwell, Fiona Elliott, Jacqueline Locke, Angela Sweeney, Stephen Wood, Olive Herlihy, Jeni Darling, Jill Little, Ewan Bell, Susan Boytha, Paula Neill, Andrew Blaikie, Laura Beveridge, Tina Coventry, Susan Fowler, Karen Gray, Linda Lister, Amanda McGregor, Sandra Pirie, Evgeniya Postovalova, Anna White, John Doig, Stephanie Brogan, Margie Duncan, Angela Gilmour, Lynn Ryan, Anne Todd, Lesley Whitelaw, Elaine Wilson, Sam Philip, Ann Cadzow, Sharlene Greig, Siby Joseph, Lynne Murray, Julie Toye, Sonia Zachariah, David Carty, Lindsey Bailey, Alison Begg, Katherine Brown, Charlotte Clark, Katharine Duffy, Shirley Fawcett, Adam Gill, Emma Hughes, David Jenkins, Laila Martin, Christine McAllister, Mhairi McIntyre, Leeanne Milne, Erin Murphy, Hilary Peddie, Katharine Sharp, Susan Speirs, Joyce Thompson, Lynne Turner, Simon Hewick, Clare Bradley, Jim Finlayson, Laura O'Keeffe, Meena Virdi, Soo Park, Murdina Bell, Maureen Brown, Linda Macliver, Jackie Quigley, Karen Madill, Daniel Beck, Freddie Burgess, Karen Charlwood, Lauren Finlayson, Nicola Freeman, Margaret McDonald, Carla Pettifor, Karen Sedstrem, Alice Thomson, Ellen Malcolm, Jackie Lindsay, Lisa Stewart, Helen Colhoun, Robert Lindsay, John Olson, Naveed Sattar.

List of supplementary material

Report Supplementary Material 1
LENS Adjudication Charter and Outcome Definitions document

Report Supplementary Material 2 LENS statistical analysis plan

Report Supplementary Material 3 LENS health economics analysis plan

Report Supplementary Material 4 Cost of admission and cost per day

Report Supplementary Material 5 Letter from Glasgow South Diabetes UK Group

Supplementary material can be found on the NIHR Journals Library article page (https://doi.org/10.3310/AAPH5610).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors, and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
AIC	Akaike information criterion
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BIC	Bayesian information criterion
BSE	better seeing eye
CCO	Central Coordinating Office
COVID-19	coronavirus disease 2019
DES	NHS Scotland's Diabetic Eye Screening Programme
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5 Dimension self-report survey
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
ETDRS	Early Treatment Diabetic Retinopathy Study
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GEE	generalised estimating equation
GLM	generalised linear model
GP	general practitioner
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ISRCTN	International Standard Randomised Controlled Trial Number
LDL	low-density lipoprotein
LENS	Lowering Events in Non-proliferative retinopathy in Scotland
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed model for repeated measures
NDPH	Nuffield Department of Population Health
NIHR	National Institute for Health and Care Research
OCT	optical coherence tomography
PIS	Prescribing Information System
PRP	panretinal photocoagulation

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QALY	quality-adjusted life-year
RNIB	Royal National Institute for the Blind
SCI Diabetes	Scottish Care Information – Diabetes
SMR00	Outpatient Appointments and Attendances – Scottish Morbidity Record
SMR01	General Acute Inpatient and Day Case – Scottish Morbidity Record
UACR	urine albumin creatinine ratio
VA	visual acuity
VEGF	vascular endothelial growth factor
VFQ-25	Visual Function Questionnaire-25
WSE	worse seeing eye
WTP	willingness to pay

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Appendix 1 Study treatment mailing error

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Each LENS study treatment pack, and the bottles of study treatment it contained, included a unique pack identifier number (pack ID). Wherever possible, these pack IDs were checked with participants at randomisation (in person) and follow-up (telephone) assessments to confirm that the correct packs of study treatment had been mailed to them (with a new pack of randomised study treatment being mailed to a participant once every 180 days). During a routine follow-up telephone assessment in late 2022, it was ascertained that a participant had received a pack of study treatment with an incorrect pack ID (i.e. a pack ID for study treatment not assigned to them, but assigned to another participant). Urgent investigation confirmed that there had been an inappropriate reordering of data in three mailing order spreadsheets by the drug distribution depot on two consecutive days. This error temporarily affected 28 participants in total, all of whom were immediately contacted. At the time of contact, 18 of the 28 participants had already started taking study treatment from the incorrect packs and 10 had not. The error was explained to the affected participants. No serious adverse events occurred during temporary exposure to study treatment from the erroneous packs. No participants requested to be unmasked, and all members of the research team also remained masked to the assigned treatment arm for these participants. All 28 participants were resupplied with randomised study treatment.

This error was reported to the Research Ethics Committee and to the MHRA, and it was categorised as a Serious Breach.

A detailed retrospective review of the handling of all 808 previous study treatment mailing orders (including both active run-in and randomised study treatment) was conducted by the drug distribution depot to confirm that no other errors in handling mailing order spreadsheets had occurred, and all 75 subsequent orders were prospectively reviewed until the end of the trial.

It was subsequently confirmed that, of the 28 participants temporarily affected by this error, 14 were mailed study treatment packs from the appropriate treatment arm and 14 were mailed study treatment packs from the incorrect treatment arm.

Appendix 2 Pre-specified efficacy assessments

Primary efficacy assessment

The primary assessment will involve an intention-to-treat comparison, among all randomised participants, of the effect of allocation to fenofibrate versus placebo on time to the first occurrence during the scheduled treatment period on the following composite primary outcome: the development of referable diabetic retinopathy or any of the following treatments for diabetic retinopathy: retinal laser therapy, vitrectomy or intravitreal injection of medication due to diabetic retinopathy

Secondary efficacy assessments

Secondary assessments based on clinical events

This will involve intention-to-treat comparisons among all randomised participants of the effects of allocation to fenofibrate versus placebo during the scheduled treatment period on time to the first occurrence of:

- The composite primary outcome in various subgroups:
  - Sex (male vs. female).
  - Age at randomisation (< 60 years vs. ≥ 60 years).
  - Type of diabetes (type 1 diabetes vs. type 2 diabetes and other types).
  - Renal function (randomisation assessment eGFR < 60 vs. ≥ 60 ml/minute/1.73 m^2).
  - HbA1c (screening assessment HbA1c < 70 mmol/mol vs. HbA1c ≥ 70 mmol/mol).
  - First primary outcome in the first year versus subsequent years of follow-up.
- The individual components of the composite primary outcome, namely
  - The development of referable diabetic retinopathy.
  - Treatment for diabetic retinopathy: any of retinal laser therapy, vitrectomy or intravitreal injection of medication due to diabetic retinopathy.

- Any progression of diabetic retinopathy across the NHS Scotland retinopathy grading
- Referable maculopathy
- Macular oedema

Secondary assessments based on questionnaires and visual acuity

This will involve intention-to-treat comparisons among all randomised participants of the effects of allocation to fenofibrate versus placebo during the scheduled treatment period on.

- Visual function (based on the Visual Function Questionnaire-25 questionnaire)
- Quality of life (based on the EuroQol-5 Dimensions questionnaire)
- Visual acuity (based on visual acuity on logarithm of the minimum angle of resolution or Snellen chart score collected during NHS retinal screening)

Health economic assessments

Please refer to the LENS Health Economics Analysis plan for further details.

Tertiary efficacy assessments

Tertiary assessments based on clinical events

This will involve intention-to-treat analyses among all randomised participants of the effects of allocation to fenofibrate versus placebo during the scheduled treatment period on time to the first occurrence of:

- The composite of any major cardiovascular event (defined as myocardial infarction, stroke, coronary or peripheral revascularisation)
- The composite of any non-traumatic lower limb amputation [defined as minor amputation (distal to the ankle) or major amputation (through or proximal to the ankle)]

Tertiary assessments based on biochemistry

Intention-to-treat analyses of the effects of allocation to fenofibrate versus placebo will be conducted on the following measures:

- Urine albumin: creatinine ratio

Appendix 3 Additional tables

TABLE 17 Serious adverse events in run-in grouped by MedDRA system organ class

	Fenofibrate (*N* = 1484)	
Cardiac disorders	4	(0.3%)
Gastrointestinal disorders	4	(0.3%)
General disorders and administration site conditions	2	(0.1%)
Hepatobiliary disorders	1	(0.1%)
Infections and infestations	9	(0.6%)
Injury, poisoning and procedural complications	4	(0.3%)
Metabolism and nutrition disorders	3	(0.2%)
Musculoskeletal and connective tissue disorders	1	(0.1%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1	(0.1%)
Nervous system disorders	1	(0.1%)
Skin and subcutaneous tissue disorders	1	(0.1%)
Surgical and medical procedures	4	(0.3%)
Vascular disorders	1	(0.1%)
Subtotal: any serious adverse event	**35**	**(2.4%)**

Note
Figures are number of participants (%).
Source
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TABLE 18 Recruitment by site

NHS Scotland Health Board	Date of R&D approval	Date of first screening visit	Attended screening visit	Approved to enter run-in	Attended randomisation visit	Randomised
NHS Ayrshire and Arran	3 May 2018	4 December 2018	141	131	116	106
NHS Borders	25 April 2018	2 November 2018	69	61	52	42
NHS Dumfries and Galloway	30 March 2018	17 January 2018	42	38	36	34
NHS Fife	10 April 2018	10 August 2018	271	232	209	195
NHS Forth Valley	17 May 2018	31 October 2018	132	126	112	97
NHS Grampian	14 May 2018	7 November 2018	138	119	112	93
NHS Greater Glasgow and Clyde	15 May 2018	31 October 2018	158	150	129	108
NHS Highland	30 March 2018	20 November 2018	71	61	51	45
NHS Lanarkshire	14 May 2018	23 July 2018	295	272	230	204
NHS Lothian	22 May 2018	17 September 2018	131	114	89	80
NHS Tayside	28 May 2018	31 July 2018	185	180	159	147
Total			**1633**	**1484**	**1295**	**1151**

R&D, research and development.

TABLE 19 Length of follow-up

	Fenofibrate (*N* = 576)		Placebo (*N* = 575)		Total (*N* = 1151)	
Full study						
Mean (SD) duration (years)	3.9	(0.7)	3.9	(0.7)	3.9	(0.7)
Patient years	2231		2234		4465	
Censored at primary outcome						
Mean (SD) duration (years)	3.4	(1.2)	3.2	(1.3)	3.3	(1.3)
Patient years	1957		1855		3812	

TABLE 20 Modalities of retinal screening and information on retinal image quality and the use of mydriasis

Modality	Retinal screening episodes *N*	Additional information	Right eye *N* (%)	Left eye *N* (%)
Routine digital screening	2815	***Image quality***[a]		
		Nerve fibre layer visible	2668 (94.8%)	2654 (94.3%)
		Nerve fibre layer not visible	47 (1.7%)	46 (1.6%)
		Small vessels blurred	25 (0.9%)	26 (0.9%)
		Major arcade vessels just blurred	12 (0.4%)	23 (0.8%)
		Image not gradable/technical failure or no information available about image quality	63 (2.2%)	66 (2.3%)
		Mydriasis		
		Mydriasis used	765 (27.2%)	765 (27.2%)
		Mydriasis not used	2050 (72.8%)	2050 (72.8%)
Slit lamp biomicroscopy	143	Mydriasis used	143 (100.0%)	143 (100.0%)
OCT Surveillance[b]	119	–	–	–

a Image quality in NHS Scotland's DES programme is rated (from best to worst) as: nerve fibre layer visible, nerve fibre layer not visible, small vessels blurred, major arcade vessels just blurred, image not gradable/technical failure; in the case of images being not gradable/technical failure, patients typically have slit lamp biomicroscopy arranged (and may continue with slit lamp biomicroscopy for routine retinal screening thereafter).

b During 2022, DES started to introduce a phased change to the management pathway of patients with referable maculopathy. In the new pathway, referable maculopathy with poor BCVA (Snellen 6/9.5 or worse) leads to OCT imaging in the first instance.

Source

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TABLE 21 Reasons for discontinuing randomised treatment

	Fenofibrate (*N* = 576)		Placebo (*N* = 575)		*p*
Serious adverse event (SAE)					
Cardiac disorders	2	(0.3%)	1	(0.2%)	
Gastrointestinal disorders	2	(0.3%)	3	(0.5%)	
Hepatobiliary disorders	3	(0.5%)	4	(0.7%)	
Infections and infestations	1	(0.2%)	1	(0.2%)	
Injury, poisoning and procedural complications	0	(0.0%)	1	(0.2%)	
Investigations	0	(0.0%)	1	(0.2%)	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5	(0.9%)	5	(0.9%)	
Nervous system disorders	4	(0.7%)	4	(0.7%)	
Renal and urinary disorders	3	(0.5%)	1	(0.2%)	
Surgical and medical procedures	1	(0.2%)	3	(0.5%)	
Subtotal: Any SAE	**21**	**(3.6%)**	**24**	**(4.2%)**	**0.64**
Non-serious adverse event (NSAE)					
Eye disorders	2	(0.3%)	2	(0.3%)	
Gastrointestinal disorders	6	(1.0%)	5	(0.9%)	
Hepatobiliary disorders	0	(0.0%)	1	(0.2%)	
Investigations	1	(0.2%)	3	(0.5%)	
Musculoskeletal and connective tissue disorders	3	(0.5%)	2	(0.3%)	
Nervous system disorders	4	(0.7%)	3	(0.5%)	
Pregnancy, puerperium and perinatal conditions	0	(0.0%)	1	(0.2%)	
Respiratory, thoracic and mediastinal disorders	1	(0.2%)	1	(0.2%)	
Skin and subcutaneous tissue disorders	0	(0.0%)	3	(0.5%)	
Subtotal: Any NSAE	**17**	**(3.0%)**	**21**	**(3.7%)**	**0.51**
Other medical reasons					
Contraindicated medication	0	(0.0%)	2	(0.3%)	
Fall in eGFR	9	(1.6%)	5	(0.9%)	
Unwilling to use contraception	2	(0.3%)	0	(0.0%)	
Subtotal: Other medical reasons	**11**	**(1.9%)**	**7**	**(1.2%)**	**0.34**
Other non-medical reasons					
Patient wishes	29	(5.0%)	30	(5.2%)	
Other reason	54	(9.4%)	42	(7.3%)	
Withdrew consent	3	(0.5%)	2	(0.3%)	
Subtotal: Other non-medical reasons	**86**	**(14.9%)**	**74**	**(12.9%)**	**0.31**
Any reason	**135**	**(23.4%)**	**126**	**(21.9%)**	**0.54**

Note
Figures are number of participants (%).

Source
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TABLE 22 Post hoc subgroup analysis of the primary outcome according to statin use at baseline

	Fenofibrate		Placebo			
	n/*N* (%)	Events per 100 person-years	*n*/*N* (%)	Events per 100 person-years	HR (95% CI)	Heterogeneity/ trend
Statin use						
Statin	97/425 (22.8%)	6.7	121/429 (28.2%)	8.8	0.75 (0.57 to 0.98)	0.25 (p = 0.62)
No statin	34/151 (22.5%)	6.6	47/146 (32.2%)	9.9	0.66 (0.42 to 1.03)	
All participants	**131/576 (22.7%)**	**6.7**	**168/575 (29.2%)**	**9.1**	**0.73 (0.58 to 0.91)**	

TABLE 23 Detailed breakdown of primary outcome

	Fenofibrate (*N* = 576)		Placebo (*N* = 575)			
	N (%)	Events per 100 person-years	*N* (%)	Events per 100 person-years	HR (95% CI)	*p*
Primary composite outcome and its components						
Referable retinopathy	41 (7.1%)	1.9	34 (5.9%)	1.6	1.17 (0.74 to 1.85)	
Referable maculopathy	107 (18.6%)	5.3	149 (25.9%)	7.9	0.66 (0.52 to 0.85)	
Macular oedema	22 (3.8%)	1.0	43 (7.5%)	2.0	0.50 (0.30 to 0.84)	
Referable retinopathy or maculopathy	130 (22.6%)	6.6	168 (29.2%)	9.1	0.72 (0.57 to 0.91)	0.005
Intravitreal injection	9 (1.6%)	0.4	12 (2.1%)	0.5	0.76 (0.32 to 1.81)	
Laser photocoagulation	10 (1.7%)	0.5	17 (3.0%)	0.8	0.50 (0.22 to 1.11)	
Vitrectomy	0 (0.0%)	0.0	4 (0.7%)	0.2		
Treatment for diabetic retinopathy: intravitreal injection, laser photocoagulation or vitrectomy	17 (3.0%)	0.8	28 (4.9%)	1.3	0.58 (0.31 to 1.06)	0.08
Primary composite outcome: referable diabetic retinopathy or treatment for diabetic retinopathy	131 (22.7%)	6.7	168 (29.2%)	9.1	0.73 (0.58 to 0.91)	0.006

TABLE 24 Visual acuity sensitivity analysis (worse eye)

	Number		Baseline-adjusted mean (SE)			
	Fenofibrate	Placebo	Fenofibrate	Placebo	Difference between groups (95% CI)	*p*
VA (worse eye)						
Baseline	548	552	0.16 (0.01)	0.14 (0.01)		
Year 1	394	367	0.16 (0.01)	0.15 (0.01)		
Year 2	233	256	0.18 (0.01)	0.18 (0.01)		
Year 3	365	354	0.17 (0.01)	0.18 (0.01)		
Year 4	376	362	0.19 (0.01)	0.19 (0.01)		
Year 5	169	159	0.20 (0.02)	0.22 (0.02)		
Average of post-randomisation results	555	557	0.18 (0.01)	0.18 (0.01)	0.00 (−0.02 to 0.02)	0.69

SE, standard error.

Note
Analyses of VA are based on BCVA.

TABLE 25 Effect of fenofibrate compared to placebo on renal function, lipids and urine albumin–creatinine ratio in participants with eGFR ≥ 60

	Number		Baseline-adjusted mean (SE)		Difference between groups (95% CI)	*p*
	Fenofibrate	Placebo	Fenofibrate	Placebo		
eGFR – ml/minute/1.73 m²						
Baseline	446	444	93.8 (0.7)	93.5 (0.7)		
Year 1	345	345	81.9 (0.5)	90.9 (0.5)		
Year 2	351	350	80.6 (0.5)	90.3 (0.5)		
Year 3	359	363	80.1 (0.6)	88.3 (0.6)		
Year 4	320	316	80.0 (0.6)	88.5 (0.6)		
Year 5	116	115	80.1 (0.9)	87.3 (0.9)		
Average of post-randomisation results	441	442	80.5 (0.5)	89.1 (0.5)	−8.5 (−9.8 to −7.2)	< 0.001
Total cholesterol – mmol/l						
Baseline	442	436	4.12 (0.05)	4.13 (0.05)		
Year 1	297	303	3.93 (0.03)	4.15 (0.03)		
Year 2	297	292	3.93 (0.04)	4.18 (0.04)		
Year 3	308	320	3.97 (0.04)	4.17 (0.04)		
Year 4	262	268	4.03 (0.04)	4.10 (0.04)		
Year 5	77	70	3.98 (0.07)	4.08 (0.08)		
Average of post-randomisation results	438	435	3.97 (0.03)	4.13 (0.03)	−0.16 (−0.25 to −0.08)	< 0.001
Non-HDL cholesterol – mmol/l						
Baseline	440	433	2.79 (0.04)	2.79 (0.05)		
Year 1	272	280	2.63 (0.04)	2.86 (0.04)		
Year 2	275	274	2.64 (0.04)	2.86 (0.04)		
Year 3	285	300	2.70 (0.04)	2.86 (0.04)		
Year 4	243	247	2.74 (0.04)	2.77 (0.04)		
Year 5	73	66	2.69 (0.07)	2.74 (0.08)		
Average of post-randomisation results	419	416	2.68 (0.03)	2.82 (0.03)	−0.14 (−0.22 to −0.06)	0.001
HDL cholesterol – mmol/l						
Baseline	440	433	1.32 (0.02)	1.32 (0.02)		
Year 1	273	280	1.28 (0.01)	1.30 (0.01)		
Year 2	275	274	1.28 (0.01)	1.29 (0.01)		
Year 3	285	301	1.27 (0.01)	1.29 (0.01)		
Year 4	243	247	1.28 (0.01)	1.31 (0.01)		
Year 5	73	66	1.28 (0.02)	1.33 (0.02)		
Average of post-randomisation results	419	416	1.28 (0.01)	1.30 (0.01)	−0.03 (−0.05 to 0.00)	0.02

continued

TABLE 25 Effect of fenofibrate compared to placebo on renal function, lipids and urine albumin–creatinine ratio in participants with eGFR ≥ 60 (*continued*)

	Number		Baseline-adjusted mean (SE)		Difference between groups (95% CI)	*p*
	Fenofibrate	Placebo	Fenofibrate	Placebo		
Triglycerides – mmol/l						
Baseline	442	436	1.54 (0.04)	1.51 (0.04)		
Year 1	222	216	1.20 (0.03)	1.51 (0.03)		
Year 2	220	205	1.22 (0.03)	1.46 (0.04)		
Year 3	223	230	1.25 (0.03)	1.50 (0.03)		
Year 4	184	183	1.26 (0.04)	1.47 (0.04)		
Year 5	48	40	1.37 (0.09)	1.62 (0.11)		
Average of post-randomisation results	352	341	1.26 (0.03)	1.51 (0.03)	−16.6% (−21.3% to −11.6%)	< 0.001
HbA1c – mmol/mol						
Baseline	415	416	66.7 (0.8)	66.9 (0.8)		
Year 1	356	367	66.1 (0.5)	67.0 (0.5)		
Year 2	349	344	67.2 (0.7)	67.8 (0.7)		
Year 3	357	359	66.5 (0.7)	66.8 (0.7)		
Year 4	315	317	67.3 (0.7)	67.3 (0.7) 66.3 (1.4)		
Year 5	112	109	67.2 (1.4)			
Average of post-randomisation results	440	440	66.9 (0.6)	67.0 (0.6)	−0.2 (−1.7 to 1.4)	0.84
HbA1c – %						
Baseline	415	416	8.26 (0.07)	8.27 (0.07)		
Year 1	356	367	8.20 (0.05)	8.28 (0.05)		
Year 2	349	344	8.30 (0.06)	8.35 (0.06)		
Year 3	357	359	8.24 (0.06)	8.26 (0.06)		
Year 4	315	317	8.31 (0.07)	8.31 (0.07)		
Year 5	112	109	8.30 (0.13)	8.22 (0.13)		
Average of post-randomisation results	440	440	8.27 (0.05)	8.28 (0.05)	−0.01 (−0.16 to 0.13)	0.84
Urine albumin–creatinine ratio – mg/g						
Baseline	236	236	12.8 (1.1)	13.5 (1.2)		
Year 1	209	201	9.8 (0.7)	10.5 (0.8)		
Year 2	192	175	9.3 (0.9)	11.4 (1.1)		
Year 3	204	212	10.4 (0.9)	13.1 (1.1)		
Year 4	180	182	11.2 (1.0)	13.9 (1.3)		
Year 5	49	54	14.3 (2.3)	13.0 (2.2)		
Average of post-randomisation results	353	364	10.9 (0.8)	12.3 (0.9)	−11.7% (−27.4% to 7.3%)	0.21

SE, standard error.

Note
Values are arithmetic means (SE) for eGFR, total cholesterol, non-HDL cholesterol, HDL cholesterol and HbA1c; geometric means (approximate SE) for triglycerides and urine albumin to creatinine ratio. For triglycerides and the urine albumin to creatinine ratio, the difference reflects a percentage difference.

TABLE 26 Effect of fenofibrate compared to placebo on renal function, lipids and urine albumin–creatinine ratio in participants with eGFR < 60

	Number		Baseline-adjusted mean (SE)			
	Fenofibrate	Placebo	Fenofibrate	Placebo	Difference between groups (95% CI)	*p*
eGFR – ml/minute/1.73 m²						
Baseline	130	131	63.3 (1.1)	65.7 (1.0)		
Year 1	115	118	54.7 (0.7)	62.0 (0.7)		
Year 2	109	108	53.5 (0.9)	59.9 (0.9)		
Year 3	116	110	53.0 (1.0)	59.2 (1.0)		
Year 4	101	100	53.0 (1.1)	58.6 (1.1)		
Year 5	35	40	51.0 (1.7)	58.0 (1.6)		
Average of post-randomisation results	128	130	53.0 (0.9)	59.5 (0.9)	−6.5 (−8.9 to −4.1)	< 0.001
Total cholesterol – mmol/l						
Baseline	130	131	3.79 (0.08)	3.82 (0.07)		
Year 1	100	95	3.80 (0.05)	3.78 (0.05)		
Year 2	89	91	3.86 (0.06)	3.80 (0.06)		
Year 3	92	87	3.81 (0.06)	3.81 (0.06)		
Year 4	82	80	3.90 (0.08)	3.76 (0.08)		
Year 5	20	26	3.89 (0.13)	3.77 (0.12)		
Average of post-randomisation results	127	126	3.85 (0.05)	3.78 (0.05)	0.07 (−0.08 to 0.22)	0.38
Non-HDL cholesterol – mmol/l						
Baseline	128	127	2.55 (0.07)	2.58 (0.07)		
Year 1	93	82	2.58 (0.05)	2.48 (0.05)		
Year 2	87	79	2.67 (0.07)	2.56 (0.07)		
Year 3	85	74	2.61 (0.07)	2.55 (0.07)		
Year 4	76	67	2.72 (0.08)	2.49 (0.08)		
Year 5	18	24	2.65 (0.13)	2.44 (0.11)		
Average of post-randomisation results	120	116	2.65 (0.05)	2.51 (0.05)	0.14 (−0.01 to 0.29)	0.07
HDL cholesterol – mmol/l						
Baseline	128	127	1.25 (0.04)	1.24 (0.03)		
Year 1	93	82	1.22 (0.02)	1.23 (0.02)		
Year 2	87	79	1.21 (0.02)	1.23 (0.02)		
Year 3	85	74	1.19 (0.02)	1.21 (0.02)		
Year 4	76	67	1.20 (0.03)	1.24 (0.03)		
Year 5	18	24	1.11 (0.05)	1.27 (0.04)		
Average of post-randomisation results	120	116	1.19 (0.02)	1.24 (0.02)	−0.05 (−0.10 to 0.00)	0.07

continued

TABLE 26 Effect of fenofibrate compared to placebo on renal function, lipids and urine albumin–creatinine ratio in participants with eGFR < 60 (*continued*)

	Number		Baseline-adjusted mean (SE)			
	Fenofibrate	Placebo	Fenofibrate	Placebo	Difference between groups (95% CI)	*p*
Triglycerides – mmol/l						
Baseline	129	127	1.73 (0.08)	1.66 (0.08)		
Year 1	68	60	1.60 (0.07)	1.61 (0.07)		
Year 2	62	58	1.65 (0.08)	1.61 (0.08)		
Year 3	60	58	1.65 (0.08)	1.74 (0.09)		
Year 4	52	42	1.61 (0.09)	1.71 (0.10)		
Year 5	10	17	1.67 (0.28)	1.61 (0.21)		
Average of post-randomisation results	97	89	1.64 (0.08)	1.66 (0.07)	−1.2% (−13.0% to 12.2%)	0.85
HbA1c – mmol/mol						
Baseline	123	123	65.2 (1.3)	64.4 (1.4)		
Year 1	111	113	65.5 (1.0)	66.4 (1.0)		
Year 2	102	106	66.0 (1.3)	66.9 (1.2)		
Year 3	108	109	65.6 (1.3)	66.4 (1.3)		
Year 4	97	96	66.4 (1.4)	65.5 (1.4)		
Year 5	30	39	66.5 (2.1)	65.4 (1.9)		
Average of post-randomisation results	128	129	66.0 (0.9)	66.1 (0.9)	−0.1 (−2.7 to 2.5)	0.93
HbA1c – %						
Baseline	123	123	8.11 (0.12)	8.04 (0.13)		
Year 1	111	113	8.15 (0.09)	8.23 (0.09)		
Year 2	102	106	8.19 (0.11)	8.27 (0.11)		
Year 3	108	109	8.15 (0.12)	8.23 (0.12)		
Year 4	97	96	8.22 (0.13)	8.14 (0.13)		
Year 5	30	39	8.24 (0.19)	8.13 (0.17)		
Average of post-randomisation results	128	129	8.19 (0.09)	8.20 (0.08)	−0.01 (−0.25 to 0.23)	0.93
UACR – mg/g						
Baseline	76	74	20.9 (4.0)	31.8 (6.3)		
Year 1	80	66	18.8 (2.3)	22.6 (3.2)		
Year 2	69	61	23.6 (2.9)	34.0 (4.5)		
Year 3	66	70	28.7 (4.3)	33.3 (5.3)		
Year 4	63	55	27.7 (5.3)	37.2 (7.5)		
Year 5	17	20	34.0 (7.4)	25.9 (6.3)		
Average of post-randomisation results	109	110	26.1 (3.0)	30.1 (3.6)	−13.4% (−37.5% to 20.1%)	0.39

SE, standard error.

Note
Values are arithmetic means (SE) for eGFR, total cholesterol, non-HDL cholesterol, HDL cholesterol and HbA1c; geometric means (approximate SE) for triglycerides and urine albumin to creatinine ratio. For triglycerides and the urine albumin to creatinine ratio, the difference reflects a percentage difference.

TABLE 27 Deaths after randomisation

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)
Cardiovascular death	15 (2.6%)	15 (2.6%)
Non-cardiovascular death	20 (3.5%)	23 (4.0%)
Unknown cause	0 (0.0%)	0 (0.0%)
All-cause death	35 (6.1%)	38 (6.6%)

Note
Figures are number of participants (%).

TABLE 28 Eye events not due to diabetic retinopathy

	Fenofibrate (*N* = 576)	Placebo (*N* = 575)
Macular oedema	2 (0.3%)	3 (0.5%)
Treatment (intravitreal injection, laser, vitrectomy)	6 (1.0%)	4 (0.7%)

Note
Figures are number of participants (%).

TABLE 29 Unit costs and sources

Resource item	How measured	Source of measurement	Unit cost[a]	Source of valuation
Study medication	Prescribed quantity and dose	Study database	£4.77 (Scottish tariff) 2.69 (English Drug Tariff) 28 pack (200 mg micronised capsules)	Drug tariff[25,26]
Biochemistry tests	Number of tests	Study database, linked from SCI-Diabetes	£0.90 per test	Scottish Health Service Costs[27]
GP time	Time associated with request and review of biochemistry tests	Assumption (5 minutes)	£178 per hour	Unit costs of Health and Social Care[28]
Practice nurse time	Time to obtain sample	Assumption (5 minutes)	£53 per hour	Unit costs of Health and Social Care[28]
Hospital admissions	Number of episodes, specialty, associated ICD-10 and OPCS codes, length of stay.	Linked SMR01 data	Variable: Scottish Health Service costs by specialty	Scottish Health Service costs[27]
Hospital outpatient attendances	Number of episodes, specialty	Linked SMR00 data	Variable: Scottish Health Service costs by specialty	Scottish Health Service costs[27]
Retinal Screening episodes	Number of episodes	DES	£44.47 (inflated from £35.98 in 2013–4 prices)	Scotland *et al.*, 2016[28,29]
OCT monitoring of maculopathy (M2)	Number of episodes	DES	£41.03 (marginal cost inflated from £33.13 in 2012–3 prices)	Scotland *et al.*, 2016[28,29]
Slit lamp examination (screening programme)	Number of episodes	DES	£36.14 (marginal cost – inflated from £27.29 in 2009–10 prices)	Olson *et al.*, 2013[28,30]
Prescribed medicines	Prescribed medicines, dose, quantities	PIS	Variable	NHS Drug Tariff[25]

continued

TABLE 29 Unit costs and sources (*continued*)

Resource item	How measured	Source of measurement	Unit cost[a]	Source of valuation
Diabetic retinopathy-related interventions				
Ophthalmology outpatient visit	Number of visits	DES and SCI diabetes systems; trial-specific questionnaires; supporting data from local NHS health records (provided by Local Clinical Centres); SMR01; and SMR00.	£232 (Scottish average) £154 (English average) inflated from £144 in 2021–2 prices	Scottish Health Service Costs, Table R044[27]/NHS Reference costs[31]
Panretinal laser photocoagulation session	Assumption regarding expected number of sessions		£164 inflated from £153 in 2021–2 prices	NHS Reference costs (BZ86)[31]
Administration of anti-VEGF injection	Assumption regarding expected number of injections		£164 inflated from £153 in 2021–2 prices	NHS Reference costs (BZ86)[31]
Vitrectomy	Number of events		£2573 inflated from £2404 in 2021–2 prices	NHS Reference costs (BZ83)[31]
Anti-VEGF drugs	Number of administrations		£551 – Ranibizumab (Lucentis); £816 – Aflibercept (Eylea)	BNF (list prices)[25]

BNF, *British National Formulary*; ICD, International Classification of Diseases; OPCS, Office of Population Censuses abd Surveys Classification of Interventions and Procedures.
a Values reflect latest available 2022–3 prices at time of analysis, except fenofibrate which reflects latest available 2024 price.

TABLE 30 Measures of statistical fit of alternative parametric curves for time to referable diabetic retinopathy (R3 or R4), with or without referable maculopathy (M2)

Parametric distribution	AIC	BIC	Average
Exponential	502.77	512.87	507.82
Weibull	504.71	519.85	512.28
Generalised gamma	506.59	526.79	516.69
Gompertz	504.26	519.41	511.84
Log normal	507.86	523.00	515.43
Log logistic	504.83	519.98	512.40

TABLE 31 Statistical fit of alternative parametric distributions for time to referable maculopathy

Parametric distribution	AIC	BIC	Average
Exponential	1794.56	1804.66	1799.61
Weibull	1789.72	1804.87	1797.29
Generalised gamma	1789.78	1809.98	1799.88
Gompertz	1795.87	1811.01	1803.44
Log normal	1801.23	1816.38	1808.80
Log logistic	1792.39	1807.53	1799.96

TABLE 32 Summary of resource use by treatment allocation group full follow-up period

Resource use category	Fenofibrate (*N* = 576)	Placebo (*N* = 575)	All participants (*N* = 1151)
Screening episodes, mean (SD)	2.66 (1.11)	2.69 (1.13)	2.67 (1.12)
Digital retinal screening	2.48 (1.06)	2.41 (1.09)	2.44 (1.07)
OCT	0.08 (0.42)	0.13 (0.58)	0.11 (0.51)
Slit lamp	0.11 (0.46)	0.14 (0.51)	0.12 (0.49)
Biochemistry tests, mean (SD)	26.14 (13.50)	25.51 (12.74)	25.82 (13.12)
Albumin/creatinine	2.44 (2.08)	2.37 (1.98)	2.40 (2.03)
HDL cholesterol	3.45 (2.06)	3.35 (2.04)	3.40 (2.05)
HbA1c	5.65 (2.85)	5.72 (2.84)	5.69 (2.84)
Triglycerides	2.65 (2.29)	2.54 (2.27)	2.60 (2.28)
Creatinine	8.16 (7.02)	7.77 (6.31)	7.96 (6.68)
Total cholesterol (mmol/l)	3.79 (2.09)	3.76 (2.01)	3.78 (2.05)
Prescribing episodes (episodes), mean (SD)	129.38 (71.17)	128.95 (71.08)	129.17 (71.09)
Blood pressure	32.33 (29.87)	30.82 (29.03)	31.58 (29.45)
Diabetes	67.91 (38.46)	67.81 (38.07)	67.86 (38.25)
Other	8.23 (17.17)	8.72 (16.39)	8.48 (16.78)
Oedema	1.45 (5.95)	1.82 (6.49)	1.64 (6.22)
Statins	19.45 (13.07)	19.78 (12.55)	19.62 (12.81)
Outpatient visits, n (%)	477 (82.8%)	471 (81.9%)	948 (82.4%)
Specialties of interest	351 (60.9%)	350 (60.9%)	701 (60.9%)
Ophthalmology	151 (26.2%)	152 (26.4%)	303 (26.3%)
Others	369 (64.1%)	342 (59.5%)	711 (61.8%)
Outpatient visits, mean (SD)	8.33 (11.09)	9.04 (12.27)	8.68 (11.69)
Specialties of interest	3.27 (4.70)	3.73 (5.31)	3.50 (5.01)
Ophthalmology	0.97 (2.78)	1.01 (2.78)	0.99 (2.78)
Others	4.09 (8.12)	4.30 (9.10)	4.19 (8.62)
Inpatient/day case admissions, n (%)	247 (42.9%)	247 (43.0%)	494 (42.9%)
Specialties of interest	175 (30.4%)	162 (28.2%)	337 (29.3%)
Others	142 (24.7%)	143 (24.9%)	285 (24.8%)
Inpatient/day case (episodes), mean (SD)	1.85 (4.43)	1.96 (3.80)	1.90 (4.13)
Specialties of interest	1.00 (2.08)	1.24 (2.97)	1.12 (2.57)
Others	0.85 (3.50)	0.72 (1.92)	0.79 (2.82)
Inpatients/day case (continuous inpatient stays), mean (SD)	1.29 (3.62)	1.24 (2.32)	1.27 (3.04)
Specialties of interest	0.58 (1.05)	0.66 (1.43)	0.62 (1.26)
Others	0.71 (3.28)	0.58 (1.59)	0.65 (2.58)

TABLE 33 Model input parameters

Parameters	Value (SD)	SE or (95% CI)	Distributional form	Source
Settings				LENS trial
Start age	61 (12.4)		First-order uncertainty	
Proportion male	0.73		First-order uncertainty	
Cycle length years	0.5			
Cycle length days	182.63			
Discount rate (costs)	0.035			
Discount rate (benefits)	0.035			
Clinical efficacy inputs (hazards expressed per 6-month model cycle)				
Non-referable to referable DR, with or without concurrent referable maculopathy (exponential function)				LENS trial
Hazard rate	0.006	0.004 to 0.009	Multivariate normal (log scale)	
HR (Fenofibrate)[a]	1.309	0.746 to 2.295		
Non-referable to referable maculopathy, alone (Weibull function)				LENS trial
Scale	0.052	0.004 to 0.068	Multivariate normal (log scale)	
Shape	0.857	0.761 to 0.965		
HR (Fenofibrate)[a]	0.661	0.513 to 0.851		
HR for the primary composite outcome (from parametric Weibull regression)				LENS trial
HR (Fenofibrate)[b]	0.73	0.58 to 0.92	Log normal	
Referable maculopathy to referable DR (exponential function)				LENS trial
Hazard rate	0.020	0.012 to 0.035	Multivariate normal (log scale)	
HR (Fenofibrate)	1.457	0.665 to 3.194		
Referable DR to referable maculopathy (exponential function)				LENS trial
Hazard rate	0.036	0.009 to 0.144	Multivariate normal (log scale)	
HR (Fenofibrate)	0.740	0.104 to 5.254		
Referable maculopathy to treatment for referable DMO (exponential function)				LENS trial
Hazard rate	0.016	0.009 to 0.030	Multivariate normal (log scale)	
HR (Fenofibrate)	0.682	0.237 to 1.963		
Referable DR to treatment for referable DR with standard care (log-normal distribution)				LENS trial
Constant	0.679	−0.425 to 1.784	Multivariate normal (log scale)	
lnSigma	0.951	0.560 to 1.341		
Referable DR to treatment for referable DR with fenofibrate (log-normal distribution)				LENS trial
Constant	2.345	1.291 to 3.399	Multivariate normal (log scale)	
lnSigma	0.445	−0.076 to 0.967		
Hazard for fenofibrate discontinuation	0.034	0.003	Normal	LENS trial
Probability of death	Age- and sex-specific UK life tables		NA	Office for National Statistics[54]

TABLE 33 Model input parameters (*continued*)

Parameters	Value (SD)	SE or (95% CI)	Distributional form	Source
Standardised mortality ratio (type 1 diabetes, male)	2.95	2.74 to 3.18	Log normal	O'Reilly *et al.*[42]
Standardised mortality ratio (type 1 diabetes, female)	4.62	4.20 to 5.08	Log normal	O'Reilly *et al.*[42]
Standardised mortality ratio (type 2 diabetes, male)	1.36	1.28 to 1.45	Log normal	Collier *et al.*[43]
Standardised mortality ratio (type 2 diabetes, female)	1.48	1.38 to 1.59	Log normal	Collier *et al.*[43]
Proportion RDR-treated patients receiving PRP	1		NA	LENS trial
Proportion PRP-treated patients also receiving vitrectomy	0.11	0.06	Beta (α = 3; β = 24)	LENS trial
Proportion of fenofibrate prescriptions that are once daily	0.72	0.005	Beta (α = 6392; β = 2483)	LENS trial
Proportion of patients first developing RDR that have concurrent referable maculopathy at time of referral	0.34	0.07	Beta (α = 17; β = 33)	LENS trial
Proportion of patients developing RDR that are treated immediately on progression	0.04	0.02	Beta (α = 3; β = 72)	LENS trial
Proportion of patients developing referable maculopathy that are treated immediately on progression	0.015	0.007	Beta (α = 4; β = 262)	LENS trial
Proportion of RDR-treated patients requiring bilateral treatment[a]	0.9	0.09 (assumed)	Beta	Expert opinion
Proportion of referable maculopathy-treated patients requiring bilateral treatment[a]	0.4	0.04 (assumed)	Beta	Expert opinion
Health state utility values				
Baseline utility	0.811 (0.23)		First-order uncertainty	LENS trial
Utility by health state and VA status				
Constant	0.142	0.037	Multivariate normal	
Time from baseline (days)	−0.00003	0.00001		
Post referable disease	−0.020	0.011		LENS trial
Baseline age	−0.0013	0.0005		
Baseline EQ-5D	0.885	0.024		
Utility coefficient for log ETDRS letters in BSE	0.1	0.027	Normal	Brazier *et al.*[44]
Utility coefficient for log ETDRS letters in WSE	0.042	0.014	Normal	Brazier *et al.*[44]
Resource use and costs				
Fenofibrate micronised 200 mg capsules (price per pack)	£4.77		NA	Scottish Drug Tariff[26]
Fenofibrate micronised 200 mg capsules (pack size)	28		NA	
Fenofibrate 67 mg micronised capsules (price per pack)	23.23		NA	Scottish Drug Tariff[26]

continued

TABLE 33 Model input parameters (*continued*)

Parameters	Value (SD)	SE or (95% CI)	Distributional form	Source
Fenofibrate 67 mg micronised capsules (pack size)	90			
Cost of fenofibrate treatment per cycle (assuming 200 mg every other day for those with reduced eGFR)	26.76		Calculated	
Cost of fenofibrate treatment per cycle (assuming 67 mg every day for those with reduced eGFR)	47.14		Calculated	
Health state background Health and Care Research Unit costs	864.10	39.02	Normal	LENS trial
Average screening costs per 6-month model cycle by cycle number and referable maculopathy status (Log e linear predictors)				
Constant	2.53	0.027	Multivariate normal	
Cycle number (6-monthly)	0.02	0.005		LENS trial
Referable maculopathy	0.31	0.036		
Cost per ophthalmology outpatient appointment (Scotland)	232	23.20 (assumed)	Normal	Scottish Health Service costs[27]
Cost per ophthalmology outpatient appointment (England)	133		NA	NHS Reference costs[31]
Cost per PRP session (Scotland)	232	23.20 (assumed)	Normal	Scottish Health Service costs[27]
Cost per PRP session (England)	159		NA	NHS Reference costs[31]
Cost of vitrectomy (unilateral)	2573	257.30 (assumed)	Normal	NHS Reference costs[31]
Cost of aflibercept (per injection)	816		NA	BNF[25]
Cost of ranibizumab (per injection)	551		NA	BNF[25]
Cost per administration of an anti-VEGF injection (Scotland)	232	23.20 (assumed)	Normal	Scottish Health Service costs[27]
Cost per administration of an anti-VEGF injection (England)	159		NA	NHS Reference Costs[31]
Number of anti-VEGF injections in year 1 of treatment for DMO	6.3	0.13 (approximated)	Gamma	Sivaprasad *et al.*[32]
Number of anti-VEGF injections in year 2 of treatment for DMO	2.9	0.115 (approximated)	Gamma	Sivaprasad *et al.*[32]
Number of anti-VEGF injections years 3–5	2.45	0.25	Gamma	Glassman *et al.*[40]
Number of additional outpatient appointments for anti-VEGF treatment monitoring	1.0		NA	Assumption
Number of additional outpatient appointments for PRP treatment monitoring	1.0		NA	Assumption
Number of PRP sessions to achieve stable PDR (assumed over 12 weeks)	2.77	0.015 (approximated)	Gamma	Sivaprasad *et al.*[45]

DMO, diabetic macular oedema; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; RDR, referable diabetic retinopathy.
a Applied only in scenario analysis.
b Applied in the base case.

TABLE 34 Model based cost-effectiveness scenario analysis

Parameter/assumption	Base case	Scenario	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case			6	0.015	406
1. Time horizon	10 years	(a) 5 years	82	0.007	12,216
		(b) 20 years	−73	0.024	Dominant
		(c) 30 years	−79	0.028	Dominant
2. Time to referable DR and referable maculopathy	Single overall treatment effect	Cause-specific treatment effects	40	0.014	2895
3. Time to referable maculopathy	Weibull curve	Exponential curve	−2	0.015	Dominant
4. Treatment effect of fenofibrate	Continuous proportional hazards	Waned from 5 years	111	0.011	10,014
5. Time from DR to DR treatment curve	Log normal	Exponential	3	0.016	165
6. Modelled visual losses	Applied to WSE	Applied to BSE	6	0.015	399
		Applied to both eyes	6	0.016	366
7. Disutility of VA loss	Based on EQ-5D	Based on VFQ-25	6	0.017	351
8. Treatment costs for DMO and proliferative DR	Applied for unilateral disease	Inflated by 40% and 90%, respectively, to account for bilateral treatment	−95	0.015	Dominant
9. Anti-VEGF drug costs	NHS indicative price of aflibercept (£816 per vial)	Discounted by 30%	67	0.015	4588
		Discounted by 40%	87	0.015	5982
		Discounted by 50%	107	0.015	7376
		Discounted by 60%	127	0.015	8770
		Discounted by 70%	148	0.015	10,163
10. Fenofibrate dosing for reduced eGFR	200 mg every second day	67 mg every day	115	0.015	7888
11. Ophthalmology referral/treatment costs	Scottish specialty costs	English HRG-based NHS reference costs	44	0.015	2997
12. Fenofibrate price	Scottish Drug Tariff (£4.77)	English Drug Tariff (£2.69)	−108	0.015	Dominant
13. Ophthalmology referral/treatment costs and fenofibrate price	Scottish specialty cost and Scottish Drug Tariff	English HRG-based NHS reference costs and English Drug Tariff	−70	0.015	Dominant
14. Fenofibrate additional monitoring costs	Assumed negligible	Additional check of renal function 1–2 months after starting fenofibrate (accounting for GP and nurse time)	25	0.015	1731

DMO, diabetic macular oedema; DR, diabetic retinopathy; HRG, healthcare resource group; VFQ, National Eye Institute Visual Function Questionnaire.

Appendix 4 Costing methods

Method of costing prescription data

The linked data set included community prescribing episodes for each patient that occurred during the LENS trial follow-up period (post randomisation, up to the date of final follow-up), with variables denoting the dispensing month, the approved drug name, and corresponding BNF code for each item prescribed. The unique name for each drug, along with its specifications, was obtained by mapping from the BNF code (BNF SNOMED mapping). Once the unique name and its specifications were determined, the appropriate dose for the indicated use was attached to each drug. For most drugs, it was assumed they were taken according to the recommended dose, starting from the first prescription date. Accordingly, an interval of time was calculated to derive the number of drug units consumed during the period between consecutive prescribing dates, and associated costs were then estimated using Drug Tariff prices or NHS indicative prices for proprietary medicines. In cases where the recommended dose was not provided in the BNF, the dose was sourced from relevant literature.

Method of costing inpatient and day case admissions

For reporting purposes, hospital inpatient and day case activity costs were divided into clinically relevant specialties in which admission could potentially be associated with the study intervention, and all other specialties. A specialty inpatient episode refers to a patient's stay in a specific hospital specialty, from admission to discharge (home, or to another specialty of hospital). This term helps compare costs across acute specialties. If a patient transfers between specialties within the same hospital, they are counted as part of a continuous inpatient stay or hospital spell, with multiple episodes across different specialties.

Clinically relevant specialties that were a priori specified in the Health Economics Analysis Plan included General Medicine, Acute Medicine, Cardiology, Endocrinology and Diabetes, Diabetes, Renal Medicine, Medical Ophthalmology, Vascular Surgery, Cardiac Surgery and Ophthalmology. The unit cost for an inpatient episode was sourced from Table R040 of the Scottish Health Service Cost Book. We used fixed and variable cost percentage splits, as reported by the Technical Advisory Group on Resource Allocation in Scotland, when applying published unit costs to episodes. *Report Supplementary Material 4* presents the percentage splits. Practically, the percentage cost splits represent the proportion of specialty episode costs that are considered fixed, and applicable per episode for each specialty, and the proportion that is considered variable by length of stay under each specialty. The variable component was divided by the average length of stay for each specialty, as reported in Table R040 of the Cost Book, and used to cost observed admitted patient care on per diem basis.

Appendix 5 Additional figures

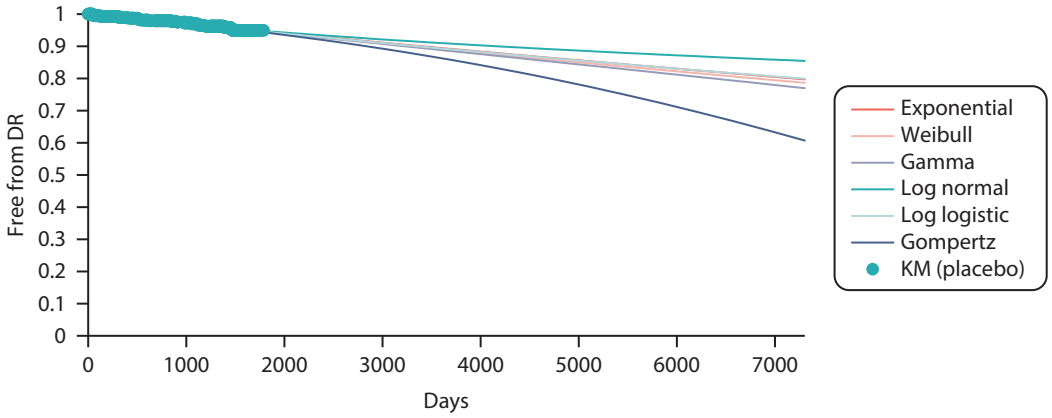

FIGURE 15 Time to referable diabetic retinopathy (R3 or R4), with or without referable maculopathy (M2), for the placebo arm of LENS. DR, diabetic retinopathy; KM, Kaplan–Meier.

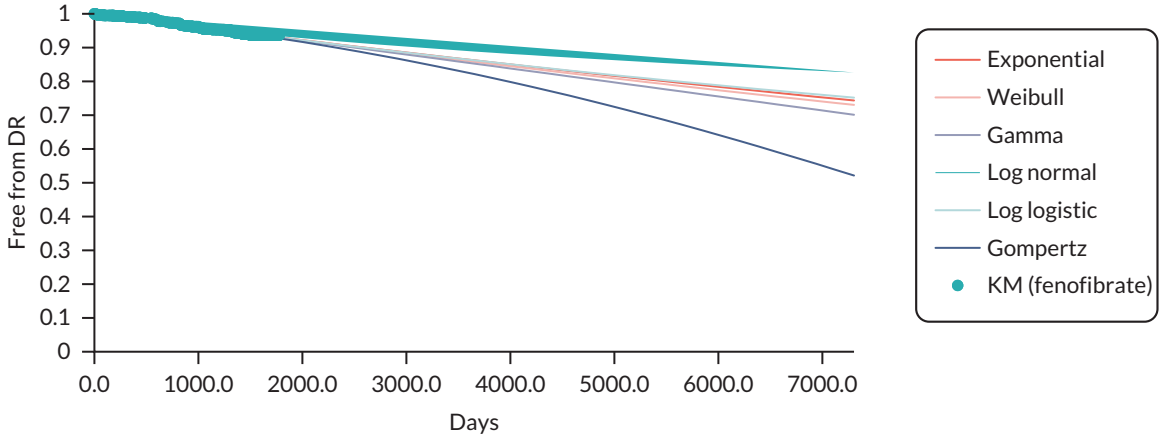

FIGURE 16 Time to referable diabetic retinopathy (R3 or R4), with or without referable maculopathy (M2), for the fenofibrate arm of LENS. DR, diabetic retinopathy; KM, Kaplan–Meier.

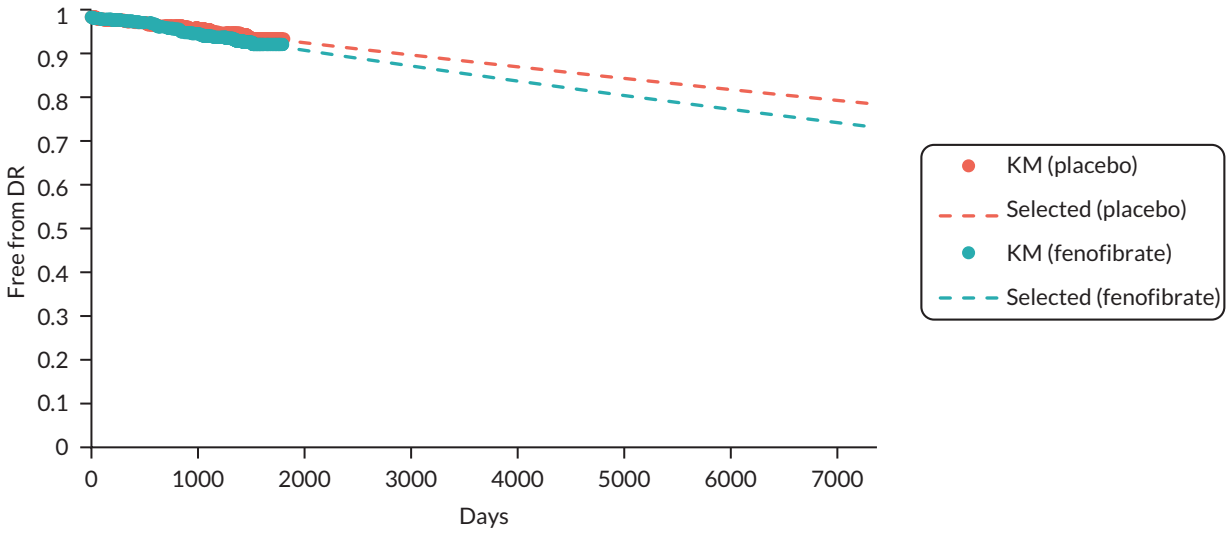

FIGURE 17 Selected exponential curves for modelling time to referable diabetic retinopathy (R3 or R4), with or without referable maculopathy (M2), in the placebo and fenofibrate arms. DR, diabetic retinopathy; KM, Kaplan–Meier.

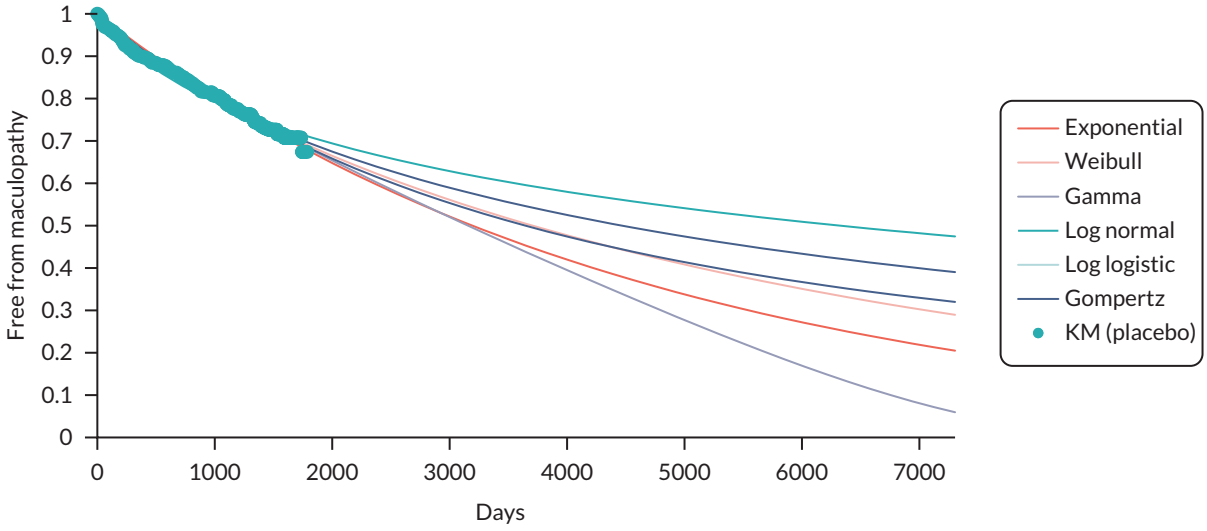

FIGURE 18 Time to referable maculopathy (M2) alone, for the placebo arm of LENS. KM, Kaplan–Meier.

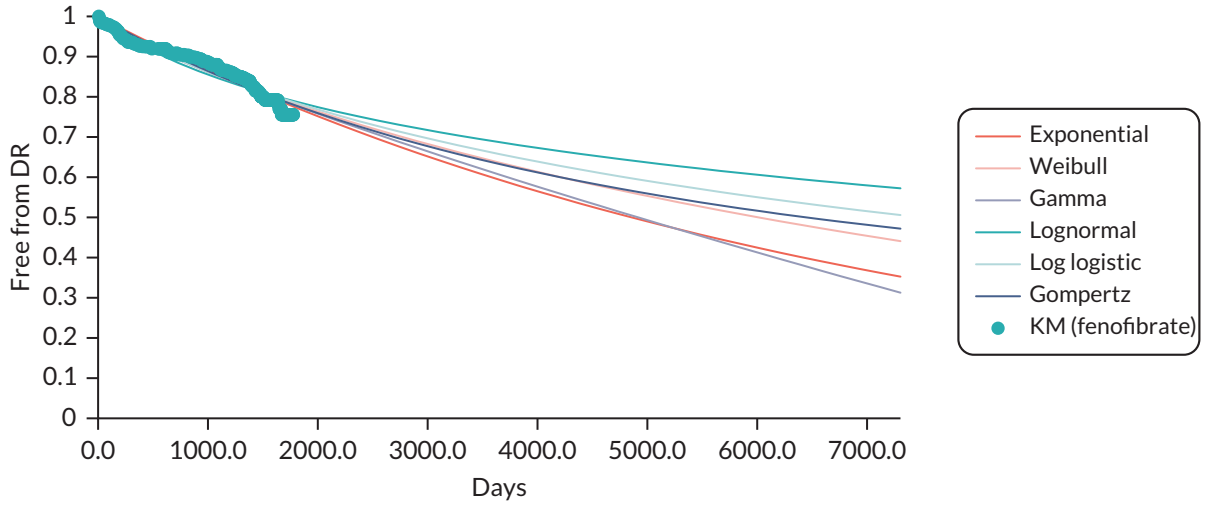

FIGURE 19 Time to referable maculopathy (M2) alone, for the fenofibrate arm of LENS. DR, diabetic retinopathy; KM, Kaplan–Meier.

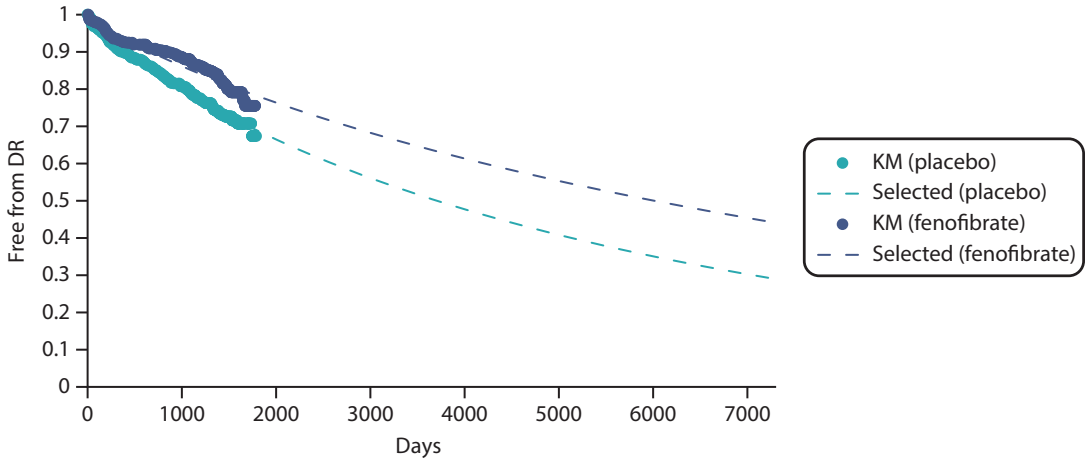

FIGURE 20 Selected Weibull curves informing transitions to referable maculopathy (M2) alone, for the placebo and fenofibrate arms. DR, diabetic retinopathy; KM, Kaplan–Meier.

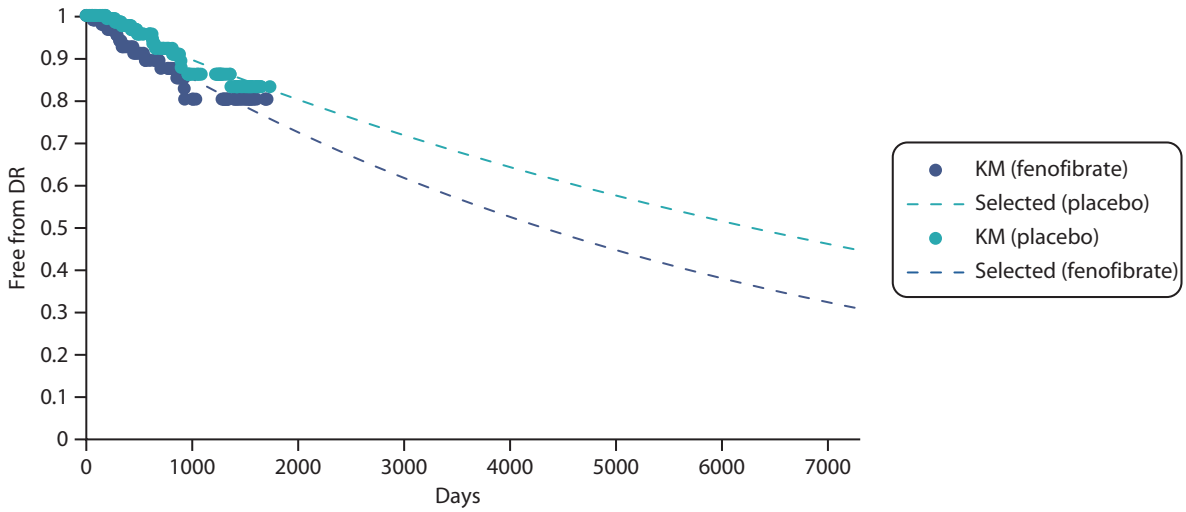

FIGURE 21 Selected exponential curves informing transition from referable maculopathy to referable diabetic retinopathy (R3/R4). DR, diabetic retinopathy; KM, Kaplan–Meier.

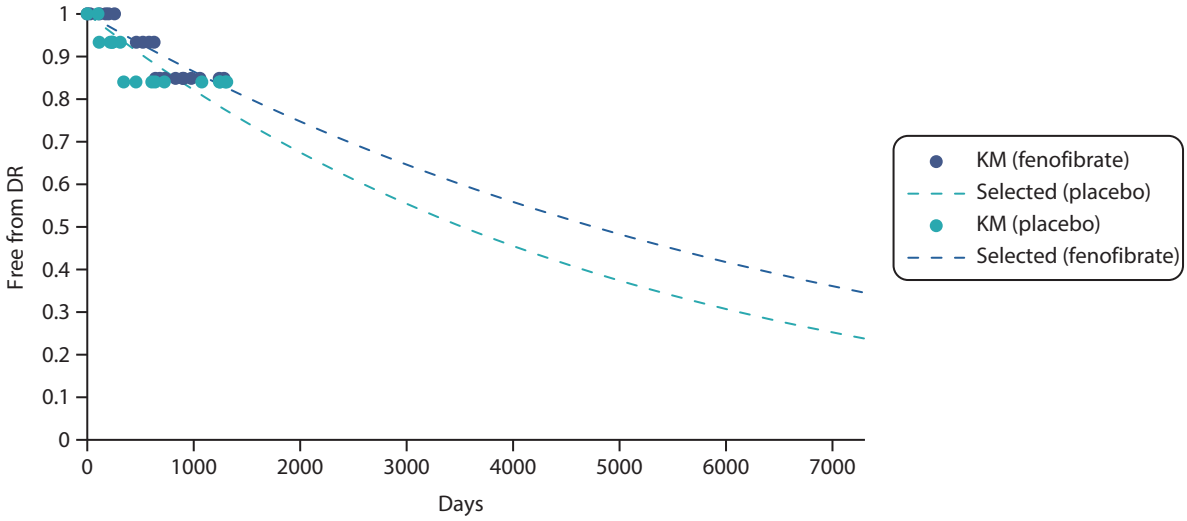

FIGURE 22 Selected exponential curves informing transitions from referable diabetic retinopathy (R3/R4) to referable maculopathy (M2). DR, diabetic retinopathy; KM, Kaplan–Meier.

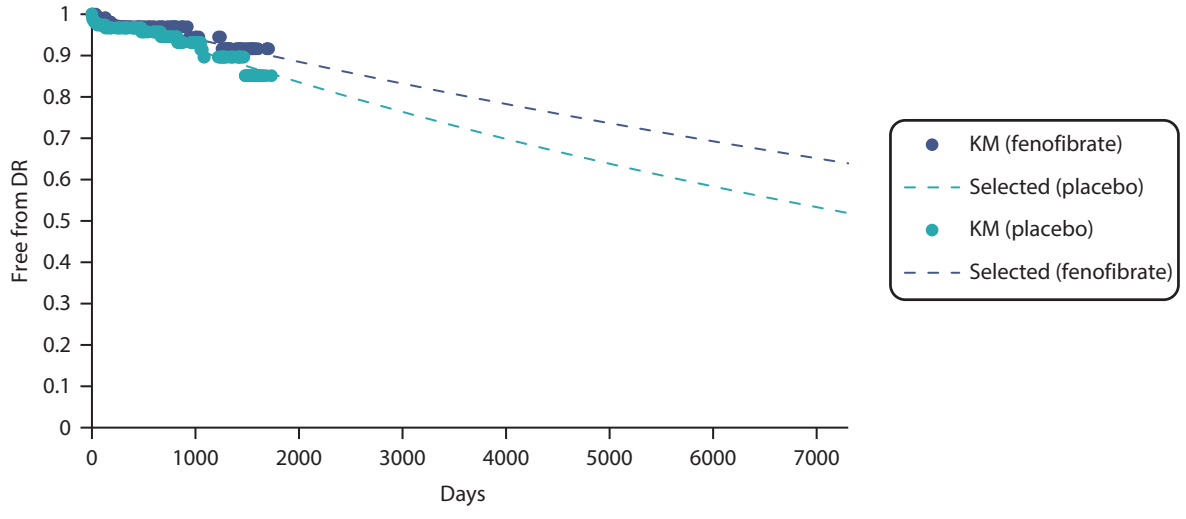

FIGURE 23 Selected exponential curves informing transitions from referable maculopathy to treatment for diabetic macular oedema. DR, diabetic retinopathy; KM, Kaplan–Meier.

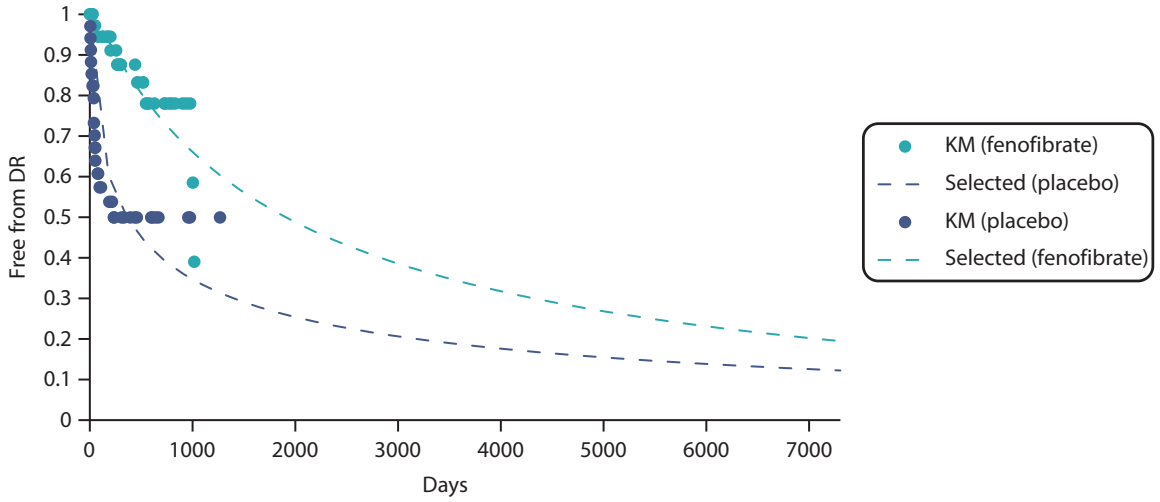

FIGURE 24 Selected independent log-normal curves informing transitions from referable diabetic retinopathy (R3/R4) to treatment for referable diabetic retinopathy. DR, diabetic retinopathy; KM, Kaplan–Meier.

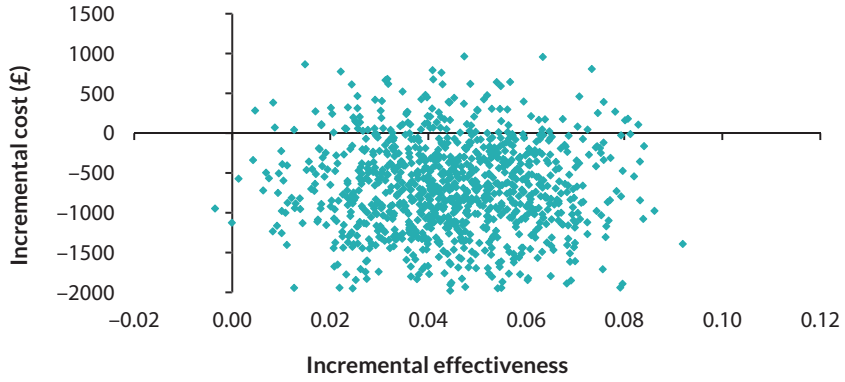

FIGURE 25 Trial-based cost-effectiveness scatterplots for fenofibrate vs. placebo (costs inclusive of inpatient episodes and outpatient visits to all specialties).

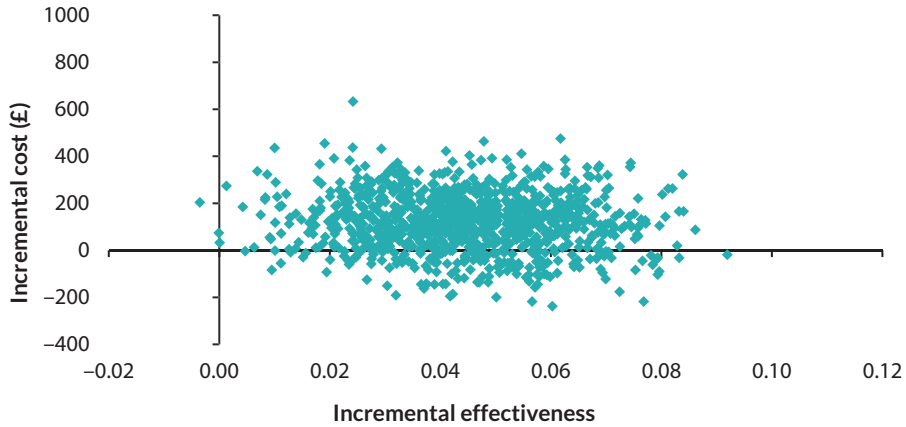

FIGURE 26 Trial-based cost-effectiveness scatterplots for fenofibrate vs. placebo (excluding all inpatient costs).

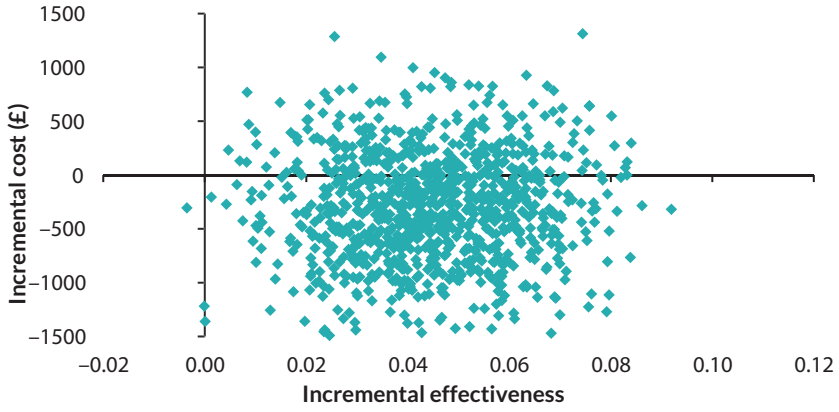

FIGURE 27 Trial-based cost-effectiveness scatterplots for fenofibrate vs. placebo scenario (inclusive of the full cost of continuous inpatient spells involving any episodes in a specialty of interest).

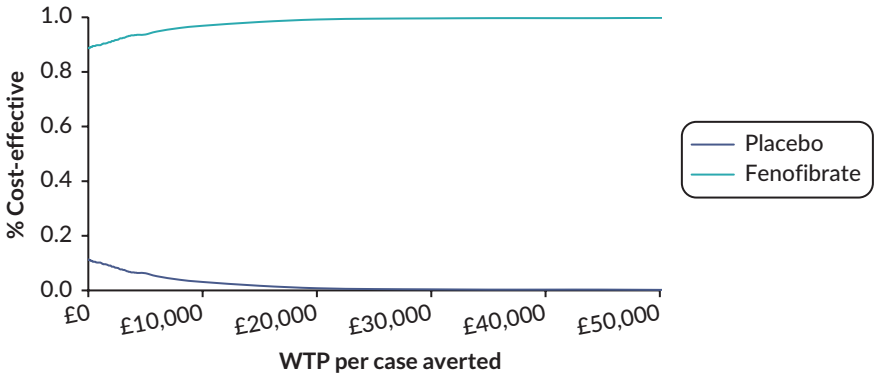

FIGURE 28 Trial-based cost-effectiveness acceptability curves for fenofibrate vs. placebo (costs inclusive of inpatient episodes and outpatient visits to all specialties).

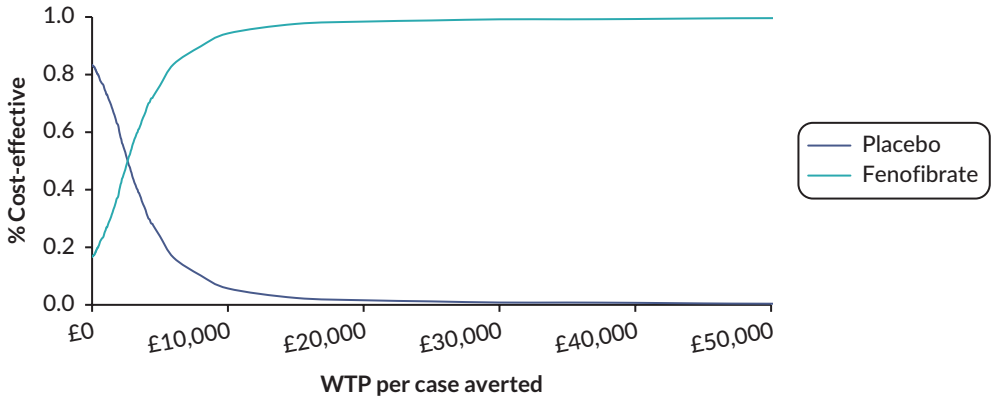

FIGURE 29 Trial-based cost-effectiveness acceptability curves for fenofibrate vs. placebo (excluding all inpatient costs).

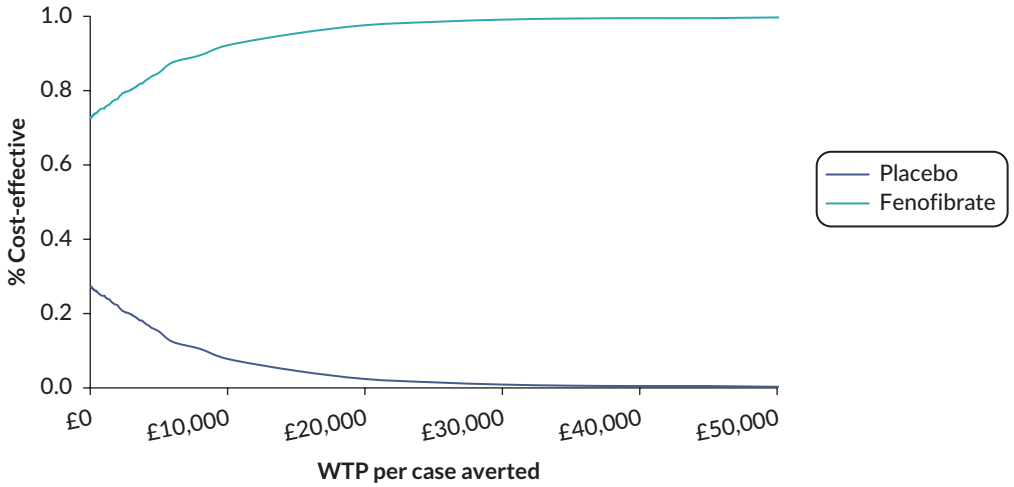

FIGURE 30 Trial-based cost-effectiveness acceptability curves for fenofibrate vs. placebo (inclusive of the full cost of continuous inpatient spells involving any episodes in a specialty of interest).