A randomised placebo-controlled trial of fenofibrate to prevent progression of non-proliferative retinopathy in diabetes

(Lowering Events in Non-proliferative retinopathy in Scotland [LENS])

Statistical Analysis Plan

EDMS #7695

Version 1.3

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1 Version History

0.1	Draft version	29 November 2021
0.2	Updated after SC comments	20 April 2022
1.0	First released version	29 June 2022
1.1	Minor clarifications to Section 5	10 January 2023
1.2	Exact subgroup categories now defined and description of MMRM models for continuous measures measured at multiple follow-up time points. Report frequency of NHS retinal screening. Add exploratory primary outcome analysis excluding first 12 months. Clarify visual acuity to be analysed as LogMAR (with conversion from Snellen where required).	12 June 2023
1.3	Appendix A: smoking was never included as minimisation variable, SAP error corrected	07 February 2024

2 Trial registration details

IRAS Number:	209579
EudraCT Number:	2016-002656-24
Clinical trials.gov Number:	NCT03439345
ISRCTN Number	ISRCTN15073006
REC Number:	16/WS/0149
Sponsor's number:	CTSULENS1
NIHR Number:	14/49/84

3 Introduction

This Statistical Analysis Plan describes the strategy, rationale and statistical methods that will guide assessment of the clinical efficacy and safety of fenofibrate in the LENS trial.

3.1 Study design

LENS is a randomised placebo-controlled trial investigating the effects of prolonged treatment with the PPAR alpha agonist, fenofibrate on the progression of diabetic eye disease. At least 1,060 participants with observable diabetic retinopathy or maculopathy will be randomised (using a minimisation algorithm, see Appendix A: Details of randomisation algorithm) between oral fenofibrate 145mg or placebo tablets. Study treatment is taken once daily in the context of normal renal function, or as one tablet every second day in the context of reduced renal function. Follow up is scheduled to continue until at least 222 primary outcome events have occurred and median follow up (counting from the date of randomisation of the median participant) is at least 4 years.

The trial is designed to be streamlined. Most data for pre-specified efficacy outcomes is obtained by linkage to NHS Scotland records. Only the Screening and Randomisation assessments occur in person, and all subsequent assessments occur by telephone or by reference to medical records. Study treatment is mailed to participants' homes. After the initial Screening visit is conducted and safety blood tests are performed, eligible individuals (who are approved to enter the run-in by the local investigator) are provided with active fenofibrate 145mg tablets to be taken (daily with normal renal function, one tablet every second day with reduced renal function) for approximately 8 weeks. They are then asked to return to the study clinic for a Randomisation assessment. If they remain eligible based on information collected at this assessment and further safety blood tests, and are willing to continue, participants are randomly allocated to fenofibrate 145mg tablets or placebo.

No research blood or urine samples are taken from randomised participants. Linkage to NHS Scotland data-sets is performed to obtain results for HbA1c, renal function (serum creatinine, eGFR, urine albumin, urine albumin creatinine ratio) and other assays (e.g. lipids) that have been collected as part of routine care.

3.2 Study objectives

The primary objective of the LENS trial is to assess the effect of allocation to fenofibrate versus placebo on progression to the composite primary outcome of referable diabetic retinopathy (DR) or any of the following treatments for diabetic retinopathy: retinal laser therapy, vitrectomy or intra-vitreal injections (see Section 4.3).

Other objectives include assessments of the effects of fenofibrate on secondary outcomes (see Section 4.4), tertiary outcomes (see Sections 4.5) and longer term follow up outcomes (to be covered in a separate analysis plan at a later date).

4 Definitions for efficacy and safety endpoints

4.1 Estimands

For the efficacy and safety endpoints based on clinical events, the estimand of interest will be the rate of first occurrence of the endpoint in the target population allocated fenofibrate relative to the rate of first occurrence of the endpoint 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 not included in the efficacy or safety endpoint being assessed.

4.2 Hypotheses

For all statistical tests, the null hypothesis will be that the effect of allocation to fenofibrate on the endpoint of interest in the target population is the same as the effect of allocation to placebo.

4.3 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[a] or any of the following treatments for diabetic retinopathy: retinal laser therapy, vitrectomy or intra-vitreal injection of medication due to diabetic retinopathy

4.4 Secondary efficacy assessments

4.4.1 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:

4.4.1.1 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[b] < 60 vs. ≥ 60 mL/min/1.73m^2)
- HbA1c (screening assessment HbA1c < 70 mmol/mol vs. HbA1c ≥ 70 mmol/mol)
- First primary outcome in the first year vs subsequent years of follow-up (because of the known reduced impact of lipid modification on cardiovascular events, and potentially reduced impact of fenofibrate on laser treatment for diabetic retinopathy, in the first year of treatment[1,2])

4.4.1.2 The individual components of the composite primary outcome, namely:

- The development of referable diabetic retinopathy[a];
- Treatment for diabetic retinopathy: any of retinal laser therapy, vitrectomy or intra-vitreal injection of medication due to diabetic retinopathy

[a] referable diabetic retinopathy is defined according to NHS Scotland's DES grading as R3 or R4 [excluding R4i as it represents inactive disease] or M2 in at least one eye in the DES grading scheme; such evidence may come from NHS retinal screening or clinical examination

[b] as entered into the eCRF by research staff using whichever formula is employed by that NHS health board

4.4.1.3 Any progression of diabetic retinopathy across the NHS Scotland retinopathy grading scale[c]

4.4.1.4 The presence of hard exudates or blot haemorrhages within 1 disc diameter of the macula[d]

4.4.1.5 Macular oedema

4.4.2 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:

4.4.2.1 Visual function (based on the Visual Function Questionnaire [VFQ]-25 questionnaire)

4.4.2.2 Quality of life (based on the EuroQol- 5 Dimension [EQ-5D] questionnaire)

4.4.2.3 Visual acuity (based on visual acuity on LogMar or Snellen chart score collected during NHS retinal screening)

4.4.3 Health economic assessments

Health economic assessments will be conducted to help guide the appropriate use of fenofibrate by health care providers. The detailed analysis plan for health economic assessments will be described in a separate document.

4.5 Tertiary efficacy assessments

4.5.1 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:

4.5.1.1 The composite of any major cardiovascular event (defined as myocardial infarction, stroke, coronary or peripheral revascularisation).

4.5.1.2 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]).

4.5.2 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:

4.5.2.1 Urine albumin: creatinine ratio

4.6 Clinical safety assessments

SAEs and reasons for stopping study treatment will be captured in the study database to be used for safety assessments. The safety assessments will include intention-to-treat analyses among all randomised participants of the effects of allocation to fenofibrate versus placebo during the scheduled treatment period (with due allowance in their interpretation for multiple comparisons) on:

4.6.1.1 Serious adverse events by Medical Dictionary for Regulatory Activities (MedDRA, version 14.0) System Organ Class classification;

[c] progression from R'X' (baseline) to >R'X' or from M'X' (baseline) to >M'X' in either eye
[d] M2 grading in the NHS Scotland grading scheme

4.6.1.2 Discontinuation of study treatment, overall and by various causes

4.7 Other laboratory assessments

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

4.7.1.1 eGFR[e]

4.7.1.2 Lipids (total cholesterol, non-HDL cholesterol, HDL cholesterol, triglycerides)

4.7.1.3 HbA1c

Invitation to routine NHS retinal screening is determined by the most recent retinal screening results (and has also been affected by the COVID-19 pandemic). The mean (standard error) number of retinal screening visits per participant will be calculated for each treatment arm.

5 Analysis sets for efficacy and safety analyses

For all outcomes, analyses will compare the outcome from randomisation to the end of the scheduled treatment period (see Section 7.5) among all those participants who are allocated at randomisation to receive fenofibrate versus all those allocated to receive matching placebo (i.e. "intention-to-treat" analyses).[3,4] Analyses of binary outcomes will be based on the first occurrence of the specified outcome. *Per protocol* analyses will not be conducted because of the potential for bias in such non-randomised assessments.

In accordance with the protocol, primary, secondary and tertiary outcomes will not be adjudicated with the exception of any medical eye procedures, any adverse event reports of vitreous haemorrhage and any adverse event reports of macular oedema. Such events will be adjudicated by clinicians blinded to the study treatment assignment (see Section 6). For those events that are subject to adjudication, analyses will include confirmed and unrefuted events (excluding any events adjudged to be related to a cause other than diabetic retinopathy).

For eye outcome events, the number of people experiencing the outcome (in one or both eyes) will be compared between the treatment groups (rather than the total number of eyes affected).

6 Ascertainment and adjudication of study endpoints

6.1 Ascertainment of information

Unless consent to follow-up is withdrawn, follow-up information is to be collected from all study participants, irrespective of whether or not they continue to receive study treatment. If a participant becomes unwilling or unable to complete follow up study assessments by telephone then study clinic staff will review the available medical records and complete the necessary Follow-up form on the clinic IT system. Information will also be collected from linkage to NHS Scotland healthcare systems and registries. Where retinopathy and maculopathy gradings of retinal images contribute to pre-specified outcomes, the grading results generated by the NHS Scotland Diabetic Eye Screening

[e] Based on calculations using serum creatinine collected by data linkage and the CKD EPI formula:
$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]
where:
Scr is serum creatinine in μmol/L; κ is 61.9 for females and 79.6 for males; α is -0.329 for females and -0.411 for males; min indicates the minimum of Scr/κ or 1; max indicates the maximum of Scr/κ or 1

program will be used. However, it is also intended to use image analysis software at a later time to repeat these analyses.

6.2 Adjudication

Adjudicators will follow the standardised procedures in accordance with the pre-specified endpoint definitions and adjudication procedures as described in the Adjudication Charter (LENS Adjudication Charter and Outcome Definitions EDMS #6781). Only one blinded adjudicator will execute the adjudication procedure for each event.

7 Statistical methodology for efficacy and safety analyses

7.1 Methods of analysis

All participants randomised to receive fenofibrate will be compared with all participants randomised to placebo, irrespective of whether they received all, some or none of their allocated treatment (i.e. intention-to-treat [ITT] analyses).[3,4]

For the time-to-event analyses, survival analytic methods will be used to evaluate the time to the first event during the entire study period. Cox proportional hazards regression analyses, adjusted for baseline covariates used in minimised randomisation, will be used to estimate the hazard ratios, 95% confidence intervals and corresponding p-values, comparing all participants allocated active fenofibrate with all those allocated placebo.[3] The proportional hazards assumption will be assessed through examination of the Schoenfeld residuals. The Kaplan-Meier estimate will also be plotted for the time to the primary outcome (with its associated log-rank p-value). When separately assessing individual elements of composite outcomes, a participant may contribute to more than one assessment if they have events of more than one type (e.g. significant retinopathy followed by laser treatment). All p-values will be 2-sided. For each of the events listed as additional safety outcomes (Section 4.6), the number of randomised participants with at least 1 event will be compared using standard tests for differences in proportions.

For continuous measures collected only at the screening visit, or which may plausibly be affected by fenofibrate treatment during the active run-in (namely visual function, quality of life, eGFR, lipids [total cholesterol, non-HDL cholesterol, HDL cholesterol, triglycerides], HbA1c, urine albumin: creatinine ratio), the screening visit value will be considered to represent the 'baseline' value to which any post-randomisation values are compared. For continuous measures not collected at the screening visit but identified in pre-randomisation NHS linkage data (namely visual acuity), the latest value within 18 months prior to randomisation will be considered to represent the 'baseline' value.

Any continuous outcomes that display substantial positive skew will be analysed on the log scale. For quality of life (Section 4.4.2.2), index values will be derived from EQ-5D-5L questionnaire data using a UK-based value set. Visual acuity (Section 4.4.2.3) will be recorded using the LogMAR or Snellen chart score. The main analysis of visual acuity will be based on the eye with best acuity at baseline, and analysis of the eye with worse acuity will be conducted as a sensitivity analysis. Where the baseline visual acuity is the same in both eyes, the right eye shall be chosen for the main analysis and the left eye for the sensitivity analysis. Analyses of visual function will be based on LogMAR values, with conversion of Snellen chart score to LogMAR values where required[f].

Visual function (Section 4.4.2.1) and quality of life (Section 4.4.2.2) are collected at baseline, at approximately 2 years and at the end of the trial as part of scheduled study assessments. By contrast, biochemical measurements (Sections 4.5.2.1 and 4.7) and visual acuity (Section 4.4.2.3) are collected at baseline and then collected at multiple times during follow-up as part of routine NHS clinical care. For all of these outcomes with baseline and repeated follow-up values, linear mixed

[f] LogMAR value = $\log_{10}$(Snellen denominator / Snellen numerator); it is recognised that conversion from Snellen chart score to LogMAR value is imperfect but it is considered adequate for comparison of fenofibrate vs. placebo

model repeated measures (MMRM) analyses will be conducted to estimate the mean values by treatment allocation at each follow-up time point, as well as a trial-averaged difference in mean follow-up levels between the randomised treatment groups. For visual function and quality of life, the relevant follow-up time points will be 2 years and the end of the trial but, for biochemical measurements and visual acuity, the follow-up time points will be the midpoint of each year of follow-up (any individuals with >1 value in a given 1-year post-randomisation window of time will have those values averaged prior to the MMRM analysis). These MMRM models will adjust for the baseline value of the measure of interest as well as the baseline minimisation criteria and will assume an unstructured covariance matrix.

7.2 Multiplicity adjustments

Assuming that the trial runs to its planned completion, the primary assessment at the final analysis will be made first and deemed statistically significant if its two-sided p-value is <0.05.

For the secondary and tertiary assessments, multiple testing will not formally be taken into account. However, given the number of such analyses, due allowance will be made in their interpretation, taking into account the nature of events (including timing, duration and severity) and evidence from other studies.[3,4]

7.3 Subgroup analyses and tests for heterogeneity

The secondary assessments (see Section 4.4.1.1) include intention-to-treat analyses among all randomised participants of the effects of allocation to fenofibrate versus placebo during the scheduled treatment period on the primary outcome in sub-categories of patient based on categories of data collected at baseline. Tests for heterogeneity of the proportional effect observed in subgroups will be used to determine whether the proportional effects in specific subcategories are clearly different from the overall effect.[2,3] (Note that for the subgroups that can be sensibly ordered [age, renal function and HbA1c] this test for heterogeneity is equivalent to a test for trend because each of the subgroups is to be split into only two categories [see Section 4.4.1.1].)

When many different subgroups are considered, chance alone may lead to there being no apparent effect in some subgroups considered in isolation, even when the effect of treatment really is about the same as is observed overall. In such circumstances, “lack of direct evidence of benefit” is not good “evidence of lack of benefit”, and clearly significant overall results would provide strong indirect evidence of benefit in subgroups where the results, considered in isolation, are not conventionally significant (or, even, perhaps, slightly adverse).[3-5] Hence, unless the proportional effect in some specific subcategory is clearly different from that observed overall, the effect in that subcategory is likely to be best estimated indirectly by applying the proportional effect observed among all patients in the trial to the absolute risk of the event observed among control patients in that category.[5]

7.4 Handling of missing and incomplete data

The study protocol and procedures have been designed to minimise loss to follow-up.[6] For any binary outcome event where the precise date of occurrence is unknown, the midpoint of the plausible range will be assumed (e.g. the middle of the month if only the month and year are reported). For subgroup analyses of the effects of fenofibrate on such events, patients with missing baseline values for that subgroup will be excluded from the subgroup-specific results but included in the overall total (with the result just among those with missing baseline data for each subgroup explicitly reported if the ‘missing’ category proves to be a non-trivial subset). Note that for analyses of the continuous measurements recorded at multiple follow-up time points, the MMRM models take account of missing data by assuming that such data can be predicted from the correlations seen between the non-missing values for other individuals, together with the other covariates in the model (i.e., the model assumes that data are ‘missing at random’).

7.5 Censoring schema for time-to-event endpoints

For all intention-to-treat analyses, participants who do not have the outcome under investigation will be censored at the end of the scheduled treatment period, which will be defined as the earliest of date of the final follow-up visit, death, or full consent withdrawal. For participants for whom information on these 3 criteria is missing, the censoring date will be set as the date when reliable information on both vital status and the occurrence/absence of the primary outcome was last reliably recorded (e.g. by completion of follow-up visit or access to relevant healthcare records).

8 Guidelines for early stopping or modification of the trial

Unblinded interim analyses will be reviewed regularly by the DMC, and will be conducted and presented by a statistician not involved in the day-to-day management of the trial. Upon review of such data, the DMC will advise the Steering Committee if, in their view, the randomised comparisons have provided both (a) proof beyond reasonable doubt that for all patients, or for some specific types, fenofibrate therapy is clearly indicated or contra-indicated; and (b) evidence that might reasonably be expected to influence materially the clinical management of many patients. The Steering Committee can then decide whether to end or modify the trial or to seek additional data, and this decision will be communicated in writing to the Chief Investigator after each Steering Committee meeting.

Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but the DMC will work on the principle that a difference of at least 3 standard errors in an interim analysis of a major outcome event may be needed to justify halting, or modifying, a study before the planned completed recruitment. This criterion has the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed[3].

9 References

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3. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; **34**(6): 585-612.

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5. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *The Lancet* 2001; **357**(9253): 373-80.

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10 Appendix A: Details of randomisation algorithm

The minimised randomisation algorithm allocates participants to the placebo arm or the active arm. The participant is allocated to the treatment arm with the lower minimisation score, with a probability of 0.9 (i.e. this occurs for 90% of randomisations). For the other 10% of randomisations, or in the event of a tie (i.e. minimisation scores are equal), treatment is allocated randomly with a probability of 0.5.

The minimisation score is calculated based on the following categories:

- Sex: male; female
- Age at randomisation visit: <30; ≥30 <50; ≥50 <70; ≥70 years
- Type of Diabetes: Type 1, Type 2, Other
- eGFR from Randomisation assessment: <60; ≥60 mL/min/1.73m^2
- HbA1c from Randomisation assessment: <64; ≥64mmol/mol; unknown
- Statin therapy: Yes; No
- Most recent macula result: consider both eyes and use the worst eye's macula result as the category (in the list below, 'i' is the best result and 'iii' is the worst result)
    i. No result available
    ii. No maculopathy
    iii. Observable diabetic maculopathy
- Most recent retina results: consider both eyes and use the worst eye's retina result as the category (in the list below, 'i' is the best result and 'iv' is the worst result)
    i. Other retinopathy (this includes 'not adequately visualised' and 'other result provided')
    ii. No retinopathy
    iii. BDR – Mild
    iv. BDR – Observable